Author's response to reviews

Title: An economic evaluation for prevention of diabetes in developing country: A modelling study

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Author's response to reviews: see over

Dear Mr. Vargas:

Thanks a million again for both your help and that of the reviewer's concerning the improvement to our manuscript. Those comments have the important guiding significance to our research. We have attached great importance to the good comments and suggestions, and careful modified the manuscript which we hope meet with approval. We enclosed a revised manuscript with the corrections, and the item-by-item responses to your comments and the reviewer's suggestion are as follows.

Once again, many thanks for providing us the opportunity to revise our manuscript. If you need further information, please do not hesitate to contact us.

Best wishes,

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1. I am ashamed that I have not noticed this earlier in the process, but I am afraid the stated cost-effectiveness ratios are incorrect. Table 4 shows that at age 25, the incremental costs for screening plus intervention are around -$16,000. Thus, the intervention costs are more than offset by the savings in health care costs because of cases of diabetes (and complications) postponed or averted. At the same time, the intervention also results in health gains of around 3.2 QALYs. In other words, the intervention gives both a reduction in costs and a gain in QALYs and is thus dominant. The calculation of the ICER (~$5000/QALY) is in error because it considers the cost savings as cost increases. Please revise the manuscript to reflect the fact that, according to your results, the interventions are cost-saving while delivering health gains, at any age. (Or alternatively, point out where I am mistaken.)

[Response] Thank you very much for this good question, and we sincerely apologize for the mistake. As you pointed out, we used the saving costs as increment costs to calculate the “ICER”, which was incorrect. The cost-saving means that interventions deliver more health benefits at a lower cost, and this is what the results showed in the study. Thus, we have revised the statements carefully. For example, in results section, we have described that preventions induced more health benefits (QALYs) and more remaining life years for subjects with IGT and diabetes, and saved more cost for the screened subjects in comparison with control. Moreover, in discussion section, we have compared the economic results with the studies performed in developed countries, then drawn conclusions that developing countries are short of effective managements of diabetes prevention for different age population, and prevention of diabetes is cost-saving and dominant in China. Besides, the appropriate age population for screening was recommended as well. Additionally, we have revised the specific contents in Table 4. For example, we removed the rows of “increment cost/QALY”, and used the “saving cost” instead of “increment costs”. The detailed descriptions were added into the text and the footnote of table. The main corrections as shown below:

When a six years intervention was assumed, all intervention strategies were associated with cost-saving versus control especially in the population aged 25, and the savings per subject were at least $2017. (Page 3 line 6-8)
On the other side, the average cost per subject for control were $20103, $13634, $8000 at initiation age of 25, 40 and 60 respectively, which were much higher than that of the prevention strategies within each initiation age. That is, screening and lifestyle interventions were associated with cost-saving (delivered more health benefits at a lower cost). From the societal perspective, the screening with exercise intervention yielded the greatest saving at all initiation ages especially in the young cohorts, though the differences between interventions were subtle. (Page 13 line 6-13)

In this study, all screening strategies saved lifetime costs about $390 or more per screened subject at all initiation ages, in other words, all prevention programs are cost-saving. These results are not only considered as very attractive by international standards[21], but also seen as better than some high income areas where diabetes preventions were proved to be cost-effective rather than cost-saving, such as Taiwan ($17113 per QALY gained)[19], Australia ($10142 per QALY gained)[53], US ($9731 per QALY gained)[18], and UK ($8358 per QALY gained)[26]. Moreover, although the saving costs induced by interventions were the least at 60 years of age based on Chinese circumstance (around $2000 saved per subject), it is still more than that of some cost-saving countries like Mexico (around $1000 saved per subject)[54], Switzerland (around $1040 saved per subject) and Germany (around $600 saved per subject)[55]. This owes to the long-term effects beyond intervention period for postponing or averting the diabetes and related complications which produced substantial high medical costs in China[4, 5], even though the interventions were performed for just six years. (Page 16 line 3-16)

Policies of one-off screening for undiagnosed diabetes and IGT, then give seemly lifestyle interventions to those with IGT are cost-saving. (Page 19 line 14-15)

2. The inability to vary the prevalence of IGT by age is not sufficiently addressed. The authors tested for +/-20%, but in reality the difference in prevalence of IGT between ages 25 and 60 is probably in the neighborhood of 500% or more - see Dunstan et al, Diabetes Care. 2002 May; 25(5):829-34 for an example in Australia. The results should be re-calculated using a base case assumption of a ratio of IGT prevalence that is realistic. If that is not available from the data source they used, the ratio of IGT prevalence can be applied from
another study. For example, the Dunstan study would suggest a ratio of about 2.5: 6.5: 20 for ages 25, 40 and 60 (Table 4). I do not expect that this will have a large impact on the results because the costs of screening are very low compared to the other costs, but it would make the study considerably stronger to make more realistic assumptions.


