

Subject:

Diabetic Medicine DME-2009-00292

Dear Editor,

Thank you for considering our manuscript in Diabetic Medicine. We have rewritten our manuscript according to the Editors/Reviewers comments and have responded to these comments one by one, which will be uploaded as a file.

We expect that this revision will be satisfactory to their expectations.

Yours sincerely,

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Editor/Associate Editor comments:

Please use UK not US spelling throughout eg haemoglobin not hemoglobin

In HbA1c, please subscript the 1c throughout

Give numbers with the number of decimal places to which they are measured eg glucose

5.8 not 5.82 mmol/l

Response: We corrected the decimal places according to the Editor comments.

コメント [K11]: この雑誌の既定にそって  
表記を小数点 2 桁から 1 桁にした。

Reviewer comments:

Reviewer: 1

Comments to the Author

The manuscript by Dr. K. Inoue, et al., entitled, "Should the threshold for definition of impaired fasting glucose be lowered?" is a follow-up study of approximately 11,000 Japanese without diabetes mellitus to estimate the conversion risk for newly diagnosed

diabetes mellitus, depending on fasting glucose values. Ultimately, this manuscript aims to determine if the definition of impaired fasting glucose, a predictor of diabetes mellitus, needs to be revised. Overall, the manuscript is well-written, but I have some major and minor issues to be addressed as follows:

Major issues:

1. The authors cited their previous publication for the description of the study population. The authors should present essential information to allow readers to accurately interpret this analysis without looking for an external citation.

Response: Description of the 'study population' is the almost same as the previous study published in Diabetic Medicine. Thus we excluded the word of 'briefly'. Compared with the previous study, we have shortened information for measurements and analysis. According to the comment, we added relevant information.

2. About half of the study's participants who underwent at least one check-up during the baseline period (N=21,885) did not return for a check-up during the follow-up period (N=11,129). Any biases, potentially generated from this loss of follow-up, need to be addressed along with the characteristics of the participants who were lost.

Response: In the previous study, to assess for the possibility of selection bias we compared the 10,475 subjects (exactly identical to this study subjects) with the remaining 9,949 persons who did not attend during the follow-up period, using the same exclusion criteria used by the previous study, with the exception of the duration of follow-up.

Those who participated during the follow-up period were older (mean (SD): 52.9 (11.6) vs. 51.8 (13.5),  $P < 0.001$ ), not obese by BMI (22.9 (3.0) vs. 22.8 (3.1),  $P = 0.10$ ), had slightly lower fasting blood glucose levels (5.27 (0.50) vs. 5.28 (0.52) mmol/l,  $P < 0.001$ ) and had slightly higher HbA1c levels (4.97 (0.40) vs. 4.95 (0.41) percent,  $P < 0.001$ ) than non-subjects.

We added this information in the Discussion.

3. There are many ways to define "optimal" cut-off point for impaired fasting glucose. Please explain how they determined this point (5.72 mmol/l), including the following information: a) the definition of "accuracy"; b) the reason why the authors chose the

**コメント [KI2]:** 今にして思うと、この General comments にたいして、謝意を述べておくべきでしたね。Thank you for your favorable comments on our manuscript.とか。ちょっと反省。

**コメント [KI3]:** 先行論文はひとまずおいて、この研究での正確な情報を記載せよとのことです、無論妥当。

**コメント [KI4]:** 先行研究と対象集団はほぼ同じでした。この論文は Short report ですので、語数を節約することもあります。しかしながら、提案ですので従います。

**コメント [KI5]:** 妥当コメント。当初の集団から追跡期間にも健診参加しているのは半分弱です。分析対象群と非対象群でかなり特性が違えば、結果の解釈が違ってきます。

**コメント [KI6]:** ですので、ベースライン時に同じ参入基準 (Inclusion criteria) を満たす 9949 名と研究対象集団の 10475 名の基本特性を比較しました。下は論文に追加記載した文章です。

**コメント [KI7]:** P 値で有意差は出ていますが、絶対値で見るとほとんど差はないですね。N が大きければこのような小差でも出ますから。

highest accuracy as the definition of the optimal cut-off point; and c) if the cut-off point with the highest accuracy was estimated by sex or a combination of both **sexes**.

**コメント [K18]:** ここは空腹時血糖時の糖尿病発症予測に関する ROC 分析の論議です。こういう技術的なものは比較的対処しやすいです。研究グループに統計分析に詳しい人を入れる理由です（筆頭著者がそうなる必要はない）。

Response: We used ROC curve analysis to find the “optimal” cut-off point for impaired fasting glucose to predict diabetes. Thus the “optimal” cut-off point means the ‘epidemiological’ cut-off to take the best balance between sensitivity and specificity. In addition, we analyzed men and women separately to find the determined this point (5.72 mmol/l) to be the best for both sexes. In our previous study, the prevalence of IFG was higher in men than in women, which motivated us to a stratified analysis by sex. We added the relevant information in **Methods**.

**コメント [K19]:** 上記質問に対する Response です。ここは共著で分析に詳しい人にまかせてもいいです。

4. All analyses were performed according to sex. The authors need to explain their motivation for this stratification and the subsequent public health implications when they propose a threshold for **screening**.

