Comparison of the contributions of impaired beta cell function and insulin resistance to the development of type 2 diabetes in a Japanese community: the Hisayama Study

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Article

Comparison of the contributions of impaired beta cell function and insulin resistance to the development of type 2 diabetes in a Japanese community: the Hisayama Study

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Abstract

Aims/hypothesis Our aim was to compare the contributions of impaired beta cell function (IBF) and insulin resistance with the development of type 2 diabetes in a Japanese community.

Methods A total of 2094 residents aged 40–79 years without diabetes underwent a health examination including a 75g OGTT in 2007. Participants were divided into four groups according to the presence or absence of IBF (insulinogenic index/HOMA-IR ≤28.5) and insulin resistance (HOMA-IR ≥1.61) and were followed up for 7 years (2007–2014). Cox's proportional hazards model was used to estimate HRs and 95% CIs for type 2 diabetes. The population attributable fractions (PAFs) due to IBF, insulin resistance, and their combination were calculated.

Results At baseline, the prevalence of isolated IBF, isolated insulin resistance, and both IBF and insulin resistance were 5.4%, 24.1%, and 9.5%, respectively. During the follow-up period, 272 participants developed type 2 diabetes. The multivariable-adjusted HRs (95% CI) and PAFs (95% CI) for type 2 diabetes were 6.3 (4.3, 9.2) and 13.3% (8.7, 17.7) in the participants with isolated IBF, 1.9 (1.3, 2.7) and 10.5% (4.0, 16.6) in those with isolated insulin resistance, and 8.0 (5.7, 11.4) and 29.3% (23.0, 35.1) in those with both IBF and insulin resistance, respectively, compared with the

participants without either.

Conclusions/interpretation The present study suggests that the combination of IBF and

insulin resistance makes the main contribution to the development of type 2 diabetes in

Japanese communities.

Research in context

What is already known about this subject?

- Impaired beta cell function (IBF) and insulin resistance are the major mechanisms

  for the development of type 2 diabetes, but IBF has been considered to be a primary

  factor among Asian populations

What is the key question?

- Given the recent rise in the burden of obesity in Asia, what is the contribution of

  IBF and insulin resistance to the development of type 2 diabetes in an Asian

  population?

What are the new findings?

- The combination of IBF and insulin resistance showed the strongest contribution in

  the development of type 2 diabetes in a general Japanese population

- The isolated IBF and the combination of IBF and insulin resistance contributed to

the development of type 2 diabetes to a similar degree in the non-obese participants, while approximately half of incident type 2 diabetes was attributable to the combination of both factors in obese participants

How might this impact on clinical practice in the foreseeable future?

- These findings suggest the importance of improving insulin resistance, in addition to IBF, to reduce the burden of diabetes in the Asian population

Keywords

Beta cell function; Epidemiology; Insulin resistance; Insulin secretion; Normal glucose tolerance; Obesity; Prediabetes; Prospective study; Type 2 diabetes

Abbreviations

2hPG, 2 h postload glucose

FPG, fasting plasma glucose

IBF, impaired beta cell function

InsAUC/GluAUC, Ratio of insulin AUC to glucose AUC during OGTT

PAF, Population attributable fraction

Introduction

Type 2 diabetes mellitus compromises the quality of life of affected people by contributing to the development of micro- and macrovascular diseases, as well as cancers and dementia [1–3]. Insulin is the main peptide hormone that regulates glucose metabolism, and insulin resistance, which is mainly caused by obesity, is a pathological condition in which the insulin sensitivity is downregulated. Impaired insulin secretion and insulin resistance are thus two essential components in the pathophysiology of type 2 diabetes [4–6]. Several clinical studies reported that Asian individuals had a lower ability to secrete insulin than white individuals, whereas insulin resistance and obesity were more prevalent in white individuals [7–9]. In addition, it has been reported that the genetic predispositions linked with the ability to secrete insulin are associated with the development of diabetes among Asian populations [10–14]. Therefore, the magnitude of the contribution of the ability to secrete insulin and insulin resistance may vary among individuals of different ethnic and genetic backgrounds. Nevertheless, given the recent rising trend in the burden of obesity in Asia, it seems reasonable to speculate that the contribution of insulin resistance to the development of diabetes at the population level could be rising relative to that of impaired insulin secretion among Asian populations [9, 15].

