PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Projecting diabetes prevalence among Mexicans aged 50 years and older: The Future Elderly Model-Mexico (FEM-Mexico)
AUTHORS	Gonzalez Gonzalez, Cesar; Tysinger, Bryan; Goldman, Dana; Wong, Rebeca

VERSION 1 – REVIEW

REVIEWER	Jon Minton University of Glasgow, Scotland, UK
REVIEW RETURNED	22-May-2017

GENERAL COMMENTS	This is a fairly strong paper addressing an interesting and important issue using an extant modelling framework, which is reasonably well described. I commend the authors for focusing on this important issue and on making use of the extant framework. Depending on the main aims of the authors, the main limitations of this paper are either largely presentational, and will require only a minor revision; or they are fundamental, and require a major revision to both the modelling framework and manuscript. The key issue, to me, seems to be that both the abstract and main manuscript strongly imply that the results contribute to an informative cost-effectiveness evaluation of interventions designed to reduce the incidence of diabetes in the over 50s, and and from this evidence-based decisions about whether to promote specific medical and lifestyle interventions can be made. However, this inference is over-reaching, because what the model instead does is shows how long-term projections in incidence and prevalence vary IF one of a number of hypothetical interventions, which reduce incidence by given proportions, were to be realised. The Results section of the abstract, as well as a number of points in the discussion section, then make claims about either the cost-savings or number of cases averted as a result of these hypothetical interventions. However, no specific interventions are modelled - instead this is a scenario analysis - and neither the evidence on the effectiveness nor cost of specific interventions are included in the model. At most, therefore, these models tell us something about the maximum acceptable cost of health interventions conditional on their effectiveness: looking at table 4 this suggests, for example, an intervention needs to cost no more than around 40 (1663 - 1624, is the unit $s or pesos?) per patient per year to be cost-neutral if it were 10% effective; around 80 per patient per year if 30% effective, and so on.

	The question this raises is therefore whether extant or nascent interventions with these levels of effectiveness are likely to be more expensive or cheaper than these thresholds. The minor revision option (which I have selected in my recommendation) is therefore to go through the manuscript carefully, and revise to avoid making claims about cost-effectiveness in this way, and instead make it clear that the scenarios are based on hypothetical interventions without costs applied to them. The major revision option (possibly a withdrawal and resubmit option) would be to redo the modelling from a genuine cost-effectiveness framework, basing scenarios on best available evidence of genuine health interventions in terms of effectiveness and cost.

REVIEWER	Jillian Oderkirk Organisation for Economic Co-operation and Development, France
REVIEW RETURNED	30-May-2017

GENERAL COMMENTS	Dear authors, Congratulations on this paper that sheds new light on the positive impact that diabetes prevention efforts could have on reducing the burden of diabetes. There are no major revisions required, however a few minor revisions would improve the ability of the paper to communicate its message more clearly. The abstract does not fully reflect the paper. For example, the objective paragraph does not mention that the purpose of the study is to project the potential health and economic impacts of policy interventions to reduce diabetes prevalence. The abstract's discussion statement misses the article's conclusions regarding the potential impacts of policy interventions. The section on strengths and limitations of the study does not indicate any limitations. Potential limitations to be included would be 1) the model is developed from self-reported data that may not fully represent the prevalence of diabetes; 2) there were only two waves of MHAS used to estimate transitions which may reduce their reliability; 3) FEM is a model that projects past trends and evidence from past observations into the future and, therefore, results are not predictive; and 4) the model is tied to the data collected within the MHAS survey and, as a result, does not consider potentially important factors or outcomes that are outside the scope of the survey. The abstract and the article should be reviewed by an English editor to correct grammar and improve readability. In the introduction paragraph 2 (page 4 lines 27 to 32) the references are missing. In the last paragraph of the introduction (page 6 lines 9 to 13) four scenarios of diabetes incidence reduction are introduced but it is not clear for the reader why these four scenarios were selected and how they relate to the conclusions of the DPP trial. A statement about the DPP findings and about how they can be translated into the FEM framework would help. Statements about why the DPP study (and not any other study) was selected and about how the DPP results may, or may not, be applicable to Mexico are needed. It would also