In the previous revision of manuscript, we used age-specific mortalities and utilities to distinguish different age groups and performed sensitivity analyses by assuming 20% changes of IGT or diabetes incidence to assess the effectiveness of prevention strategies for different populations. However, as you pointed out, these assumptions might not enough to reflect the reality.

By reviewing the studies which included the information about the prevalence of diabetes in China, we found that the impact of age on the prevalence of diabetes (1: 3.6: 6.4 for ages 20-39, 40-59 and >60 respectively) is greater than that of on the prevalence of prediabetes (1: 2: 3 for ages 20-39, 40-59 and >60 respectively) (Wenying Yang, Juming Lu, Jianping Weng, et al: Prevalence of Diabetes among Men and Women in China. The New England Journal of Medicine 2010, 362:1090-1101.), however, it is hard to calculate the annual incidence of diabetes directly based on prevalence of diabetes, since few studies reported the duration of onset diabetes of the samples. In the light of your good suggestion of using ratio of disease prevalence to estimate the prevalence of disease by age, we recalculated the transition rate of diabetes for baseline models of different age groups. The odds ratio of age (per year) was used to calculate the ratio of diabetes incidence, and it was suggested by the Dunstan study (David W. Dunstan, Paul Z. Zimet, et al: The rising prevalence of diabetes and impaired glucose tolerance. Diabetes care 2002, 25:829-834.). Because the national diabetes surveys of China did not report odds ratio of age (1.Kam Cheong Wong, Wang Z: Prevalence of type 2 DM in mainland China, Hong Kong, and Taiwan. Diabetes Research and Clinical Practice 2006, 73:126-134. 2. D. Gu1, K.

In terms of calculations, we first determined the baseline estimates of diabetes incidence for 40 year-old subjects. For the intervention groups, the parameters came from the cumulative incidence of diabetes at the 6th years (the median age of the sample was around 40). (Xiaoren Pan, Guangwei Li, Yinghua Hu, et al: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. Diabetes care 1997, 20:537-544.) For control group, it came from the 3 years cumulative incidence of diabetes (the median age of the sample was around 50). (Jia WP, Pang C, Chen L, et al: Epidemiological characteristics of diabetes mellitus and impaired glucose regulation in a Chinese adult population: the Shanghai Diabetes Studies, a cross-sectional 3-year follow-up study in Shanghai urban communities. Diabetologia 2007, 50:286-292.). Then, the ratio of disease incidence was used to estimate the annual transition rates of diabetes for the age of 25 and 60 by adjusting the baseline estimates of age 40. This ratio was about 1:2.6: 8 for the age of 25, 40 and 60. As we expected, the updated results were still supported our main conclusion, that is preventions of diabetes are cost-saving compared with control in China.

On the other hand, since the difference in prevalence of IGT between ages 25 and 60 is about 200% in China (Wenying Yang, Juming Lu, Jianping Weng, et al: Prevalence of Diabetes among Men and Women in China. The New England Journal of Medicine 2010, 362:1090-1101.), we performed sensitivity analyses to test the sensitivity of savings to +200% or -100% of transition rate of IGT for different ages. The comparisons of the four prevention strategies with control were insensitive in terms of saving cost. We have added more detailed descriptions into the new revision, as shown below:

At last, in order to truly reflect the diverse nature history of diabetes in different ages, the various transition rates from IGT to onset diabetes were used. For initiation age of 40, the baseline transition rates for prevention groups were gained from the cumulative incidence of diabetes at the 6th years [33], The same parameter for control was derived
from a 3 years cumulative incidence of diabetes[36]. With respect to the calculation of the annual incidence of diabetes for age of 25 and 60, the ratio of diabetes incidence of different ages were used to adjust the baseline estimate of initiation age at 40. The ratio was about 1:2.6:8 for initiation age of 25, 40 and 60, according to Dunstan et al[37]. (Page 8, line 20; Page 9, lines 1-8).

