

# Novel analytical approach for diabetes education based on screening outcomes from Japanese physical examination

Atsushi Kumakura (✉ [kumakurikuri@gmail.com](mailto:kumakurikuri@gmail.com))

Kamakura Clinic <https://orcid.org/0000-0001-6531-2388>

**Junpei Shikuma**

Tokyo Medical University

**Kenshi Kan**

Tokyo Medical University

**Mariko Ito**

Tokyo Medical University

**Yusuke Kakizaki**

Tokyo Medical University

**Takashi Miwa**

Tokyo Medical University

**Masato Odawara**

Tokyo Medical University

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## Research article

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# Abstract

**Background:** We examined the time-course changes in four variables, namely, fasting plasma glucose (FPG) level, fasting insulin level (FIL), homeostasis model assessment beta (HOMA-b) score, and homeostasis model assessment-insulin resistance (HOMA-IR) score. The variables were examined before and after the onset of diabetes mellitus (DM).

**Methods:** In total, 1,333 Japanese men underwent four annual screenings for diabetes from April 2006 to March 2010. DM was defined as an FPG level  $\geq 126$  mg/dL or glycated hemoglobin level  $\geq 6.5\%$ . The variables were examined in healthy men and those with DM in the body mass index [BMI]  $\geq 25$  and  $< 25$  kg/m<sup>2</sup> groups. The projected FPG level and FIL were assessed based on the simulated HOMA-b and HOMA-IR scores, which is considered a novel analytical approach.

**Results:** In total, 99 (7.4%) men developed DM at any point of the screening periods. The HOMA-b values of the BMI  $\geq 25$  kg/m<sup>2</sup> group were  $117.6\% \pm 72.9\%$ ,  $60.4\% \pm 29.8\%$ , and  $43.1\% \pm 28.1\%$  at baseline, onset, and 4 years after the onset, respectively. Thus, the decrease in the values was steep. Meanwhile, the HOMA-IR values of the BMI  $< 25$  kg/m<sup>2</sup> group were  $1.7 \pm 0.8$  and  $2.2 \pm 1.2$  at 1 year before onset and at onset. Hence, there was an important but slight increase in the values. This result indicates that patients presented with reduced insulin secretion and elevated IR during the onset of diabetes. The values of the four variables remained within normal ranges in healthy men.

**Conclusions:** The novel analytical approach has clinical relevance as it provides a visual material for diabetes education, which is useful in providing caution against the risk of developing DM.

## Background

Diabetes mellitus (DM) is a group of metabolic disorders characterized by chronic hyperglycemia due to impaired insulin secretion and increased insulin resistance (IR) due to the reduced actions of insulin. The United Kingdom Prospective Diabetes Study<sup>16</sup> has shown that the homeostasis model assessment beta (HOMA- $\beta$ ) score decreased by up to approximately 50% at the time of type 2 DM diagnosis. Moreover, the pancreatic  $\beta$ -cell function decreased progressively and gradually about 12 years before the onset of DM.<sup>1</sup> In terms of race, a difference was observed in pancreatic  $\beta$ -cell function. That is, the Japanese population has a lower pancreatic  $\beta$ -cell function than the Western population. Therefore, DM in the Japanese population is predominantly characterized by impaired insulin secretion. However, no study has examined the pancreatic  $\beta$ -cell function of the Japanese population with DM. Thus, this retrospective clinical study aimed to investigate the time-course changes in four variables, namely, fasting plasma glucose (FPG), fasting insulin level (FIL), HOMA- $\beta$  score, and HOMA-IR score, in Japanese men who underwent screening for DM.

## Methods

# Study population

In total, 11,787 Japanese adult men underwent health checkup at the Center for Health Surveillance and Preventive Medicine, Tokyo Medical University Hospital, from April 2006 to March 2007. Among them, 1,333 were included in this study, which retrospectively analyzed the onset of DM. The age of the participants ranged from 26 to 86 years. The inclusion criteria were as follows: 1) patients who did not receive pharmacotherapy for DM, hypertension, or dyslipidemia and 2) those who underwent four annual screenings. DM was defined as FPG level  $\geq 126$  mg/dL or glycated hemoglobin (HbA<sub>1c</sub>) level  $\geq 48$  mmol/mol according to the International Federation of Clinical Chemistry and Laboratory Medicine or 6.5% based on the National Glycohemoglobin Standardization Program.