	help the reader if the DPP intensive lifestyle intervention could be briefly described. (The question of why the four scenarios were modelled arises again when reading page 9 lines 40 to 56.) References for all statements indicating the DPP trial evidence pointed to a 60% reduction in diabetes incidence are needed. In the methods section (page 7 lines 29 to 36) the estimated prevalence of diabetes in 2012 is compared with the observed estimate from MHAS 2012. This is an important dimension of the paper and could be expanded upon. The MHAS 2012 observed results could be used to validate the projections of other key outcomes of this study (population, population by BMI category, number of medical visits). On page 10 and in table 1 the results of the MHAS for 2012 are presented but the MHAS 2012 results did not contribute to the FEM. Table 1 could become more important to the results section if it was expanded to include a column presenting the characteristics projected by the FEM for 2012. Then table 1 could contribute to the validation of the FEM results. On page 12 lines 3-11, US results for a treatment cost multiplier are applied to Mexican data. A statement is needed to explain why evidence for Mexico was not available and to indicate the degree to which treatment costs in the US are similar to or different from costs in Mexico. The first paragraph of the discussion on page 14 (lines 6-19) should explain (again) how the four scenarios relate to the DPP study results. Is written now, paragraph two on page 14 becomes confusing for readers because it seems to imply that the scenarios relate to a body of evidence from clinical studies and not specifically to the DPP. The text needs to be revisited to make it clear that the DPP is part of a larger body of evidence but was selected for this modelling effort because of certain reasons x, y and z. Figure 1 is repetitive of table 2 and could be cut. The technical appendix paragraph 2 (lines 25-28) is missing a reference and it would be wrong to say that the details of the FEM are published everywhere (probably it should say elsewhere). The technical appendix figure 1 (page 31) refers to the HRS-FEM but the text of the paper refers to the FEM-US. Please use consistent terminology throughout.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jon Minton
Institution and Country: University of Glasgow, Scotland, UK
Please state any competing interests: None Declared

Comment:
This is a fairly strong paper addressing an interesting and important issue using an extant modelling framework, which is reasonably well described. I commend the authors for focusing on this important issue and on making use of the extant framework.
Depending on the main aims of the authors, the main limitations of this paper are either largely presentational, and will require only a minor revision; or they are fundamental, and require a major revision to both the modelling framework and manuscript.
The key issue, to me, seems to be that both the abstract and main manuscript strongly imply that the results contribute to an informative cost-effectiveness evaluation of interventions designed to reduce the incidence of diabetes in the over 50s, and from this evidence-based decisions about whether to promote specific medical and lifestyle interventions can be made.
However, this inference is over-reaching, because what the model instead does is shows how long-term projections in incidence and prevalence vary IF one of a number of hypothetical interventions, which reduce incidence by given proportions, were to be realized. The Results section of the abstract, as well as a number of points in the discussion section, then make claims about either the cost-savings or number of cases averted as a result of these hypothetical interventions.
However, no specific interventions are modelled - instead this is a scenario analysis - and neither the evidence on the effectiveness nor cost of specific interventions are included in the model.

Response:
We have addressed the concerns of the Reviewer 1. Indeed, the purpose of the paper is-not to make a cost-effectiveness evaluation. Thus, we avoid language that refers to cost effectiveness or cost benefit. We made adjustments in the manuscript accordingly to make clear that we are modeling hypothetical scenarios. The abstract, results and discussion sections were modified.

Comment:
At most, therefore, these models tell us something about the maximum acceptable cost of health interventions conditional on their effectiveness: looking at table 4 this suggests, for example, an intervention needs to cost no more than around 40 (1663 - 1624, is the unit $s or pesos?) per patient per year to be cost-neutral if it were 10% effective; around 80 per patient per year if 30% effective, and so on.

Response:
It is a very good idea to think the results as the maximum acceptable cost of health interventions conditional on their effectiveness. However, we prefer to keep our discourse in terms of possible/potential diabetes cases avoided if some of the proposed scenarios could be reached.

Comment:
The question this raises is therefore whether extant or nascent interventions with these levels of effectiveness are likely to be more expensive or cheaper than these thresholds.

Response:
We agree with the reviewer that questioning the cost thresholds is an interesting perspective, but again, beyond the scope of this paper. However, we incorporated some of these ideas in the discussion section.

Comment:
The minor revision option (which I have selected in my recommendation) is therefore to go through the manuscript carefully, and revise to avoid making claims about cost-effectiveness in this way, and instead make it clear that the scenarios are based on hypothetical interventions without costs applied to them.
The major revision option (possibly a withdrawal and resubmit option) would be to redo the modelling from a genuine cost-effectiveness framework, basing scenarios on best available evidence of genuine health interventions in terms of effectiveness and cost.