**コメント [K110]:** なぜ性別で解析したのか、説明せよと。妥当ですが、**糖尿病の有病率も性差がありますし**。

Response: As mentioned above, the prevalence of IFG was higher in men than in women in our previous study, which motivated us to a stratified analysis by sex. We added the relevant information in **Methods**.

**コメント [K111]:** 先行研究で性差があったことを説明して、論文にも記載した旨を書いた。

5. In the Discussion, the authors concluded that the results of their study are compatible to the evidence that the ADA cited to revise the impaired fasting glucose criteria. However, the authors did not support the ADA’s lowering of the threshold for a variety of reasons. This latter part of the discussion itself sounds valid in general, but I wish the authors had found ways to present their overall discussions better so that what they observed in their analysis would better support their **conclusions**.

**コメント [K112]:** Discussion の重要なポイントで、結果の解釈に関わるものであつた。ROC 分析での最適カットオフは 103mg/dl 付近で、Classic IFG (110mg/dl) より New IFG (100mg/dl) に近いのですが、後者では 3-4 倍に IFG が増えてしまいます。

Response: This study analysis aimed to decide ‘epidemiologically’ optimal cut-off point of IFG. However, it is a different matter whether this result should direct apply to the public health policy. We added relevant information in **Discussion**.

**コメント [K113]:** 上記について、研究結果をそのまま保健行政に反映させるのは別の Matter であると記載。

Minor issues:

1. I suggest that title be more **specific**.

**コメント [K114]:** タイトルをもっと当てたものにせよということですね、妥当。

Response: According to the comments of both Reviewers, we modified the **title**.

**コメント [K115]:** 疑問形をやめました。

2. The authors wrote, “The three baseline FPG categories (<5.56, 5.56-6.06, and 6.11-6.94 mmol/l),” in the Abstract and Results sections. Please explain why the category for 6.06-6.11 is **missing**.

Response: This phenomenon happened due to the original measurement unit of FPG was mg/dl (<100, 100-109, and 110-125 mg/dl). Thus, we rounded FPG categories to one decimal point throughout the manuscript as follows; <5.6, 5.6-6.1, and 6.1-6.9 mmol/l). It also accords with the Editor/Associate Editor **comments**.

**コメント [K116]:** このあたりは表記を mmol/l に変えたことによって起こる問題です。(実は筆頭著者は未だ、mol 表記にピンときません;;)

**コメント [K117]:** 上記を受けて変更した旨記載。

3. In the Introduction, the recommendations from three organizations (ADA, EDEG, and JDA) were cited. Please add the years when those recommendations were published as they change over **time**.

Response: We added the years of these **statements**.

**コメント [K118]:** 確かに最近の変化を書くべきかと思います。ややこしいので。

**コメント [K119]:** コメントどおり記載。

4. In the Discussion, the authors stated “Second, there was 5-7 fold difference in relative risk of diabetes incidence between the original (6.11-6.94 mmol/l) IFG and the IFG newly added by the ADA (5.56-6.06 mmol/l) both in men and women.” Is the estimate of 5-7 fold difference based on this study? The text in Results section does not state incidence or relative risk. Clearer presentation is **desired**.

Response: We agree with this comment. We moved the statement in Results and simplified it in **Discussion**.

**コメント [K120]:** 確かに新基準によって何倍に増えたかを記載するべきでしょう。妥当。

**コメント [K121]:** 合意して記載。

5. In the Discussion, the authors mentioned that the study subjects participated on a voluntary basis and that they might be **healthier** than the general population. Are the authors implying that the optimum cut-off for this study—5.72 mmol/l—could have been even lower if they had studied the general population?

Response: We do mean not as such but indicate need of caution applying this result to a general population. We added relevant information in **Discussion**.

**コメント [K122]:** 査読者はこう思ったかもしれませんが、著者の意図はそうではありませんでした。

**コメント [K123]:** ので、その旨記載です。

Reviewer: 2

Comments to the Author

**The** authors focus on the important question of whether the cut-off value of fasting plasma glucose for diagnosing impaired fasting glucose (IFG) should be lowered or not,

**コメント [C124]:** Reviewer 2 も好意的です。最後を読むと、校正したら受理を支持してくれそうです。ここに感謝の文章を入れるのだったと、(Reviewer 1 同様) 今見て少し反省しました。

using data from a large Japanese population.

They conducted a retrospective cohort study, and calculate the optimal cut-off FPG value to predict diabetes was 5.72 mmol/l both for men and women. They concluded that it may be reasonable to retain the conventional lower FPG limit for IFG and treat FPG values of 5.56-6.06 mmol/l as non-diabetic hyperglycemia, considering the four to five fold increase in individuals classified as IFG when the new cut-off is applied. This paper is very interesting for following many subjects for a long term, so I would support publication after the topics below have been addressed by the authors.

Major Points:

1) (Page 6, Discussion) The authors wrote “Risk evaluation according to continuous glucose levels in various populations should be performed for diabetes and cardiovascular disease.”