On the other hand, insulin secretion is affected mutually by beta cell function and insulin resistance. Insulin secretion is accelerated compensatorily with the exacerbation of insulin resistance. A recent clinical study has reported that the beta cell functions estimated by the disposition index are comparable between Asian people and white people, and the lower insulin secretion ability in Asian people compared with white people can be explained by the higher insulin sensitivity due to the difference in body composition [8]. The disposition index, which is the ratio of measures of insulin secretion and insulin resistance, has been considered to be more appropriate than the index of insulin secretion to accurately assess beta cell function, because the disposition index accounts for the compensatory increase in insulin secretion associated with the exacerbation of insulin resistance [16].

However, there have been no population-based prospective cohort studies examining the population attributable risks of impaired beta cell function (IBF) as assessed by the disposition index and insulin resistance on the development of type 2 diabetes among general populations. The aim of the present study, therefore, was to compare the contributions of IBF and insulin resistance to the development of type 2 diabetes in a general Japanese population.

Methods

Study population A population-based prospective cohort study investigating CVD, diabetes and lifestyle-related diseases has been underway since 1961 in the town of Hisayama, a suburb of the Fukuoka metropolitan area on Kyushu Island, Japan. According to the national census, the age and occupational distributions and major nutrient intake levels of the Hisayama population were similar to those of Japan during the period between 1960 and 2010 [17]. In 2007, a total of 2957 Hisayama residents aged 40–79 years (77.1% of the total population of this age group) underwent a health examination. After excluding eight individuals who did not consent to participate in the examination, 484 individuals with diabetes at baseline, 172 who did not undergo an OGTT, 58 whose data on insulinogenic index were not available at baseline, 14 whose data on alcohol consumption were missing at baseline, and 127 who did not undergo re-examinations during follow-up, the remaining 2094 individuals (880 men and 1214 women) were enrolled in the present study. This study was conducted with the approval of the Kyushu University Institutional Review Board for Clinical Research. Written informed consent was obtained from all participants.

Evaluation of glucose intolerance status, the status of beta cell function, and insulin

resistance at baseline At baseline, the study participants underwent a 75g OGTT between 08:00 and 10:30 hours after an overnight fast of at least 12 h. Plasma glucose was obtained in a fasting state, and at 30 min and 2 h during an OGTT. Plasma glucose levels were determined by a hexokinase method. Glucose tolerance status was defined by the WHO criteria in 2006 as follows. Normal glucose tolerance: fasting plasma glucose (FPG) <6.1 mmol/l and 2 h postload glucose (2hPG) <7.8 mmol/l; prediabetes: FPG 6.1–6.9 mmol/l and 2hPG <7.8 mmol/l or FPG <7.0 mmol/l and 2hPG 7.8–11.0 mmol/l; and diabetes: FPG ≥7.0 mmol/l, 2hPG ≥11.1 mmol/l, and/or the use of glucose-lowering medications [18]. Serum insulin levels were determined by electrochemiluminescence immunoassay (ECLusys 2010; Roche Diagnostics, Basel, Switzerland). Insulin secretion was evaluated using the insulinogenic index, defined as [30 min insulin (pmol/l) − fasting insulin (pmol/l)]/[30 min glucose (mmol/l) − fasting glucose (mmol/l)] [19]. Insulin resistance was evaluated using the HOMA-IR, defined as fasting insulin (pmol/l) × fasting glucose (mmol/l)/135 [20]. Disposition index was calculated as insulinogenic index/HOMA-IR [21]. IBF was defined as insulinogenic index/HOMA-IR ≤28.5, and insulin resistance was defined as HOMA-IR ≥1.61 based on the previous reports [22–24].

