

## Title

Should the threshold for definition of impaired fasting glucose be lowered?

## Abstract

### Aims/hypothesis

We examined whether the cut-off value of fasting plasma glucose (FPG) for diagnosing impaired fasting glucose (IFG) should be lowered or not, using ~~a~~prospective data ~~offrom~~ a large Japanese population.

### Methods

A retrospective cohort study was conducted from 1998 to 2006. Follow-up (2002-2006) data were merged with baseline (1998-2002) data, yielding 11,129 persons who had been evaluated during both time periods. Among these, 10,475 persons who had neither diabetes (known diabetes or defined as fasting plasma glucose  $\geq 7.00$  mmol/l) or suspected diabetes (hemoglobin A1c  $\geq 6.4\%$ ) were analyzed.

### Results

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 ~~to~~ diabetes. The optimal cut-off ~~value~~ ~~of~~-FPG ~~value~~ to predict diabetes was 5.72 mmol/l both for men (sensitivity;84.2%, specificity; 76.9%) and women (81.6%, 91.0%). However, lowering the cut-off from 6.11 to 5.72 mmol/l increased the prevalence of IFG ~~by~~2.7 ~~fold in~~ (men) and 3.0 ~~timesfold in~~ (women). Lowering ~~the value further~~ to 5.56 mmol/l increased the prevalence of IFG by ~~a factor of 3.8 in men and 3.0 times in women.(men) and 4.9 times (women)~~

### Conclusions

It may be reasonable to retain the conventional lower FPG limit for IFG (6.11 mmol/l) and treat FPG ~~values~~ of 5.56-6.06 mmol/l as non-diabetic hyperglycemia, considering the four to five fold increase ~~of~~in individuals classified as IFG when the new cut-off (5.56 mmol/l) is applied.

## Note

[Link to the published version of the Article](#)

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

## Introduction

The lower limit of impaired fasting glucose (IFG) was lowered from 6.11 mmol/l to 5.56 mmol/l by the American Diabetes Association (ADA) {The Expert Committee on the Diagnosis and Classification of Diabetes, 2003 #743}, whereas the European Diabetes Epidemiology Group (EDEG) recommended ~~to retaining~~ the original cut-off point (6.11 mmol/l) ~~for IFG~~. Recently, ~~the~~ Japan Diabetes Association (JDA) declared ~~that~~ fasting plasma glucose (FPG) ~~values~~ between 5.56 and 6.06 mmol/l ~~should to be considered as~~ 'high-normal', ~~remaining but stating~~ the range for IFG to be unchanged {, 2008 #1780}. We examine ~~where~~ the optimal cut-off point of FPG for predicting diabetes in a Japanese population ~~is~~ and discuss whether the conventional IFG criteria should be lowered.

## Research Design and Methods

The data set ~~were was~~ obtained from the health screening program performed by the Yuport Medical Checkup Center in Tokyo, whose details were described previously {Inoue, 2008 #1779}. Briefly, we set ~~the a~~ 4-year baseline period ~~to be~~ between April 1998 and March 2002 and the 4-year follow-up period between April 2002 and March 2006. During the baseline period, 21,885 persons underwent checkups at least once. If subjects underwent more than one checkup, ~~the~~ initial checkup data were used. During the follow-up period, 23,547 persons underwent checkups. If subjects underwent more than one checkup during the follow-up period, all the data were used to identify incident diabetes. Follow-up data were merged with baseline data, yielding 11,129 persons ~~who had been~~ evaluated during both time periods.

Among them, 129 with known diabetes at baseline were excluded, leaving 11,000 persons. ~~Next~~ ~~Of these~~, 411 who had baseline FPG levels  $\geq 7.00$  mmol/l were ~~further~~ excluded. Then 114 who had baseline hemoglobin A1c levels greater than 6.4 percent were excluded, since a hemoglobin A1c level of 6.4% corresponds to a FPG level of diagnosed diabetes (7.00 mmol/l) {Takahashi, 2001 #592}. Thus the remaining 10,475 persons were analyzed as ~~this~~ study subjects. ~~They were and comprised~~ 5,372 men (age,  $51.8 \pm 12.0$  years; BMI,  $23.5 \pm 2.8$ ) and 5,103 women (age,  $54.0 \pm 11.2$  years; BMI,  $22.3 \pm 3.0$ ). Informed consent for anonymous participation in epidemiological research was obtained at every checkup {Inoue, 2008 #1779}. All the blood samples were obtained after overnight fasting and measured at the Center's laboratory. Plasma glucose levels ~~were was~~ measured using the hexokinase-G6PD method.