Response:
We appreciate all the constructive comments from the reviewer. We opted for the recommended minor revision. We went through the entire document to avoid cost-effectiveness statements. The revised manuscript makes emphasis on modeling scenarios using microsimulation, making clear that the various scenarios are based on hypothetical interventions.

Reviewer: 2

Reviewer Name: Jillian Oderkirk
Institution and Country: Organisation for Economic Co-operation and Development, France
Please state any competing interests: None declared

Dear authors, Congratulations on this paper that sheds new light on the positive impact that diabetes prevention efforts could have on reducing the burden of diabetes. There are no major revisions required, however a few minor revisions would improve the ability of the paper to communicate its message more clearly.

Comment:
The abstract does not fully reflect the paper. For example, the objective paragraph does not mention that the purpose of the study is to project the potential health and economic impacts of policy interventions to reduce diabetes prevalence. The abstract's discussion statement misses the article's conclusions regarding the potential impacts of policy interventions.

Response:
As suggested by the reviewer, we have made the appropriate changes – rewriting the objectives and adding the potential impacts of policy interventions in the revised abstract.

Comment:
The section on strengths and limitations of the study does not indicate any limitations. Potential limitations to be included would be 1) the model is developed from self-reported data that may not fully represent the prevalence of diabetes; 2) there were only two waves of MHAS used to estimate transitions which may reduce their reliability; 3) FEM is a model that projects past trends and evidence from past observations into the future and, therefore, results are not predictive; and 4) the model is tied to the data collected within the MHAS survey and, as a result, does not consider potentially important factors or outcomes that are outside the scope of the survey.

Response:
We agree with the reviewer, all these limitations are related to the nature of the data (MHAS) and now they are included in the abstract and in the discussion section.

Comment:
The abstract and the article should be reviewed by an English editor to correct grammar and improve readability.

Response:
We went through the entire manuscript to correct grammar, and an editor has revised the manuscript to improve readability.

Comment:
In the introduction paragraph 2 (page 4 lines 27 to 32) the references are missing.

Response:
We have added the references in the revised version as suggested by the Reviewer.

Comment:
In the last paragraph of the introduction (page 6 lines 9 to 13) four scenarios of diabetes incidence reduction are introduced but it is not clear for the reader why these four scenarios were selected and how they relate to the conclusions of the DPP trial. A statement about the DPP findings and about how they can be translated into the FEM framework would help. Statements about why the DPP study (and not any other study) was selected and about how the DPP results may, or may not, be applicable to Mexico are needed.

Response:
We added a couple of sentences relating to the likely applicability of DPP results to the case of Mexico. We add that the DPP trial included Hispanic population and the effects of the clinical trial were similar in all racial and ethnic groups. Even though in population based studies there is a difference among racial and ethnic groups, perhaps the sample selection in the DPP resulted in a reduced difference. The DPP lifestyle intervention has similar results than those obtained in other countries (Finland and China). Also, the Mexican and American populations share some characteristics associated with the onset of diabetes, for example, overweight levels, sedentary lifestyles, and diet.
The DPP findings show that among persons with impaired glucose tolerance, an intensive lifestyle intervention reduces the incidence of type 2 diabetes by about 50%, while the drug metformin reduces the incidence by about 30%. We are using information on what can be achieved under different diabetes incidence reduction scenarios.

Comment:
It would also help the reader if the DPP intensive lifestyle intervention could be briefly described. (The question of why the four scenarios were modelled arises again when reading page 9 lines 40 to 56.)

Response:
A detailed description of the scenarios is now provided in the last paragraph of page 9. We selected the scenarios based on evidence from clinical trials, and thinking in what is possible, what is probable and what is desirable to achieve in the Mexican population in order to reduce the prevalence of diabetes by 2050.

Comment:
References for all statements indicating the DPP trial evidence pointed to a 60% reduction in diabetes incidence are needed.

Response:
We have added the reference in the revised version as suggested by the Reviewer.

Comment:
In the methods section (page 7 lines 29 to 36) the estimated prevalence of diabetes in 2012 is compared with the observed estimate from MHAS 2012. This is an important dimension of the paper and could be expanded upon. The MHAS 2012 observed results could be used to validate the projections of other key outcomes of this study (population, population by BMI category, number of medical visits).