Participants were divided into 2×2 categories according to the presence or absence of IBF and insulin resistance: a normal group, a group with isolated IBF

(individuals with IBF and without insulin resistance), a group with isolated insulin

resistance (individuals with insulin resistance and without IBF), and a group with both

IBF and insulin resistance.

For the sensitivity analyses, alternative indices for beta cell function and IR

were calculated. The ratio of insulin AUC to glucose AUC during the OGTT

(InsAUC/GluAUC) was calculated using the trapezoid method as ([fasting insulin

(pmol/l) + 30 min insulin (pmol/l)]/2 × 30 + [30-min insulin (pmol/l) +2 h insulin

(pmol/l)/2 × 90]) /([fasting glucose (mmol/l) + 30 min glucose (mmol/l)]/2 × 30 + [30

min glucose (mmol/l) + 2 h glucose (mmol/l)]/2 × 90) [25]. The Matsuda index was

calculated as 10,000 per square root of {fasting glucose (mmol/l) × fasting insulin

(pmol/l) × [fasting glucose (mmol/l) × 15 + 30 min glucose (mmol/l) × 60 + 2 h glucose

(mmol/l) × 45]/120 × [fasting insulin (pmol/l) × 15 + 30-min insulin (pmol/l) × 60 + 2 h

glucose (pmol/l) × 45]/120} according to the previously reported method [26, 27]. The

product of InsAUC/GluAUC and the Matsuda index (InsAUC/GluAUC×Matsuda

index) was used as an alternative index for beta cell function [21], and the Matsuda

index was used as an alternative index for IR. The IBF and IR were defined

alternatively as InsAUC/GluAUC×Matsuda index of ≤131.8 and Matsuda index of

≤4.97, respectively. The cut-off values of the insulinogenic index/HOMA-IR,

InsAUC/GluAUC×Matsuda index, and Matsuda index were determined as the point

maximising the Youden index [= max (sensitivity + specificity − 1)] that optimises the

discriminatory ability for the risk of incident diabetes [28, 29] (ESM Table 1).

Follow-up survey and determination of type 2 diabetes The participants were e

prospectively by an annual health examination including OGTT until 30 November 2014

(the median follow-up period was 6.9 years [range 0.6–7.4 years]; follow-up rate: 94.3%).

During the follow-up period, the incidence of type 2 diabetes was defined by either the

results of the OGTT or the measurements of plasma glucose as FPG ≥7.0 mmol/l, 2hPG

or casual plasma glucose ≥11.1 mmol/l, and/or the use of glucose-lowering medications

(oral hypoglycaemic agents, injectable glucagon-like peptide analogues, or insulin),

according to the 2006 WHO criteria. When a participant died, we reviewed all available

clinical information including the use of glucose-lowering medication. Participants were

censored at the time of death, the latest occasion of the health examination, or the date of

the diagnosis of type 1 diabetes (one participant was diagnosed as having type 1 diabetes

during follow-up).

Measurement of other risk factors Each participant completed a self-administered

questionnaire covering: medical history; use of medications for hypertension, diabetes, and dyslipidaemia; alcohol intake; smoking habits; and regular exercise during leisure time. Diabetes in first-degree relatives was considered as a present family history of diabetes. Alcohol intake and smoking habits were classified as either current use or not. Daily amounts of alcohol (g/day) were estimated according to the frequency of habitual alcohol intake per week or month, and the kinds and amounts of alcoholic beverages customarily consumed, and were classified into three categories: no (0 g/day), moderate (1–33 g/day), and heavy (over 34 g/day) alcohol intake. Participants engaging in sports or other forms of exertion at least three times per week during their leisure time were defined as the regular exercise group. BP was measured three times using a standard automated sphygmomanometer in the sitting position after at least 5 min of rest. The mean of these three measurements was used in the analysis. Hypertension was defined as BP $\geq$140/90 mmHg, and/or use of antihypertensive agents. The height and weight of each participant, wearing light clothes without shoes, were measured and BMI (kg/m^2) was calculated. Obesity was defined as a BMI level $\geq$25.0 kg/m^2. According to the obesity classifications of the Japan Society for the Study of Obesity, participants were also categorised into the following three groups: BMI <18.5, 18.5–24.9, and $\geq$25.0 kg/m^2 [30]. Serum levels of total cholesterol, HDL-cholesterol and triacylglycerols were measured

enzymatically.