Particularly, the assumptions concerning the incidence of IGT were increased by 200% and decreased by 100%, since the difference in prevalence of IGT between the young people and the elders is large in China: almost in the neighborhood of 200%[3]. (Page 11, lines 11-14)

Meanwhile, sensitivity of savings concerning the change of the transition rate of IGT which increased 200% and decreased 100% were also reported. (Page 13, lines 18-19)
## Additional file: Sensitivity of saving costs to different assumptions by screening initiated at different ages

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Different prevention strategies</th>
<th>-100%</th>
<th>200%</th>
<th>-100%</th>
<th>200%</th>
<th>-100%</th>
<th>200%</th>
<th>-100%</th>
<th>200%</th>
</tr>
</thead>
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<td>Incidence of IGT at initiation age of 25</td>
<td>screening and diet intervention</td>
<td>6836.34</td>
<td>6724.19</td>
<td>6877.04</td>
<td>6727.03</td>
<td>6876.77</td>
<td>6728.52</td>
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<td>836.46</td>
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<tr>
<td>Incidence of IGT at initiation age of 40</td>
<td>screening and exercise intervention</td>
<td>3969.94</td>
<td>3858.65</td>
<td>3986.16</td>
<td>3823.47</td>
<td>3968.42</td>
<td>3827.65</td>
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<td>377.80</td>
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<tr>
<td>Incidence of IGT at initiation age of 60</td>
<td>screening and duo intervention</td>
<td>2021.38</td>
<td>1914.01</td>
<td>2085.12</td>
<td>1979.72</td>
<td>2072.44</td>
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<td>294.07</td>
</tr>
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</table>
3. As discussed previously, the life expectancies in this study are low compared with life expectancies in the general population of PR China. From your response I get the impression that the life expectancies you state are those for people who were found positive for IGT - not for the total population in each arm of the trial. (The latter would include people who tested negative, and those with diabetes.) However, to me, that was not clear from the text of the tables. For example, the results section starts with "Based on the hybrid decision tree Markov model, the remaining survival year was 30.7 (19.8 to 41) for individuals underwent screening followed with any of the three active lifestyle interventions strategies (diet, exercise, and duo-intervention) started at 25 years of age". In my reading that would include people who tested negative, since these also underwent the screening. So if my supposition is correct, please emphasize in the text that these life expectancies apply only to people who are found positive for IGT.

[Response] Thank you for your good question. We are sorry for we did not put our ideas over clearly enough. Our objective was to select the dominated prevention strategies by comparing the clinical and economic outcomes of prevention strategies with control. Thus, for the results which were calculated from clinical point of view, we reported them for the subjects who were screened and found with IGT or diabetes, because the gains in health benefits were just given to the IGT or diabetic subjects who underwent preventions. These results included the average remaining survival years, the average QALYs per subject diagnosed with IGT or diabetes, as well as the remaining survival life years gained, and the QALYs gained per subject diagnosed with IGT or diabetes in prevention groups. For the results which were calculated from economic point of view, we reported them for the subjects who were screened (subjects who were tested negative or positive), since the screening costs for those who were found not to have IGT or diabetes were taken into account. These results included the average costs per subject, and the saving costs per subject in prevention groups. Following your suggestion, we have emphasized these in abstract, text and footnote. The main revisions as shown below:

The reported outcomes were the remaining survival years, the quality-adjusted of life years (QALYs) per diabetes or IGT subject, the cost (calculated from the societal
perspective) per subject underwent strategies and the comparisons between preventions and control over forty years. (Page 2 lines 16-19; Page 3, lines 1)

Based on the hybrid decision tree Markov model, the remaining survival year was 30.7 (19.8 to 41) years for screened diabetic subjects and subjects with IGT who received any of the three active lifestyle interventions (diet, exercise, and duo-intervention) started at 25 years of age, and it was 30.2 (18.7 to 40.5) years for screening alone, 29.0 (18.5 to 40.3) years for control. The remaining life years gained that were induced by preventions ranged from 1.2 to 1.7 years compared with control. (Page 12, lines 2-7)

Footnote of Table 4:

Ⅰ: The figures for prevention strategies were the average remaining survival years per subject diagnosed with IGT or diabetes compared with control. For control, they were the mean values of remaining survival years per subject with IGT or diabetes. Ⅱ: Costs (US$) were the average cost (95% credible intervals) per subject, which arise for individuals from prevention of diabetes and treatments of diabetes-related disorders during 40 years. (Page 39, lines 4-8)

4. I think the regression coefficient of age of -0.0003 per year that was applied to average utility is very low. Compared to a 40-year old, the background morbidity due to unrelated disease would probably reduce the quality of life of a 60-year old much more than the 0.006 that is now used. And I do not see anywhere that this background morbidity is taken into account in another way.