Response:
We agree that the validation of the estimated prevalence in 2011-2013 is an important dimension of the manuscript, however, we cannot validate the projections for other results. For validation of the diabetes prevalence, we used information from the population that in 2003 was between 55 and 56 years old, then we projected the prevalence of diabetes for 2011 and 2013, so this cohort would be 64 and 65 years old in 2012 and this projections could be compared with the observed prevalence of diabetes in MHAS 2012 for this age group (65+).
The key outcomes in the manuscript are for the population aged 50 and older. In order to address the comment, we did the validation of the projections for these outcomes, but for the population aged 65 and over. The results of the FEM-Mexico are similar to the results observed in the MHAS 2012, we have considered not to include them in the table, but we added a paragraph to support the idea.

Comment:
On page 10 and in table 1 the results of the MHAS for 2012 are presented but the MHAS 2012 results did not contribute to the FEM.

Response:
We agree with the reviewer. We are presenting data from MHAS for 2012, as this period is the start point for the projections and was not part of the FEM-Mexico results. We have revised the paragraph and added a couple of sentences to support this idea.

Comment:
Table 1 could become more important to the results section if it was expanded to include a column presenting the characteristics projected by the FEM for 2012. Then table 1 could contribute to the validation of the FEM results.

Response:
As mentioned above, the results of the FEM-Mexico were compared with the observed data from the MHAS 2012 to do the validation, but the comparison is for the population 65 years and older. Including, in Table 1, a column for each cohort would confuse and divert the attention from the results that we want to show. In addition, the information presented in Table 1 is about descriptive characteristics and are not part of the key outcomes. Therefore it was decided not to modify the table.

Comment:
On page 12 lines 3-11, US results for a treatment cost multiplier are applied to Mexican data. A statement is needed to explain why evidence for Mexico was not available and to indicate the degree to which treatment costs in the US are similar to or different from costs in Mexico.

Response:
We have clarified this point. We are using only the ratio (3.5 times greater) from the NY State Diabetes Prevention and Control Program; we are not using treatment cost from the United States. We obtained the annual average cost for a person with diabetes in Mexico ($ 3,193 dollars), and applied the 3.5 ratio obtaining the cost per patient without diabetes ($ 912 dollars). There is a lot of evidence regarding the cost of diabetes in Mexico but we were unable to find information about the cost of treatment for a person without diabetes. Thus, we are assuming that the ratio (3.5) is appropriate for the Mexican population.

Comment:
The first paragraph of the discussion on page 14 (lines 6-19) should explain (again) how the four scenarios relate to the DPP study results.

Response:
We added a sentence stating that the hypothetical scenarios come from the DPP study.

Comment:
As is written now, paragraph two on page 14 becomes confusing for readers because it seems to imply that the scenarios relate to a body of evidence from clinical studies and not specifically to the DPP. The text needs to be revisited to make it clear that the DPP is part of a larger body of evidence but was selected for this modelling effort because of certain reasons x, y and z.

Response:
We have now added a sentence. The DPP has certain characteristics that made us choose its results to apply them with the FEM-Mexico projections. For example, the DPP focuses on lifestyle modifications and Mexico is promoting some public policies to change diet and increase physical exercise among the population. Also, the DPP recommended the use of metformin, a drug that is proven to delay the onset of diabetes, and this drug could be a feasible alternative in the Mexican population because of its low cost.

Comment:
Figure 1 is repetitive of table 2 and could be cut.

Response:
We agree. Figure 1 was removed from the manuscript.

Comment:
The technical appendix paragraph 2 (lines 25-28) is missing a reference and it would be wrong to say that the details of the FEM are published everywhere (probably it should say elsewhere).

Response:
We have added a reference, and corrected the word to “elsewhere”.

Comment:
The technical appendix figure 1 (page 31) refers to the HRS-FEM but the text of the paper refers to the FEM-US. Please use consistent terminology throughout.

Response:
We have corrected the inconsistencies in the document, and use FEM-US throughout.

VERSION 2 – REVIEW

REVIEWER	Jon Minton University of Glasgow, Scotland, UK
REVIEW RETURNED	02-Aug-2017