Statistical analysis Mean values and frequencies of potential risk factors for diabetes were estimated and compared between the normal group and the groups with IBF, insulin resistance, or both IBF and insulin resistance by using the generalised linear model, respectively. The insulinogenic index, HOMA-IR, insulinogenic index/HOMA-IR, and serum triacylglycerols were presented as median values and their IQRs. The incidence rates of type 2 diabetes were estimated using the person-years method. Cox's proportional hazards model was used to estimate the HRs with 95% CIs for the incidence of diabetes in the groups with IBF, insulin resistance, or both IBF and insulin resistance. Adjustments were made for age, sex, BMI categories, family history of diabetes, serum total cholesterol, serum HDL-cholesterol, log-transformed serum triacylglycerols, use of lipid-lowering medication, hypertension, smoking habits, alcohol consumption, and regular exercise. The interaction of IBF and insulin resistance was tested by using the relevant Cox model including the multiplicative interaction term. In the subgroup analyses, the participants were divided by obesity (BMI <25.0 or ≥25.0 kg/m^2) and the status of glucose intolerance at baseline (normal glucose tolerance and prediabetes). The heterogeneities between subgroups were tested by adding a multiplicative interaction term of the status

of IBF or insulin resistance with the indicator of the group to the relevant model. The population attributable fraction (PAF) for diabetes due to the status of IBF and insulin resistance at baseline was calculated using the formula PAF = PD (HR − 1)/HR, where PD denotes the proportion of total cases in the population arising from the cases exposed to a risk factor [31] and the multivariable-adjusted HR of each group compared with the normal group without either IBF or insulin resistance. The 95% CIs of the PAF were estimated by the method proposed by Greenland [32]. In addition, the risk of the development of type 2 diabetes according to the quartiles of indices of insulin secretion, insulin resistance and beta cell function were evaluated. Two-sided values of $p<0.05$ were considered to indicate statistical significance in all analyses. Statistical analyses were conducted using Statistical Analysis Software (SAS) version 9.4 (SAS Institute, Cary, NC, USA).

Results

The mean age of the total participants was 60.0 years, 42.0% were male, and the mean BMI was 23.0 kg/m^2. The median value (IQR) of the insulinogenic index, HOMA-IR, and insulinogenic index/HOMA-IR were 82.4 (49.3–147.1), 1.27 (0.88–1.88), and 63.4 (36.4-118.1), respectively. According to the baseline status of IBF and insulin

resistance, there were 1277 normal participants (61.0%), 114 participants (5.4%) with

isolated IBF, 504 (24.1%) with isolated insulin resistance, and 199 (9.5%) with both IBF

and insulin resistance (Table 1). Participants with isolated IBF were the oldest and more

likely to be male. They also had the highest frequencies of smoking habits and alcohol

intake across the four categories. Participants with isolated insulin resistance had higher

BMI and the highest frequencies of use of lipid-lowering medication. In this group, the

insulinogenic index was highest, but the disposition index was lower than in the normal

group. The participants with both IBF and insulin resistance had the highest median

values of serum triacylglycerols and the highest frequency of family history of diabetes,

prediabetes, obesity and hypertension. HOMA-IR was the highest in this group. In

addition, they had the lowest disposition index, comparable to that in the participants with

isolated IBF.