The current study was conducted in accordance with the Declaration of Helsinki and the ethical guidelines for Clinical Research and Epidemiologic Research by the Ministry of Health, Labor and Welfare of Japan. Furthermore, the study was approved by the ethical review board of Tokyo Medical University Approval No.2092 and Approval date 6/27/2012.

## Measurements

FPG was measured automatically according to the hexokinase and glucose-6-phosphate dehydrogenase method using a glucose kit (L-type Wako, Wako Pure Chemical Industries, Osaka, Japan). FIL was measured using the chemiluminescence enzyme immunoassay method with an insulin kit (Elecsys® Systems; Roche Diagnostics GmbH, Mannheim, Germany). Insulin resistance was assessed using HOMA-IR (FPG [mg/dL] · FIL [ $\mu$ U/mL]  $\div$  405), and HOMA- $\beta$  was used to evaluate insulin secretion {FIL [ $\mu$ U/mL] · 360  $\div$  (FPG [mg/dL] – 63)}.<sup>2</sup> BMI was obtained by calculating body weight (kg) divided by height (m<sup>2</sup>).

## Statistical analysis

All values were expressed as mean  $\pm$  standard deviation. The two groups were evaluated according to the unpaired student's *t*-test using the Statistical Package for the Social Sciences software for Windows version 10.07J (SPSS Japan, Tokyo, Japan). A *P* value  $< 0.05$  was considered statistically significant.

## Results

In total, 99 patients developed DM at any point of the screening periods, and the following values were obtained at the time of DM onset. The mean age of the participants was  $55.4 \pm 9.6$  years ( $53.2 \pm 10.0$  and  $57.2 \pm 8.9$  years in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). The age of the BMI  $\geq 25$  kg/m<sup>2</sup> group was significantly lower than that of the BMI  $< 25$  kg/m<sup>2</sup> group (*P* = 0.038). Furthermore, the mean BMI was  $24.5 \pm 3.0$  kg/m<sup>2</sup> ( $27.1 \pm 1.8$  and  $22.4 \pm 1.8$  kg/m<sup>2</sup> in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). The BMI was significantly lower in the BMI  $< 25$  kg/m<sup>2</sup> group than in the BMI  $\geq 25$  kg/m<sup>2</sup> group (*P*  $< 0.01$ ). The mean FPG level was  $130.2 \pm$

22.0 mg/dL ( $134.3 \pm 23.6$  and  $126.8 \pm 20.2$  mg/dL in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). However, this variable did not significantly differ between the two groups. The HbA<sub>1c</sub> level was  $45.0 \pm 9.7$  mmol/mol ( $6.3\% \pm 0.9\%$ ;  $47.3 \pm 11.0$  mmol/mol [ $6.5\% \pm 1.0\%$ ] and  $43.0 \pm 8.0$  mmol/mol [ $6.1\% \pm 0.7\%$ ] in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). The BMI  $< 25$  kg/m<sup>2</sup> group had a significantly higher HbA<sub>1c</sub> level than the BMI  $\geq 25$  kg/m<sup>2</sup> group ( $P = 0.027$ ; Table 1). The total HOMA- $\beta$  score was more likely to decrease ( $70.3\% \pm 56.4\%$  at baseline [4 years before onset in each patient with DM],  $51.3\% \pm 31.1\%$  at onset, and  $39.4\% \pm 27.8\%$  4 years after onset). The HOMA- $\beta$  scores of the BMI  $\geq 25$  kg/m<sup>2</sup> group were as follows:  $117.6\% \pm 72.9\%$  at baseline,  $60.4\% \pm 29.8\%$  at onset, and  $43.1\% \pm 28.1\%$  4 years after onset. Thus, the decrease in the values was steep. The patients with DM in the BMI  $< 25$  kg/m<sup>2</sup> group had reduced insulin secretion at baseline ( $44.5\% \pm 19.0\%$ ), and a further decrease was not observed at onset ( $43.7\% \pm 19.0\%$ ) and 4 years after onset ( $36.3\% \pm 27.7\%$ ) (Fig. 1a). The total HOMA-IR scores were  $2.6 \pm 2.0$  at baseline,  $2.9 \pm 1.5$  at onset, and  $2.4 \pm 1.8$  4 years after onset. Patients with DM in the BMI  $\geq 25$  and  $< 25$  kg/m<sup>2</sup> groups had a slight increases in HOMA-IR scores between 1 year before onset ( $3.1 \pm 1.6$  and  $1.7 \pm 0.8$ , respectively) and onset ( $3.6 \pm 1.4$  and  $2.2 \pm 1.2$ , respectively) (Fig. 2a). The healthy men in the BMI  $\geq 25$  and  $< 25$  kg/m<sup>2</sup> groups did not present with evident changes in both HOMA- $\beta$  and HOMA-IR scores in all four annual screening periods (Figs. 1b and 2b).