GENERAL COMMENTS	I have just five very minor suggestions, but would be happy for the paper to be accepted as-is: Minor 1. ".. since the analysis is based on self-reported data and maybe underestimated the prevalence of diabetes" – change 'maybe' to 'may'. 2. P.6 : Sentences "Were hypothetical interventions to be implemented to reduce the .. " and … "And how would the healthcare burden of diabetes diminish" – I think these aims are clear and should be made clearer by breaking the paragraph into two paragraphs. I suggest writing "The two main questions we answer are:" before these two sentences. Then end the paragraph at "… to treat the diseases". Make the sentence beginning "To address these questions, …" the start of the next paragraph. 3. P. 13: sentence "If we compare the total number of medical visits year by year for the no intervention scenario" – This sentence is unclear. "medical visits year by year" – please correct. 4. P. 14 – "Nevertheless, the evidence shows that the interventions intended to delay diabetes result in significant savings…" – again this is over-claiming as the cost of the intervention is unknown. Change to something like "…may result in significant savings if the costs of the intervention were less than the costs treatments costs averted." Possibly also mentioned broader potential economic productivity benefits due to having a healthier workforce, as mentioned later. 5. I would suggest adding a sentence near the end, when discussing further research, stating that further research evaluating the cost and effectiveness of public health interventions aimed at reducing diabetes incidence should be prioritised, as without such information it is not at this stage possible to know if such interventions are likely to reduce the net future healthcare cost, and if so by how much.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jon Minton
Institution and Country: University of Glasgow, Scotland, UK
Please state any competing interests: None Declared

Please leave your comments for the authors below
I thank the authors for making the suggested revisions, and think the new manuscript is an improvement over the previous submission.

I have just five very minor suggestions, but would be happy for the paper to be accepted as-is:
Minor suggestions
1. ".. since the analysis is based on self-reported data and maybe underestimated the prevalence of diabetes" – change 'maybe' to 'may'.
RESPONSE: THANK YOU FOR THIS SUGGESTION. WE CHANGED THE WORD 'MAYBE' TO 'MAY'.

2. P.6 : Sentences "Were hypothetical interventions to be implemented to reduce the .. " and … "And how would the healthcare burden of diabetes diminish" – I think these aims are clear and should be made clearer by breaking the paragraph into two paragraphs. I suggest writing "The two main questions we answer are:" before these two sentences. Then end the paragraph at "… to treat the diseases". Make the sentence beginning "To address these questions, …" the start of the next paragraph.
RESPONSE: THANK YOU FOR YOUR SUGGESTION, WE MADE ADJUSTMENTS TO THE TEXT AS FOLLOWS:
The goal of the study was to estimate the future prevalence of diabetes among Mexico's older adults in order to assess the current and future health and economic burden of diabetes. We estimate future levels of diabetes under different scenarios for the population aged 50 years and older in Mexico. Were hypothetical interventions to be implemented to reduce the incidence of diabetes, the two main questions we answer are: how much would the prevalence of diabetes change? And how would the health care burden of diabetes diminish, in terms of medical resources to treat the disease?
To address these questions, we modeled the trajectory of future diabetes in Mexico from 2012 to 2050 using a microsimulation model, the Future Elderly Model (FEM).

3. P. 13: sentence "If we compare the total number of medical visits year by year for the no intervention scenario" – This sentence is unclear. "medical visits year by year" – please correct.
RESPONSE: WE MADE ADJUSTMENTS TO THE TEXT AS FOLLOWS
If we compare the total number of medical visits in each year of the projection for the no-intervention scenario versus the 10% reduction in two-year diabetes incidence, we cannot find a large difference.

4. P. 14 – "Nevertheless, the evidence shows that the interventions intended to delay diabetes result in significant savings…" – again this is over-claiming as the cost of the intervention is unknown. Change to something like "…may result in significant savings if the costs of the intervention were less than the costs treatments costs averted." Possibly also mentioned broader potential economic productivity benefits due to having a healthier workforce, as mentioned later.
RESPONSE: THANK YOU FOR THIS SUGGESTION, WE MADE THE PERTINENT ADJUSTMENTS AND THE SENTENCE NOW READS:

Nevertheless, the evidence shows that the interventions intended to delay diabetes may result in significant savings if the cost of the intervention were less than the costs treatments.

5. I would suggest adding a sentence near the end, when discussing further research, stating that further research evaluating the cost and effectiveness of public health interventions aimed at reducing diabetes incidence should be prioritised, as without such information it is not at this stage possible to know if such interventions are likely to reduce the net future healthcare cost, and if so by how much.
RESPONSE: THANK YOU FOR YOUR SUGGESTION. WE HAVE NOW ADDED A SENTENCE AT THE END OF THE PARAGRAPH TO HIGHLIGHT THE IMPORTANCE OF RESEARCH EVALUATING COST AND EFFECTIVENESS OF PUBLIC HEALTH INTERVENTIONS.
Also, research evaluating the cost and effectiveness of public health interventions aimed at reducing diabetes incidence is essential and should be prioritized, as without such information it is not possible at this stage to know if such interventions are likely to reduce the net future healthcare cost, and if so by how much.