During the follow-up, 272 (13.0%) participants developed diabetes. The age- and

sex-adjusted HRs of developing diabetes increased significantly in the groups with

isolated IBF (HR 6.89, 95% CI 4.73, 10.05, $p<0.001$), isolated insulin resistance (HR 2.11,

95% CI 1.51, 2.95, $p<0.001$), and both IBF and insulin resistance (HR 9.87, 95% CI 7.27,

13.41, $p<0.001$) compared with those with normal glucose tolerance (Table 2). This

association remained unchanged after adjustment for age, sex, BMI categories, family

history of diabetes, serum total cholesterol, serum HDL-cholesterol, log-transformed

serum triacylglycerols, lipid-lowering medication, hypertension, smoking habits, alcohol

consumption and regular exercise. Consequently, the contribution to the estimated

proportion of cases was the highest in individuals with both IBF and insulin resistance

(PAF 29.3%, 95% CI 23.0, 35.1%), followed in order by those with isolated IBF (PAF

13.3%, 95% CI 8.7, 17.7%), and those with isolated insulin resistance (PAF 10.5%, 95%

CI 4.0, 16.6%) (Fig. 1).

In both subgroups of BMI levels <25.0 and ≥25.0 kg/m^2, the multivariable-

adjusted HRs for the development of type 2 diabetes were the highest for the participants

with both IBF and insulin resistance, followed in order by those with isolated IBF, those

with isolated insulin resistance, and those with normal beta cell function and normal

insulin resistance (Table 2). In the subgroup of BMI <25.0 kg/m^2, the HRs (95% CIs) for

the development of type 2 diabetes were 7.91 (5.10, 12.27) in participants with both IBF

and insulin resistance; 6.53 (4.28, 9.96) in those with isolated IBF; and 1.84 (1.17, 2.89)

in those with isolated insulin resistance. In the subgroup of BMI ≥25.0 kg/m^2, the

corresponding values were 9.28 (4.36, 19.77), 7.29 (2.78, 19.10), and 2.26 (1.03, 4.95),

respectively. The PAFs of both IBF and insulin resistance and that of isolated IBF were

equally high in the subgroup with BMI <25.0 kg/m^2, while the PAF of both IBF and

insulin resistance was highest, followed by that of isolated insulin resistance, in the subgroup with BMI ≥25.0 kg/m^2 (Fig. 1).

Next, we estimated the difference in the contributions of IBF and insulin resistance status to the development of type 2 diabetes between subgroups of participants with normal glucose tolerance and prediabetes (Table 3). The contributions of isolated IBF, isolated insulin resistance, and both IBF and insulin resistance were similar in the participants with normal glucose tolerance, while in those with prediabetes, the PAF of both IBF and insulin resistance was the highest.

In the sensitivity analyses, the contributions of IBF and insulin resistance to the incidence of type 2 diabetes using an alternative index for beta cell function (InsAUC/GluAUC×Matsuda index) and insulin resistance (Matsuda index) (ESM Table 2) were similar to those using insulinogenic index/HOMA-IR and HOMA-IR (Table 2 and 3). We also investigated the associations between the risk of type 2 diabetes and each of the following: the index of insulin secretion, insulin resistance, and the disposition index. As a consequence, all indices were linearly associated with the development of type 2 diabetes (ESM Table 3).

Discussion

The present study demonstrated that the presence of IBF estimated by the disposition index, insulin resistance, or both IBF and insulin resistance were associated with increased risk of the development of type 2 diabetes, and approximately 30% of incident type 2 diabetes in a general Japanese population was attributable to the combination of IBF and insulin resistance, which made the strongest contribution to the development of type 2 diabetes. The PAF of isolated IBF and that of both IBF and insulin resistance for incident type 2 diabetes were similar at approximately 17% in participants without obesity, while approximately half of incident type 2 diabetes was attributable to both IBF and insulin resistance in those with obesity. In addition, the contributions of isolated IBF, isolated insulin resistance, and both IBF and insulin resistance on incident type 2 diabetes were similar in the participants with normal glucose tolerance, but the combination of IBF and insulin resistance made the strongest contribution in the prediabetic participants. Our findings suggest that the clinical importance of the management of insulin resistance, in addition to IBF, should receive more attention, in light of the recent obesity epidemic [17], for reducing the burden of type 2 diabetes in the Japanese population.