It will be better to note the prevalence of cardiovascular disease of the IFG subjects, and to note whether there is a particular cut-off FPG value for estimating the risk of cardiovascular **disease**.

**コメント [Ci25]:** 心血管疾患の頻度は重要ですね。

Response: We agree with the comment. Here, however, we meant that such evaluations are needed as the further direction. Of note is that one study showed that the 1997 IFG definition yielded greater risks of CVD in women, but not in men. We added this paper as the reference **8**.

**コメント [Ci26]:** ですがもちろんこの研究のデータにはないので、文献を引用します。当初の Discussion での記載は、「[研究の将来的方向](#)」としてあげたものでした。

2) (Page 5, Discussion) The authors wrote “Second, there was 5-7 fold difference in relative risk of diabetes incidence between...”

It will be better to compare their study to Funagata Study in Japan (Tominaga et al. J Japan Diab Soc 2008;51: 473-475.), which is also focused on the cut-off value of fasting plasma glucose as concerned by JDA (Kadowaki et al. J Japan Diab Soc 2008;51: 281-283.) in the **discussion**.

**コメント [Ci27]:** 山形県の舟形スタディを引用しろということです。もちろん、ありがたく受けます。もしかしたらこの査読者は日本人かもしれませんね。ここからも言えることですが、獨創性を誇示するために To our knowledge, this is the first to examine....などと言うのは要注意です。査読者はこの道の物知りなのですから。

Response: Thank you Reviewer. We added the Funagata Study as a reference in Discussion.

3) (Page2, Title, Conclusions) Although the authors mentioned the limitations of this study in the discussion, the title and the conclusions seem to suggest the whole Japanese population.

It will be better that the authors include the word taking into account the limitations in the title and the **conclusions**.

**コメント [Ci28]:** タイトルと結論が日本人全体に適用するような印象を持ったようです。著者らは意図していませんでしたが。

Response: We modified the title according to the comments of both reviewers. As the conclusion is moderate in expression (that is, 'It may be reasonable to retain...'), we think the conclusion is acceptable in the current **form**.

**コメント [Ci29]:** タイトルは2名の査読者に指摘されたので仰せの通りに変更。ですが **Conclusion** は十分控え目だと思っているのでこのままにすると記載しました。何が何でも査読者の言うとおりにしなければいけないわけではありません。

4) In the authors' previous study (Inoue et al. Diabetic Medicine 2008;25: 1157-1163.), they excluded 433 people with <2 years between their baseline and follow-up check-ups, but in this study, they don't.

It will be better that the authors write the reason why they included these subjects who were removed from previous **study**.

**コメント [Ci30]:** この査読者はありがたいです、**我々の先行論文**をちゃんと読んでくれています。先行論文で除外した人をなぜ今回は入れているか、という質問です。

Response: In our previous study, we used Cox proportional hazard model analysis, which requires an assumption of the constant hazard holds during the observation period. In this study, we used no such analysis. Thus, we could include rapid progressors to diabetes in this study. We briefly mentioned the latter information in **Methods**.

**コメント [Ci31]:** これは分析に関わるものです。Cox 比例ハザードモデルで解析を行うときの前提は、**観察期間中ある曝露によるハザードの割合が同じである**ということです。観察期間中に急速（短時間）に糖尿病に進展した例はそうであるとは限らず、よって先行研究では除外しました。ですが、この論文ではそういう解析はしていないので、含めたということです。いづれにせよ、そのように明瞭にレスポンスしないといけません。

#### Minor Points:

1) (Page 2) The authors wrote "During follow-up of an average of 5.4 years, 279 (5.2%) out of 5,372 men and 98(1.9 %) out of 5,103 women developed diabetes. According to the three baseline FPG categories (<5.56, 5.56-6.06, and 6.11-6.94 mmol/l), 28/3,401 (0.8%), 91/1,456(6.3%) and 160/515 (31.1%) respectively in men and 13/4,218 (0.3%), 30/695(4.3%) and 55/177 (31.1%) respectively in women developed diabetes."

The total subjects of the three categories of women (4218+695+177=5090) are not equal to the total subjects of women (5103). The data should be **corrected**.

**コメント [Ci32]:** 本当によく見てくれていて、頭が下がります。

Response: We are very grateful to Reviewer. Yes, we miswrote here the number of non-IFG subjects (n=4, 218). We corrected **it**.

2) In this paper, the authors used the word "diabetes", which means perhaps about type 2 diabetes, but it should be noted if there is another type of diabetes or **not**.

**コメント [Ci33]:** 確認したところ、タイプミスでした。なので訂正。

Response: The reviewer is correct. We meant type 2 diabetes in this paper. Where

**コメント [Ci34]:** 糖尿病にはI型もある。

appropriate, we used the word “type 2 diabetes” so that the readers would understand the topic to be type 2 diabetes.

コメント [Ci35]: II 型を対象にしているの  
で、当然その旨記載。

Date Sent:  
17-Jul-09

#### Note

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The definitive version is available at [www.blackwell-synergy.com](http://www.blackwell-synergy.com).