[Response] Thank you for pointing this out. Elixhauser et al. ever stated that the severity of diseases can be reflected by the existence of coexisting conditions in addition to the mortality of disease (Elixhauser, Anne; Steiner, Claudia; Harris, D. Robert; Coffey, Rosanna M: Comorbidity Measures for Use with Administrative Data. Medical care 1998, 36:8-37). Thus, it is reasonable to estimate the utilities of health states for different ages by incorporating the impacts of coexisting conditions and age.
With respect to the calculations, the unadjusted median utilities for different health states of diabetes were assigned to the individuals at initiation age of 40, since they represented median age and median social demographic individuals with diabetes. For the older subjects with diabetes, it has been proved that they have higher mortalities and one more coexisting conditions than the younger adults have. (Paula M. Trief, Michael J. Wade, Denise Pine, et al: A comparison of health-related quality of life of elderly and younger adults with diabetes. Age and Ageing 2003, 32:613-618.)

Thus, for the older diabetic subjects (subjects at initiation age of 60 in this study) with complication, the coefficient of age and three disorder conditions (include diabetes and a given complication) were used to adjust the baseline estimates of initiation age at 40. For example, the utility of the diabetic subjects with CVD at initiation age of 60 was 0.584. It was derived from the median utility of diabetes with CVD (0.674) subtracting 0.006 ((60-40)*(-0.0003)) and 0.084 (coefficient of three conditions included diabetes and CVD).

For the young diabetic subjects (subjects at initiation age of 25), the calculation of utilities only considered the impact of age (coefficient of age was used to adjust the baseline estimates of initiation age at 40), since no differences in severity of disease have been found between the young and the mid-age subjects with diabetes (Amir Tirosh, Iris Shai, Dorit Tekes-Manova, et al: Normal fasting plasma glucose levels and type2 diabetes in young men. New England Journal of Medicine 2005, 353:145-162).

For instance, the utility of the diabetic subjects with CVD at initiation age of 25 was 0.679, It was derived from the median utility of diabetes with CVD (0.674) subtracting 0.0045 ((40-25)*(-0.0003)).

In the current revision, we have added the specific contents as shown below:

The unadjusted median utilities for diabetes related disorders were assigned to the subjects at age of 40[43, 44], since they represented the median age and the median social demographic of individuals having diabetes. The utilities of subjects aged 25 and 60 were calculated based on the age-related characteristics of diabetes. Compared with the younger subjects with diabetes, the elders have one more coexisting conditions universally[45]. Thus, the utilities of the 60 years of age diabetic subjects with complication were estimated by using the coefficient of age and three coexisting conditions (include diabetes and a given complication) to adjust the baseline estimates of subjects aged 40. For example, the utility
of the diabetic subjects with CVD at initiation age of 60 was 0.584. It was derived from the median utility of diabetes with CVD (0.674) subtracting 0.006 ((60-40)*(-0.0003)) and 0.084 (the coefficient of three conditions). For the individuals aged 25, the calculation of utilities only considered the impact of age [44], since no differences in severity of disease have been found between the young and the mid-age subjects with diabetes[46]. (Page 10, lines 10-21; Page 11, lines 1-2)

5. Lastly, although the English has greatly improved, further improvement is still very desirable. The BMC editorial office can assist if this is required.

[Response] Thank you for your good suggestion. Writing paper in English is an opportunity to improve the quality of our study. According to your comment, we have checked our spelling again and rewritten or modified a number of expressions in the abstract, text, tables and footnote of tables. And the manuscript has been polished and the grammar has been edited by a professional colleague fluent in English as well. Please see: Page 2 line 3; Page 2 lines 7; Page 2 lines 12-15; Page 3 lines 6-8; Page 3 lines 10; Page 4 lines 13-15, 20; Page 5 lines 1-2, 20; Page 6 lines 10; Page 7 lines 11; Page 8 lines 20; Page 9 lines 1,5; Page 11 lines 1-2; Page 12 lines 11,14; Page 13 lines 10-11; Page 14 lines 2-4; Page 15 lines 19-21; Page 16 lines 5-6; Page 17 lines 4-5; Page 17 lines 21, Page 19 lines 17; Page 31 lines 5; Page 39 lines 4-5.