It has been reported that IBF has a great impact on the development of diabetes in Asian people [33], but this is still an area of controversy. A systematic review and

meta-analysis of studies showed that Asian people have lower insulin secretion and lower insulin resistance than African people and white people [7]. Several cross-sectional studies suggested that impaired insulin secretion is the main cause of deteriorating glucose tolerance in Asian populations [34–37]. However, a recent clinical study reported that Asian people had lower insulin secretion and higher insulin sensitivity than white people, but the significant differences disappeared after adjusting for BMI, and the disposition index in both groups was comparable [8]. Insulin resistance upregulates insulin secretion, and insulin secretory capacity may appear normal in individuals with IBF [16]. On the other hand, even if beta cell function is normal, it may appear that there is impaired insulin secretion due to low insulin resistance. Therefore, it may be reasonable to suppose that beta cell function should be estimated by the disposition index, which considers both measures of insulin secretion and insulin resistance.

Several population-based studies have reported the magnitude of the contribution of impaired insulin secretion and insulin resistance [13, 14, 38]. Two prospective studies conducted in Asian populations, the Korean Genome and Epidemiology Study [13] and the Saku Study [14], reported that impaired insulin secretion made an approximately threefold greater contribution to the development of

type 2 diabetes than insulin resistance. In contrast, the China Cardiometabolic Disease

and Cancer Cohort (4C) Study of 95,000 people in China reported that the contribution

of insulin resistance was greater than that of impaired insulin secretion [38]. In the

present study, however, isolated IBF estimated by the disposition index and isolated

insulin resistance made comparable contributions, and the contribution of both IBF and

insulin resistance was pronouncedly higher. The exact reason for these discrepancies in

findings is unclear, but it might be related to differences in the characteristics of

participants. Individuals with normal glucose tolerance were enrolled in the Korean

Genome and Epidemiology Study [13], and participants in the Saku Study may have

been more health-conscious [14], since they participated in a hospital-based medical

checkup of their own accord, while approximately 40% of participants in the 4C study

were obese [38]. Moreover, the discrepancy may be in part attributable to the difference

in the methods used to evaluate IBF, i.e., the index of insulin secretion in the previous

studies vs the disposition index in the present study. Because the index of insulin

secretion is affected by the extent of insulin resistance (e.g., the impact of impaired

insulin secretion is likely to be underestimated in obese populations due to the

compensatory secretion), the disposition index is thought to be more suitable for

evaluating beta cell function to determine the contributions of impaired insulin secretion

and insulin resistance. Our findings should be validated in a similar manner among other Asian populations.

The findings of the present study are important in terms of preventing the development of diabetes in Japanese individuals, in consideration of the pathophysiological changes in the general Japanese population. Our results revealed that the combination of IBF and insulin resistance made the greatest contribution to the process of incident diabetes, and that this effect was more prominent in obese individuals, possibly suggesting that the management of both insulin resistance and IBF has become increasingly important with the rising burden of obesity in Asian populations [9, 15]. The ADA guidelines recommend a diabetes prevention programme that emphasises weight reduction and moderate physical activity [39]. In clear agreement with this recommendation, several randomised controlled trials for Asians with impaired glucose tolerance have shown that lifestyle intervention including exercise and diet modifications significantly reduced the incidence of diabetes [40]. Intriguingly, the present study showed that IBF and both IBF and insulin resistance contributed to the same extent in the development of diabetes in non-obese individuals. Visceral fat, ectopic fat, muscle loss and a low-grade inflammation are generally considered to be involved in the development of type 2 diabetes through increased

insulin resistance in non-obese individuals, especially in individuals with IBF [41-44].

Moreover, in the present study the PAFs of isolated IBF, isolated insulin resistance, and

both IBF and insulin resistance for the onset of diabetes were similar in participants

with normal glucose tolerance, while the PAF of the combination of IBF and insulin

resistance was highest in participants with prediabetes. In this study, we could not assess

whether IBF was due to genetic predisposition or decompensation for insulin resistance,

but the Korean Genome and Epidemiology Study showed that insulin resistance

worsened in the participants who developed diabetes during the follow-up period, and

those with genetically low beta cell function could not compensate for worsened insulin

resistance [13]. These findings suggest that insulin resistance plays as important a role

in the mechanism of deteriorated glucose tolerance as IBF. Therefore, a public health

approach to improving insulin resistance at an earlier stage of glucose intolerance is

required to reduce the diabetic risk.