Table 1  
Demographic characteristics of the patients with diabetes mellitus at onset

	N = 99	Body mass index, kg/m <sup>2</sup>		P value
		< 25 (n = 54)	$\geq 25$ (n = 45)	
Age (years)	$55.4 \pm 9.6$	$57.2 \pm 8.9$	$53.2 \pm 10.0$	0.038
Height (cm)	$169.4 \pm 5.9$	$169.1 \pm 5.5$	$169.8 \pm 6.4$	0.54
Weight (kg)	$70.5 \pm 10.0$	$64.0 \pm 6.3$	$78.3 \pm 7.9$	0.001
Waist (cm)	$88.3 \pm 7.9$	$83.2 \pm 5.8$	$94.3 \pm 5.5$	0.001
Body mass index (kg/m <sup>2</sup> )	$24.5 \pm 3.0$	$22.4 \pm 1.8$	$27.1 \pm 1.8$	0.001
Fasting plasma glucose (mg/dL)	$130.2 \pm 22.0$	$126.8 \pm 20.2$	$134.3 \pm 23.6$	0.092
Fasting insulin level ( $\mu$ U/mL)	$8.9 \pm 4.4$	$7.1 \pm 3.9$	$11.0 \pm 4.0$	0.001
Glycated hemoglobin (mmol/mol)	$45.0 \pm 9.7$	$43.0 \pm 8.0$	$47.3 \pm 11.0$	0.027

The HOMA-IR and HOMA- $\beta$  scores were calculated using FPG level as the x-axis and FIL as the y-axis. Moreover, the following equations were used:  $y = 405 \cdot \text{HOMA-IR} \div x$  and  $y = (x - 63) \cdot \text{HOMA-}\beta \div 360$ . Figure 3 depicts a diagram showing time-course changes in simulated HOMA- $\beta$  and HOMA-IR scores using the abovementioned formulae. The healthy men had the following measured values at baseline.

The age of these participants was  $48.8 \pm 9.3$  years ( $47.9 \pm 8.8$  and  $49.1 \pm 9.5$  years in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). This variable did not significantly differ between the two groups. The BMI was  $23.1 \pm 2.7$  kg/m<sup>2</sup> ( $26.5 \pm 1.9$  and  $22.1 \pm 2.0$  kg/m<sup>2</sup> in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). The BMI  $< 25$  kg/m<sup>2</sup> group had a significantly lower BMI than the BMI  $\geq 25$  kg/m<sup>2</sup> group ( $P = 0.001$ ). The FPG level was  $96.7 \pm 8.6$  mg/dL ( $98.2 \pm 8.0$  and  $96.2 \pm 8.0$  mg/dL in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). The FBG level was significantly higher ( $P = 0.001$ ) in the BMI  $\geq 25$  kg/m<sup>2</sup> group than in the BMI  $< 25$  kg/m<sup>2</sup> group. The HbA<sub>1c</sub> level was  $31.3 \pm 3.4$  mmol/mol ( $5.1\% \pm 0.3\%$ ;  $32.0 \pm 3.5$  [ $5.1\% \pm 0.3\%$ ] and  $31.6 \pm 3.3$  mmol/mol [ $5.0\% \pm 0.3\%$ ] in the BMI  $\geq 25$  kg/m<sup>2</sup> group and the BMI  $< 25$  kg/m<sup>2</sup> group, respectively). No significant difference was found in this variable between the two groups (Table 2).

