Author’s response to reviews

Title: Predicting Diabetes Clinical Outcomes Using Longitudinal Risk Factor Trajectories

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Author’s response to reviews:

Please refer to the 'Response to the Editor and Reviewers R2.docx' file for a formatted version of our response letter. We uploaded it as 'Supplemental Materials'.

We appreciate the second review of our manuscript and wish to thank the Editor and the Reviewers for your thoughtful comments. We believe we have addressed the new comments and provided the necessary changes to the manuscript. Below we address the specific comments in detail.

Reviewer 1:

From the current analysis, in fact, there is no way of telling how many of those who are classified as 'healthy' are in fact with undiagnosed diabetes, and simply visiting less often the clinic (possibly because overtly reassured by an occasional past negative FPG result). The data which is included in the response to reviewers reinforces my concern, as the authors acknowledge, but is not addressed in the paper. If this concern is not addressed, the current results may have the effect of further putting pressure on patients who are already correctly diagnosed and reinforce in those who are not regularly monitored the belief that they are risk-free.

In order to address this, I recommend to

1) reformat Table 1 by including one column per exposure strata; in this table all the characteristics now described for the whole cohort should be described for each stratum;
additionally, number of measurements before baseline and after baseline should be described as well

This is a great suggestion and we created a new Table 3 in the section of the manuscript that studies these subpopulations. We elected to include a new Table rather than expand Table 1 so that Table 3 can be in close proximity to Table 4.

2) explain more clearly in the Methods how missing data were imputed, and in the results which was the impact on each exposure strata of the imputation

We expanded our explanation of the missing value imputation:
“Laboratory results and vital signs completely missing throughout the years 2000-2005 were handled through mean imputation with the addition of missingness indicator variables. When results were missing for one of the three time periods, carry-forward imputation was used. Patients with missing fasting glucose measurements were discarded.”

3) a sensitivity analysis could be conducted among those with no imputation (3+ measurement before baseline and at least 5 after baseline).

We performed this analysis. Please refer to the 'Response to the Editor and Reviewers R2.docx' file for the result table. The results show the same tendencies as Table 4: patients who had a prediabetes event before baseline (2000-2001 or 2002-2003) and returned to normal in 2004 have lower risk at the index date (2005) than patients who were prediabetic in 2004; but they have a higher risk than patients who were normoglycemic throughout 2000-2005.

From the current analysis, in fact, there is no way of telling how many of those who are classified as 'healthy' are in fact with undiagnosed diabetes, and simply visiting less often the clinic (possibly because overtly reassured by an occasional past negative FPG result).

Among the patients included in the 5 subpopulations 97% had at least 2 and 92% had 3 or more FPG tests during 2000-2005. While false negatives are possible, two or three consecutive false negatives are unlikely. (Note that the 3 FPG tests may not cover all three time periods, hence the subpopulations in the Sensitivity Analysis are smaller than 90% of the cohort.)

Reviewer 1 is concerned that false negative results may overtly reassure patients who may, as a result, not get screened at an appropriate frequency. This is an important and valid concern, but clinically speaking, the recommendation for screening frequency is not based on a single (potentially false negative) FPG test. Recommendations for screening frequency used in the United States are laid out in the American Diabetes Association (ADA) Standards of Care guidelines (Diabetes Care, Volume 41, Supplement 1, Jan. 2019), and take many factors into account, including familial history and risk factors (other than FPG) such as age, obesity, ethnicity, history of cardio-vascular conditions, hypertension, HDL, triglycerides, lack of physical activity, etc. Being overtly reassured based on a single erroneous FPG test is unlikely. We appreciate the Reviewer’s concern for patient safety.
The data which is included in the response to reviewers reinforces my concern, as the authors acknowledge, but is not addressed in the paper.

The data Reviewer 1 refers to shows the number of FPG results over the 13-year study period. Depending on the subpopulation, the median number of FPG measurements ranged from 7 to 11. These numbers are consistent with the ADA recommendations, which recommends screening frequencies between 1 to 3 years depending on the patients’ risk factors.

Patients without impaired FPG (100-125 mg/dL) between 2000-2005 had a median of 7 FPG measurements as compared to patients with impaired FPG measurements who had a median of 11 FPG measurements. This also reflects the ADA guidelines: patients with fewer risk factors need to be screened less frequently.

Patients in the Sensitivity Analysis have higher risk than the patients in Table 4. This is also consistent with the screening recommendations: patients in our Sensitivity Analysis have more frequent screening, because they having more risk factors (39 %patients in the Sensitivity Analysis takes antihypertensive medications as opposed to 22% in the entire cohort; 35% takes antihyperlipidemic medications vs 18% in the cohort). These risk factors also contribute to their risk of developing overt diabetes.

We appreciate the Reviewer taking the time to help us improve the manuscript.

Reviewer 2:

GENERAL COMMENTS: Everything is fine. However, a detailed description of the Cumulative Exposure model is lacking and it needs to be added to the methods section.

We have further clarified the Cumulative Exposure model with a particular focus on the missing value imputation part.

We wish to thank the Editor and the Reviewers once again for your constructive and thoughtful comments. We believe you have helped us make our paper clearer and more valuable.