Minor comments:

6. Page 2 line 15: "social" should be societal.

[Response] Thanks for your help. We have used “societal” instead of “social” in the current revision. Please see: Page 2, lines 18

7. Page 6, line 16, "PG": Please add the full term at first use of each abbreviation.

[Response] Thank you for your carefully reviewing our manuscript. We have added the full term of “PG” into the manuscript, and made sure that the full terms were added at the first use of all abbreviations. Please see: Page 6, lines 20
8. Table 3: Is this the extra time per person who is found to have IGT, or per person screened? Please make this clear in the header.

[Response] Thank you for carefully reviewing our manuscript. Actually, the extra time in Table 3 is the extra time per subject who is found to have IGT. We have revised the title of Table 3, and made this clear in the text and the footnote. Please see: Page 38, lines 1-2

9. Table 4: The title suggests that this table is about 'total costs', but the footnote makes clear that the figures are average per person costs, not total costs for the whole population. Furthermore, if my understanding is correct the total costs are not per person screened but per person found to have IGT. If that is correct, please revise the title and replace 'total costs' with 'average cost per person diagnosed with IGT' or something similar. If these costs are indeed per person with IGT, it is not clear if the screening costs for those who were found not to have IGT were taken into account. The more usual (intuitive) way of presenting the results would be to give the average results per person screened, or per person in the population. This would lead to much lower numbers, but it would automatically take into account those screening costs. (This latter suggestion is optional, though.)"

[Response] Thank you for your help. Considering your good suggestion, we have reported the average costs and the saving costs per person simulated in each arm (included all subjects who were screened) in the Table 4. Meanwhile, since the gains in health benefits were only given to the IGT and diabetic subjects who underwent preventions, we added the average remaining life years and the remaining life years gained per subject diagnosed with IGT or diabetes into the Table 4. In addition, we have replace the title 'the total costs, QALYs and cost-effectiveness of prevention strategies at different initiation ages' with 'the clinical and economic outcomes of prevention strategies and control (or compared with control) for individuals at different initiation ages'. And we have added the details in the footnote of table to make each outcome clear. The specific contents as shown below and more details please see Table 4 (Page 40-41):
According to the exhibition of results in Table 4, screening or intervention increased QALYs of diabetic or IGT subjects compared with control (p<0.0001 within each age group). Besides, QALYs gained were much lower for all prevention strategies at 60 years of age. Therefore, the younger the screening was performed, the more benefits were achieved. On the other side, the average cost per subject for control were $20103, $13634, $8000 at initiation age of 25, 40 and 60 respectively, which were much higher than that of the prevention strategies within each initiation age. That is, screening and lifestyle interventions were associated with cost-saving (delivered more health benefits at a lower cost). From the societal perspective, the screening with exercise intervention yielded the greatest saving at all initiation ages especially in the young cohorts, though the differences between interventions were subtle. (Page 13, lines 3-13)

Footnote of Table 4:

Ⅰ: The figures for prevention strategies were the average remaining survival years per subject diagnosed with IGT or diabetes compared with control. For control, they were the mean values of remaining survival years per subject with IGT or diabetes. Ⅱ: Costs (US$) were the average cost (95% credible intervals) per subject, which arise for individuals from prevention of diabetes and treatments of diabetes-related disorders during 40 years. Ⅲ: Saving costs were the average cost per subject in prevention groups in comparison with that of control; Increment QALYs were the average QALYs per subject diagnosed with IGT or diabetes in prevention groups in comparison with that of control. Ⅳ: QALYs were the average QALYs per subject with IGT or diabetes (95% credible intervals). (Page 39, lines 4-12)
Reviewer(s)' Comments:

To reviewer #1

Dear Dr. Backholer:

Many thanks for your kind comments and precious suggestions. We have revised the manuscript according to your recommendation.

1. Quality of written English: Needs some language corrections before being published

[Response] Thank you for your help. Writing paper in English is an opportunity to improve the quality of our study. According to your suggestion, we have checked our spelling again and rewritten or modified a number of expressions in the abstract, text, tables and footnote of tables. And the manuscript has been polished and the grammar has been edited by a professional colleague fluent in English as well. Please see: Page 2 line 3; Page 2 lines 7; Page 2 lines 12-15; Page 3 lines 6-8; Page 3 lines 10; Page 4 lines 13-15, 20; Page 5 lines 1-2, 20; Page 6 lines 10; Page 7 lines 11; Page 8 lines 20; Page 9 lines 1,5; Page 11 lines 1-2; Page 12 lines 11,14; Page 13 lines 10-11; Page 14 lines 2-4; Page 15 lines 19-21; Page 16 lines 5-6; Page 17 lines 4-5; Page 17 lines 21, Page 19 lines 17; Page 31 lines 5; Page 39 lines 4-5.