Table 2  
Demographic characteristics of healthy men at baseline

	N = 1,234	Body mass index, kg/m <sup>2</sup>		P value
		< 25 (n = 940)	$\geq 25$ (n = 294)	
Age (years)	$48.8 \pm 9.3$	$49.1 \pm 9.5$	$47.9 \pm 8.8$	0.051
Height (cm)	$170.2 \pm 5.8$	$170.1 \pm 5.8$	$170.8 \pm 5.8$	0.052
Weight (kg)	$67.2 \pm 9.1$	$64.0 \pm 6.9$	$77.3 \pm 7.9$	0.001
Waist (cm)	$84.0 \pm 7.3$	$81.6 \pm 5.9$	$91.7 \pm 5.9$	0.001
Body mass index (kg/m <sup>2</sup> )	$23.1 \pm 2.7$	$22.1 \pm 2.0$	$26.5 \pm 1.9$	0.001
Fasting plasma glucose (mg/dL)	$96.7 \pm 8.0$	$96.2 \pm 8.0$	$98.2 \pm 8.0$	0.001
Fasting insulin level ( $\mu$ U/mL)	$6.3 \pm 4.1$	$5.5 \pm 3.5$	$8.9 \pm 4.8$	0.001
Glycated hemoglobin (mmol/mol)	$31.7 \pm 3.4$	$31.6 \pm 3.3$	$32.0 \pm 3.5$	0.076

## Discussion

The risk of developing DM increases linearly, which is parallel to the severity of obesity.<sup>3-7</sup> However, although the prevalence of obesity is high in Western countries, the prevalence of DM in Asian countries, including Japan, is similar to that in Western countries.<sup>8</sup> In the current study, the mean BMI of the group with DM in Japan was  $24.5 \pm 3.0$  kg/m<sup>2</sup>. Meanwhile, that of patients with DM in the United States is approximately  $30$  kg/m<sup>2</sup>, indicating a difference in the phenotype of DM in terms of race.<sup>9</sup> In addition to environmental factors (e.g., aging, excessive nutrition, and lack of physical activity and genetic predisposition, impaired insulin secretion in pancreatic  $\beta$ -cells and increased insulin resistance in the liver and peripheral tissues causes type 2 DM.<sup>10,11</sup> Several individuals with type 2 DM have both impaired insulin secretion and insulin resistance. However, these two factors have different roles in increasing

blood glucose level according to each individual and race. The low initial secretion of insulin in pancreatic  $\beta$ -cells and low  $\beta$ -cell volume are involved in the pathogenesis of DM in lean Asian individuals, including Japanese.<sup>12-14</sup>

Several studies have reported the associations between the onset of DM and decreased insulin secretion.<sup>15-17</sup> Patients with DM in the BMI  $\geq 25$  kg/m<sup>2</sup> group had steep decreases in HOMA- $\beta$  scores from baseline to 4 years after onset, and these clinical outcomes are consistent with the current data. By contrast, patients with DM in the BMI  $< 25$  kg/m<sup>2</sup> group had slight decreases in HOMA- $\beta$  score, thereby presenting a pattern different from that currently known. In contrast, healthy men in the BMI  $\geq 25$  kg/m<sup>2</sup> group had HOMA- $\beta$  values  $\geq 90\%$ . Meanwhile, those in the BMI  $< 25$  kg/m<sup>2</sup> group had HOMA- $\beta$  scores ranging from 61–65%. However, significant changes were not observed. In the study of Sakuraba et al., the islet cells of the pancreas and the volume of pancreatic  $\beta$ -cells in autopsied patients with DM were assessed.<sup>18</sup> However, changes in  $\alpha$ -cells and specific decreases in the volume of  $\beta$ -cells in the pancreas were not observed. Furthermore, Butler et al. have reported a decrease in pancreatic  $\beta$ -cell volume by 63% and 40% in obese and lean patients with DM, respectively.<sup>19</sup> Thus, decreased pancreatic  $\beta$ -cell volume contributed to the low HOMA- $\beta$  scores.

The patients with DM in the BMI  $\geq 25$  kg/m<sup>2</sup> group had elevated HOMA-IR scores at baseline, and the healthy men in the BMI  $\geq 25$  kg/m<sup>2</sup> group had HOMA-IR scores ranging from 2.0 to 2.2 during the four annual screening periods. We considered that both reduced insulin secretion and elevated insulin resistance contributed to disease onset in patients with DM in the BMI  $\geq 25$  kg/m<sup>2</sup> group. In contrast, Gautier et al.<sup>20</sup> have reported that an increase in waist circumference was associated with the onset of DM in patients with a BMI  $< 25$  kg/m<sup>2</sup>. An increase in abdominal circumference reflects an elevated insulin resistance. The current study supports this finding because a slight elevation in insulin resistance without a further decrease in insulin secretion contributed to disease onset in patients with DM in the BMI  $< 25$  kg/m<sup>2</sup> group. That is, the pathogenic patterns differ between obese and nonobese patients with DM in the Japanese population.