In follow-up evaluations, diabetes was defined as a follow-up FPG level  $\geq 7.00$  mmol/l, in accordance with the ADA, JDA criteria [1997 #1; 1999 #58] or as a diagnosis of diabetes by a physician during the follow-up period. We used the receiver operating characteristic (ROC) curve to define the optimum cut-off level of FPG to predict the progression to diabetes. We calculated the positive and negative predictabilities between two cut-off values of baseline FPG levels (ADA, WHO and EDEG criteria) and diabetes at follow-up. Men and women were analyzed separately. All analyses were performed using the SPSS15.0 and MEDCALC 10.0 for Windows.

## Result

The 10,475 subjects (5,372 men and 5,103 women; age,  $52.9 \pm 11.6$  years; BMI,  $22.9 \pm 3.0$ ) were followed up for an average of 5.4 years (range, 0.5- 8.0 years). During follow-up, 279 men (5.2%) and 98 women (1.9 %) developed diabetes. When baseline FPG were classified into three categories using the IFG cut-off values employed by ADA and EDEG criteria ( $< 5.56$ ,  $5.56-6.06$ , and  $6.11-6.94$  mmol/l), 28/3,401 (0.8%), 91/1,456 (6.3%) and 160/515 (31.1%) men and 13/4,218 (0.3%), 30/695 (4.3%) and 55/177 (31.1%) women developed diabetes, respectively.

Figure 1 shows ROC curves for predicting diabetes which plot the sensitivity versus 1-specificity for the baseline FPG levels in men and women. The area under the ROC curve for corresponding to the FPG and used to diagnose diabetes was 0.877 (95% confidence interval, 0.868–0.885) for men and 0.920 (0.912–0.927) for women. The optimal cut-off value for FPG used to predict diabetes was 5.72 mmol/l both for men (sensitivity 84.2% [95% confidence interval 79.4 - 88.3] and specificity 76.9% [75.7 - 78.1]), and for women (sensitivity 81.6% [72.5 - 88.7]; specificity 91.0% [90.2 - 91.8]).

Table 1 shows the performance of various cut-off points to predict diabetes obtained by using ROC curves analysis for predicting diabetes. Applying a FPG value of 5.56 mmol/l to the study participants as the IFG cut-off value (like according to ADA criteria), IFG included 90% of male and female the subjects who went on to developed diabetes- both men and women. Compared with the conventional IFG parameters (FPG of  $6.11-6.94$  mmol/l), however, adding including subjects with FPG  $5.56-6.06$  mmol/l increased the prevalence of IFG by 3.8 times (36.7% versus 9.6 %) in men and 4.9 times (17.1% versus 3.5%) in women. The positive likelihood of progressing to diabetes in subjects with IFG values that meet of this criteria ( $5.56-6.94$  mmol/l) were lower than

in those with FPG [value](#) of 5.72 (the optimum cut-off in this study) -6.94 mmol/l and 6.11-6.94 mmol/l (conventional criteria).

Next, using [a FPG value](#) of 5.72 mmol/l as the lower limit of IFG provided reasonable sensitivity and specificity as a screening test for progression to diabetes than the cut-off ~~of~~ [FPG value of 5.56](#) or 6.11 mmol/l. Compared with the conventional IFG, however, this definition of IFG (5.72-6.94 mmol/l) increased the prevalence of IFG by 2.7 times (-26.2% versus 9.6 %) in men and 3.0 times (10.4% versus 3.5%) in women.

Then, using [a FPG value](#) of 6.11 mmol/l as the cut-off, IFG included ~~less than 60% of~~ [male and female](#) ~~the~~ subjects who developed diabetes ~~both men and women~~, whereas a FPG >6.11 mmol/l highly excluded ~~those with false positive results due to its superior specificity~~. The positive likelihood of progressing to diabetes in subjects with this criteria of IFG (6.11-6.94 mmol/l) were, higher than in those with the other two [FPG cut-offs](#) ~~of FPG~~.