Figure 3 shows a novel analytical approach that can be used to project FPG levels and FIL based on the simulated HOMA- $\beta$  and HOMA-IR scores. Consequently, patients with DM in the BMI  $\geq 25$  kg/m<sup>2</sup> group had a significant increase in FPG level from baseline to 4 years after onset, and this result is in accordance with the time-course changes in HOMA- $\beta$  scores. Furthermore, they exhibited no remarkable change in FIL from 1 year before onset to onset. However, a slight increase in HOMA-IR score (probably attributed to an increase in FPG) was observed. In contrast, patients with DM in the BMI  $< 25$  kg/m<sup>2</sup> group had an increase in FIL from 1 year before onset to onset. However, such increase does not result in an elevated FPG level, which is represented by a slight elevation in HOMA-IR score.

In healthy men and patients with DM in the BMI  $\geq 25$  and  $< 25$  kg/m<sup>2</sup> groups, the values of the four variables remained at extremely narrow ranges during the four annual screening periods. Obesity is a risk factor for insulin resistance, and our study supports this concept because the BMI  $\geq 25$  kg/m<sup>2</sup> group had

higher HOMA-IR scores than the BMI < 25 kg/m<sup>2</sup> group at baseline. In contrast, prior to onset, patients with DM in the BMI ≥ 25 kg/m<sup>2</sup> group and the BMI < 25 kg/m<sup>2</sup> group had HOMA-IR values > 2.5 and 1.5, respectively.

In the DECODE study, approximately 31.3% of patients with DM were missed during the screening for DM because only FPG level was used and OGTT was not performed.<sup>21</sup> However, we did not perform the tolerance test, and the patients were diagnosed with DM based on the FPG and HbA<sub>1c</sub> values alone. Therefore, we did not accurately assess this cohort of patients with DM.

The functions of pancreatic β-cells are regulated by pancreatic β-cell volume and insulin secretion by β-cells. The HOMA-β score indicates basal insulin secretion by β-cells. However, we cannot refer to additional insulin secretion by β-cells because the tolerance tests for glucose, glucagon, and arginine were not performed. Moreover, the pancreatic β-cell volume cannot be used as it cannot be identified unless necropsy is conducted. Due to the retrospective nature of the study and the fact that only male adults were included in the study, selection bias might have affected the study results.

## Conclusions

We developed a novel analytical approach that has clinical relevance as it provides a visual material for diabetes education. Moreover, this approach is useful in providing caution against the risk of developing DM, offering lifestyle guidance for the prevention of DM, and emphasizing the importance of maintaining the values of the four variables within normal ranges in Japanese men with BMI values ≥ 25 and < 25 kg/m<sup>2</sup> who present with HOMA-IR values > 2.5 and > 1.5, respectively.

## List Of Abbreviations

FPG, fasting plasma glucose

FIL, fasting insulin level

HOMA-β, homeostasis model assessment beta

HOMA-IR, homeostasis model assessment-insulin resistance

DM, diabetes mellitus

HbA<sub>1c</sub>, glycated hemoglobin

## Declarations

**Ethics approval and consent to participate**

This study was approved by the ethical review board of Tokyo Medical University Approval No.2092 and Approval date 6/27/2012.

### **Consent for publication**

Post a poster about using the data obtained at the Center for Health Surveillance and Preventive Medicine, Tokyo Medical University Hospital and consent was obtained.

### **Availability of data and materials**

Data are stored in the Center for Health Surveillance and Preventive Medicine, Tokyo Medical University Hospital database.

### **Competing interests**

The authors declare that they have no competing interests.

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### **Authors' contributions**

Dr. Kumakura planned the study design and collected the data. He considered the composition of this research paper.

Dr. Shikuma planned the study design and collected the data. And he proofread the research paper.

Dr. Kan analyzed the data.

Dr. Ito and Dr. Kakizaki collected the data.

Dr. Miwa and Dr. Odawara supervised the entire research.