## Discussion

Since FPG is a continuous variable, defining ~~the~~ [definition of](#) IFG with a certain cut-off is always a matter of trade-off between sensitivity and specificity. In this study, a FPG [value](#) of 5.72 mmol/l was the optimal point to distinguish individuals who will develop diabetes after 5.4 years of mean follow-up. This cut-off value is identical to that obtained in a Dutch population, and the top one among those of the four population (5.22-5.72 mmol/l) reported by [the ADA](#) {The Expert Committee on the Diagnosis and Classification of Diabetes, 2003 #743}. Thus, ~~a~~ [FPG >=5.56](#) mmol/l suggested by ADA, may be acceptable as the 'epidemiological' cut-off for [the](#) prediction of diabetes.

On the other hand, this study also questioned the utility of {Forouhi, 2006 #1692} the new range of FPG (5.56-6.94 mmol/l) for IFG suggested by [the ADA](#), considering the undue burden it possibly imposes on the population. Including FPG [values](#) of 5.56-6.06 mmol/l in [the](#) IFG category creates a remarkably higher prevalence of IFG (three to four fold-increase) as concerned by EDEG\_ {Forouhi, 2006 #1692} and JDA {[??](#), 2008 #1780}. Furthermore, it is important to reconsider the benefit and disadvantage of labelling more individuals with IFG since there is no current evidence of the primary prevention of diabetes or CVD among those with IFG\_ {Forouhi, 2006 #1692}. Second, there was 5-7 fold difference ~~of~~ [in](#) relative risk of ~~incident~~ diabetes [incidence](#) between

the original (6.11-6.94 mmol/l) IFG and the IFG newly added ~~IFG~~-by the ADA (5.56-6.06 mmol/l) both in men and women. Considering these differences, it may not be legitimate to lower the cut-off of IFG without careful consideration ~~for~~of its potential impact on populations. In our view, it is reasonable to preserve ~~IFG~~in the original definition of IFG, and treat ~~as a~~-FPG of 5.56-6.06 mmol/l as non-diabetic hyperglycemia{Forouhi, 2006 #1692} or higher normoglycemia{??, 2008 #1780} just as EDEG and JDA suggested. When a next step is needed, a glucose tolerance test should be recommended to ~~know~~determine the presence of impaired fasting glucose.

This study examined the proper cut-off of FPG ~~to~~for predicting future diabetes in a large Japanese population. Extending to Asian populations, a Korean cohort study examined the same research question, concluding that the FPG cut-off for optimal sensitivity and specificity was 5.11 mmol/l. This particular study subjects ~~include~~were only male and ~~are~~were much younger (age, 36.6±4.7 years) than ours, which may explain the difference between the~~of~~ cut-off from our study.

The ~~l~~imitations ~~is~~of this study are as follows. First, since the study subjects participated on a voluntary basis, they may be healthier than the general population. Second, there were subjects who rapidly progressed to diabetes during the baseline period, who therefore were not eligible to participate during the follow-up period, which may cause an underestimation of the incidence of diabetes. Third, ~~at~~for follow-up evaluations, we used a single FPG level, even though the diagnosis of diabetes requires two sequential measurements of FPG or a 2-hour glucose tolerance test. Although it is considered acceptable to be based upon a single fasting glucose measurement for epidemiological estimates of diabetes prevalence and incidence{, 1997 #1}, it is possible that some cases defined as diabetes had, by chance, FPG levels higher than the defined cut off ~~by~~chance.

Further research should investigate unanswered questions for non-diabetic hyperglycemia including IFG. Risk evaluation according to continuous glucose levels in various populations should be performed for diabetes and cardiovascular disease. Of more importance is whether diabetes could be prevented or at least delayed with ~~pharmacological~~ and life-style interventions in individuals who have non-diabetic hyperglycemia, like impaired fasting glucose.

-Acknowledgments

We are indebted to Mrs. Tetsuya Hayashi and Kiyonori Uchiyama for their assistance with data collection.