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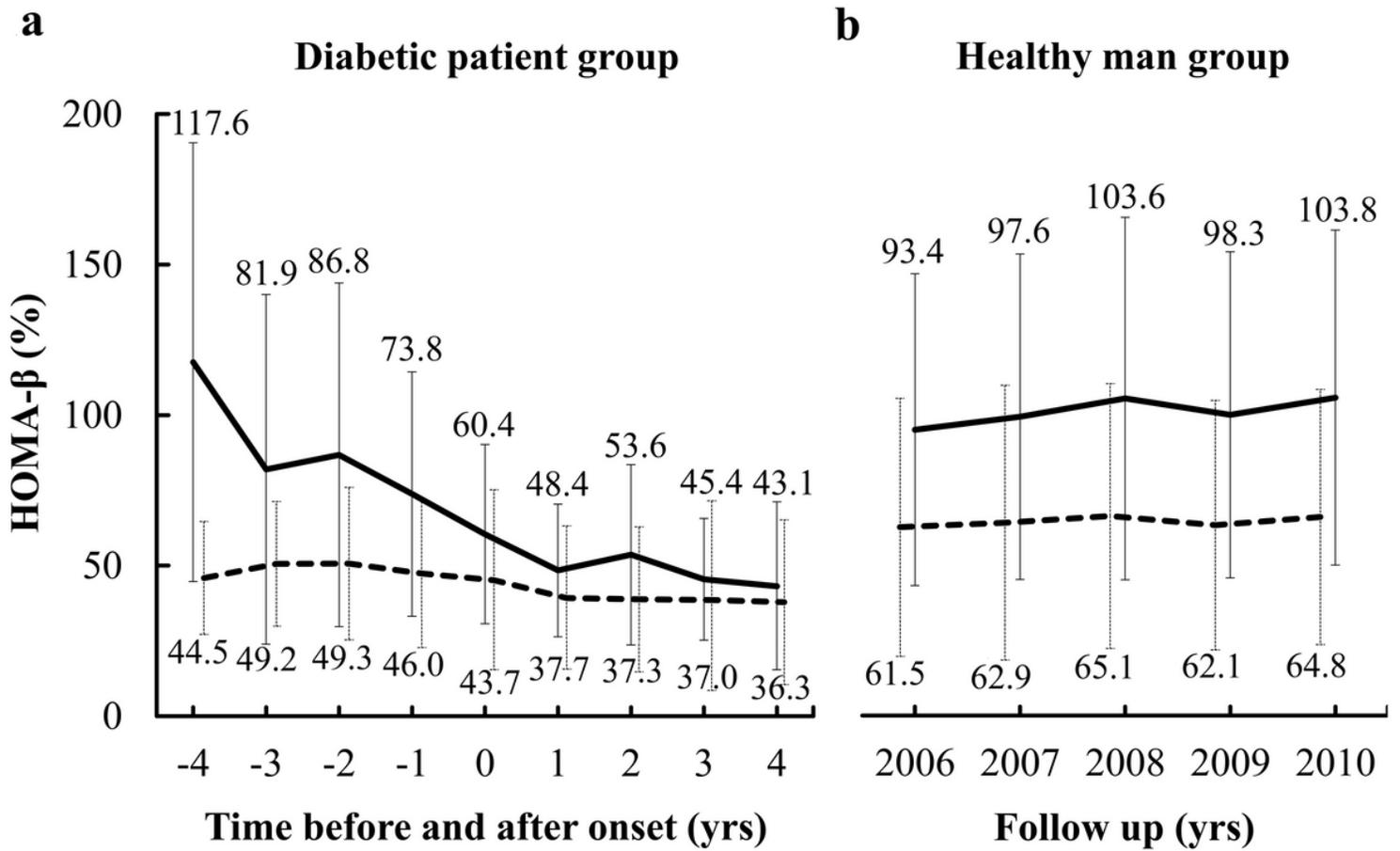
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