Figure 1: The ROC curve for fasting plasma glucose predicting the progression to diabetes in 5,372 men and 5,130 women

Figure legend

The round mark indicates a point of the highest accuracy.

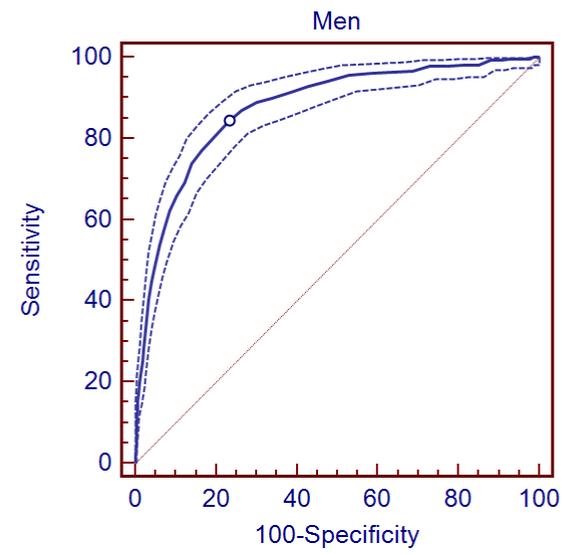
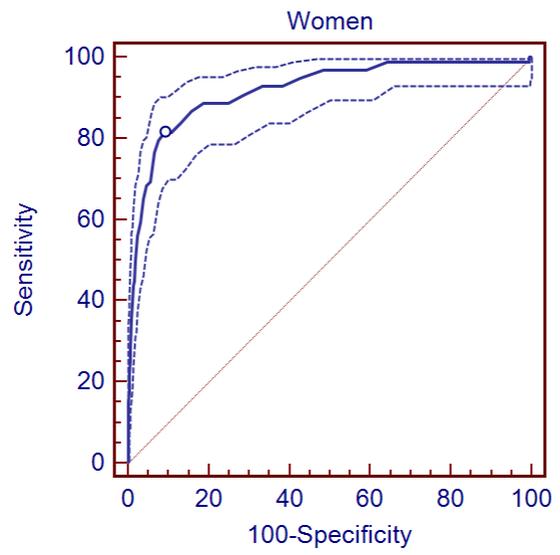


Table 1. Sensitivity, Specificity and Predictabilities of Diabetes at Each Cut-off Level of Baseline Fasting Plasma Glucose (FPG)

Men <sup>a</sup> (N=5,372)						
Cut-off level of FPG(mmol/l)	Defined as impaired fasting glucose	Progressed to diabetes, %	Incidence densities, n/1000 person-years	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive likelihood ratio, % (95% CI)
5.56	1971	251(12.7)	23.2	90.0(85.8 - 93.2)	66.2(64.9 - 67.5)	2.7(2.5 - 2.8)
5.72(Optimum) <sup>b</sup>	1410	235(16.7)	30.3	84.2(79.4 - 88.3)	76.9(75.7 - 78.1)	3.7(3.5 - 3.8)
6.11	515	160(31.1)	56.9	57.4(51.3 - 63.2)	93.0(92.3 - 93.7)	8.2(7.4 - 9.1)
Women <sup>a</sup> (N=5,103)						
Cut-off level of FPG(mg/dl)	Defined as impaired fasting glucose	Progressed to diabetes, %	Incidence densities, n/1000 person-years	Sensitivity, % (95% CI)	Specificity, % (95% CI)	Positive likelihood ratio, % (95% CI)
5.56	872	85(9.7)	18.2	86.7(78.4 - 92.7)	84.3(83.2 - 85.3)	5.5(5.1 - 6.0)
5.72(Optimum)	531	80(15.1)	28.9	81.6(72.5 - 88.7)	91.0(90.2 - 91.8)	9.0(8.2 - 10.0)
6.11	177	55(31.1)	58.4	56.1(45.7 - 66.1)	97.6(97.1 - 98.0)	23.0(19.3 - 27.4)

<sup>a</sup> During follow-up, 279 men and 98 women developed to diabetes.

<sup>b</sup> Optimal cut-off levels of FPG to predict diabetes, defined using ROC curves.