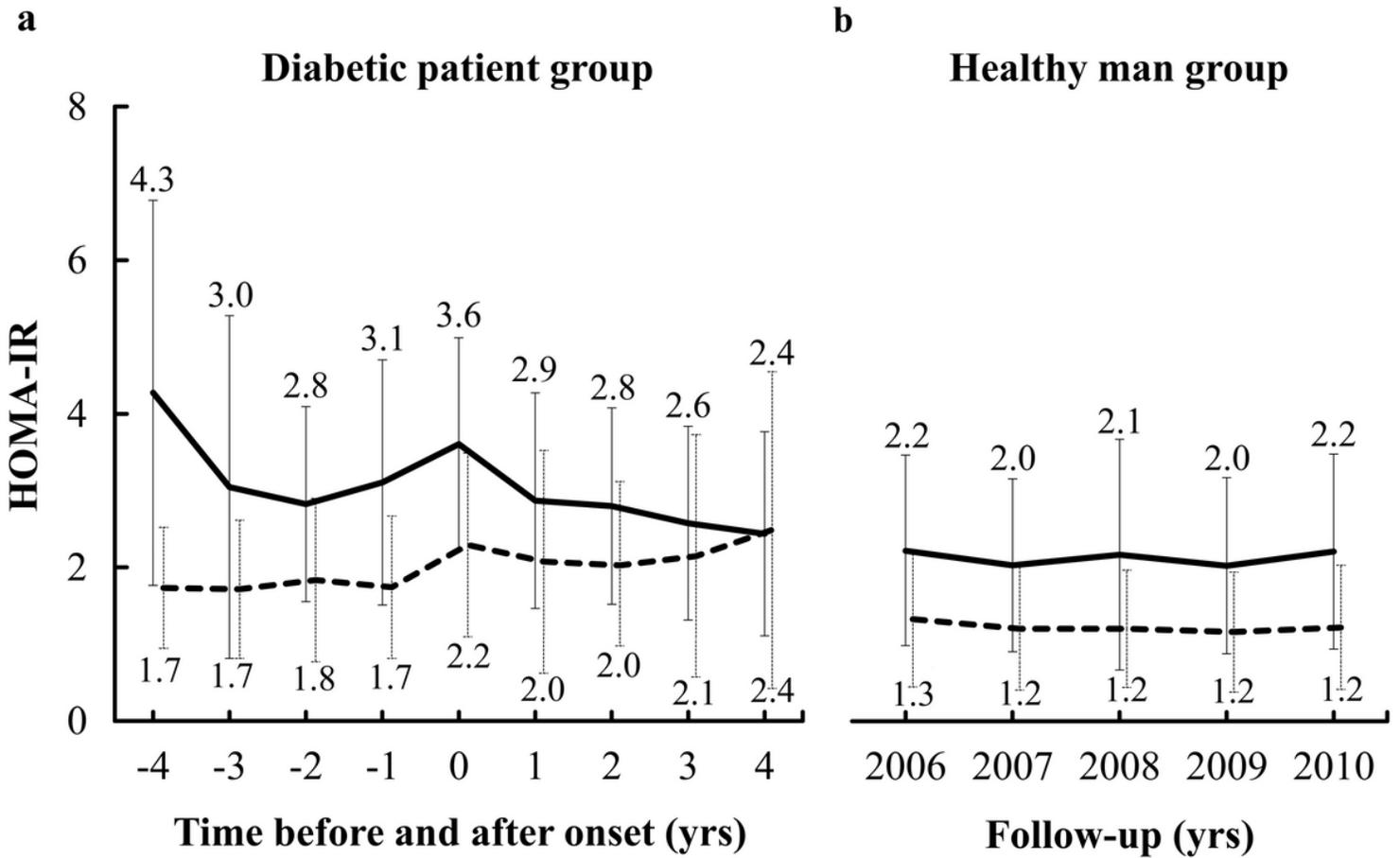
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## Figures



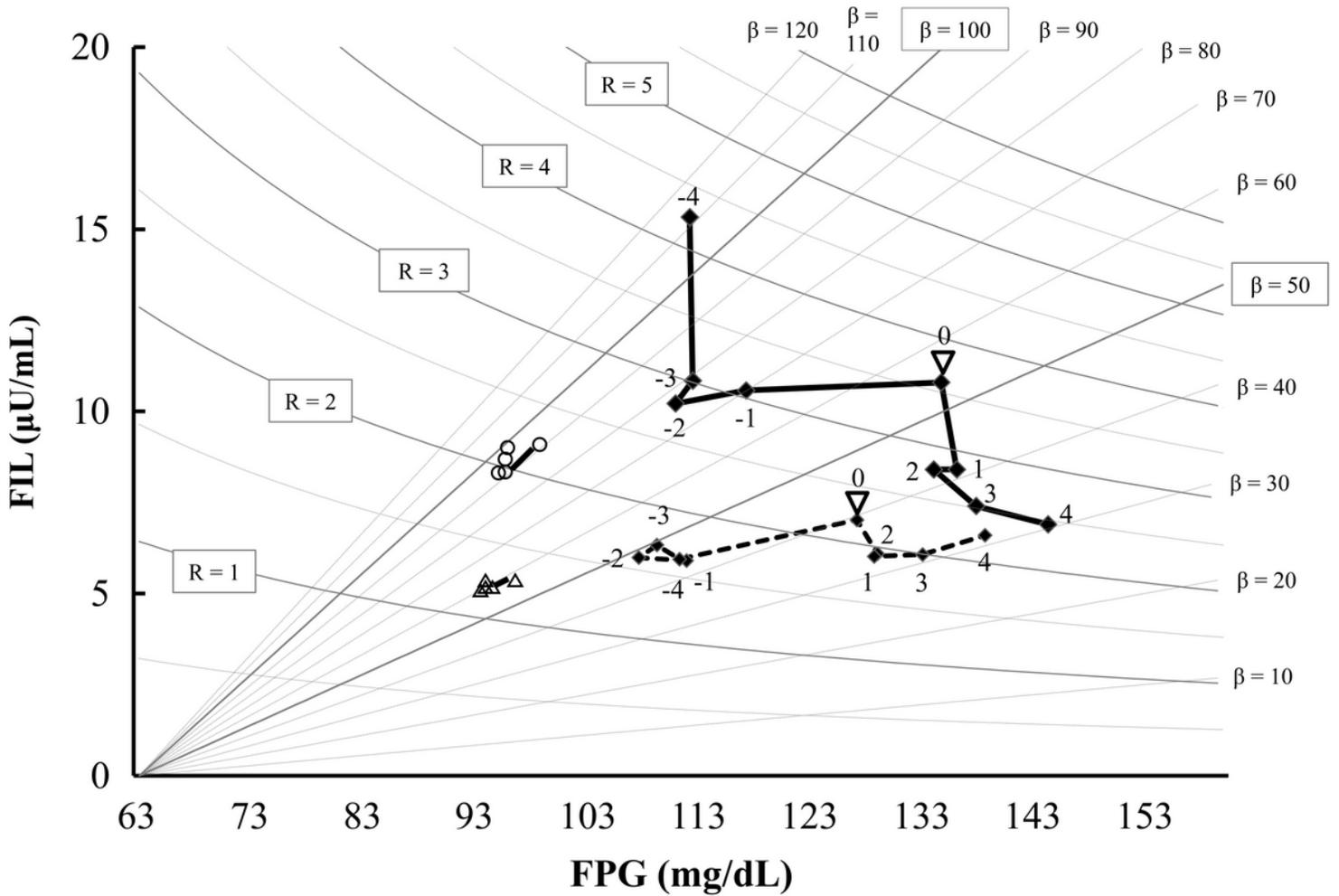
**Figure 1**

Time-course changes in HOMA- $\beta$  scores according to BMI Solid line: the BMI  $\geq 25$  kg/m<sup>2</sup> group, broken line: the BMI  $< 25$  kg/m<sup>2</sup> group a: Diabetic patient group, b: Healthy man group BMI, body mass index; HOMA- $\beta$ , homeostasis model assessment beta model



**Figure 2**

Time-course changes in HOMA-IR scores according to BMI Solid line: the BMI  $\geq 25$  kg/m<sup>2</sup> group, broken line: the BMI  $< 25$  kg/m<sup>2</sup> group a:Diabetic patient group, b:Healthy man group BMI, body mass index; HOMA-IR, homeostasis model assessment-insulin resistance



**Figure 3**

Time-course changes in FIL and FPG level based on the simulated HOMA- $\beta$  and HOMA-IR scores Solid line: the group of patients with BMI  $\geq 25$  kg/m<sup>2</sup> and diabetes mellitus; broken line: the group of patients with BMI < 25 kg/m<sup>2</sup> and diabetes mellitus; circle: the group of healthy men with BMI  $\geq 25$  kg/m<sup>2</sup>; triangle: the group of healthy men with BMI < 25 kg/m<sup>2</sup> FIL, fasting insulin level; FPG, fasting plasma glucose

## Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [FCSTROBEchecklistv4combined25.8.docx](#)