The strengths of the present study include its prospective population-based

design, long-term duration of follow-up, high rate of participation and follow-up, and

precise diagnosis of type 2 diabetes by including 75g OGTT. Limitations of the present

study should also be noted. The assessment of IBF and insulin resistance at baseline was

based on a single measurement of plasma glucose and serum insulin concentration.

During the follow-up, the levels of these risk factors could have been changed due to modifications of lifestyle, and thus misclassification of the status of IBF or insulin resistance was possible. This limitation might weaken the association observed in the current study, biasing the results toward the null hypothesis. Second, data on quantitative assessment of leisure physical activity were not available. Finally, the generalisability of our findings to other ethnic Asian populations may be limited, since we specifically considered glucose tolerance in a Japanese community. Studies in patients with different genetic and glucose tolerance backgrounds will be needed to confirm the applicability of our results to other populations.

In conclusion, the present study suggests that insulin resistance, in addition to IBF, contributed strongly to the development of type 2 diabetes in a Japanese population. It is reasonable to expect that the approach to improving insulin resistance will become increasingly crucial for reducing the burden of diabetes in future Asian populations.

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Table 1 Baseline characteristics of the study participants according to the status of IBF and insulin resistance

Variable	Overall	Status of IBF and IR[a]			
		Normal	Isolated IBF	Isolated IR	Both IBF and IR
	(n=2094)	(n=1277)	(n=114)	(n=504)	(n=199)
Age, years	60.0 (10.3)	59.7 (10.6)	62.9 (9.2)*	60.3 (9.8)	59.4 (9.7)
Men, n (%)	880 (42.0)	505 (39.6)	73 (64.0)*	193 (38.3)	109 (54.8)*
Family history of diabetes, n (%)	331 (15.8)	190 (14.9)	18 (15.8)	81 (16.1)	42 (21.1)*
Prediabetes, n (%)	639 (30.5)	227 (17.8)	72 (63.2)*	186 (36.9)*	154 (77.4)*
FPG, mmol/l	5.46 (0.51)	5.29 (0.43)	5.84 (0.46)*	5.58 (0.43)*	6.06 (0.48)*
30 min postload glucose, mmol/l	8.85 (1.79)	8.42 (1.65)	10.64 (2.10)*	8.82 (1.48)*	10.63 (1.46)*
2hPG, mmol/l	6.76 (1.57)	6.36 (1.43)	7.61 (1.87)*	7.03 (1.38)*	8.10 (1.62)*
Insulinogenic index, pmol/mmol	82.4 (49.3–147.1)	81.3 (49.8–136.2)	23.5 (15.5–28.5)*	134.9 (88.1–208.3)*	49.4 (38.3–66.9)*
HOMA-IR	1.27 (0.88–1.88)	0.99 (0.73–1.25)	1.20 (0.92–1.37)*	2.11 (1.83–2.55)*	2.52 (1.98–3.29)*
Disposition index (insulinogenic index/HOMA-IR)	63.4 (36.4-118.1)	85.6 (52.4-153.2)	20.7 (16.7-23.6)*	56.0 (39.0-92.8)*	20.6 (15.9-24.4)*
BMI, kg/m^2	23.0 (3.2)	21.8 (2.6)	22.8 (2.8)*	24.8 (3.0)*	25.8 (3.4)*
Obesity, n (%)	500 (23.9)	141 (11.0)	25 (21.9)*	218 (43.3)*	116 (58.3)*
Serum total cholesterol, mmol/l	5.46 (0.94)	5.43 (0.92)	5.31 (0.97)	5.56 (0.99)*	5.52 (0.94)
Serum HDL-cholesterol, mmol/l	1.76 (0.46)	1.86 (0.47)	1.68 (0.41)*	1.60 (0.40)*	1.52 (0.37)*
Serum triacylglycerols, mmol/l	1.11 (0.81–1.58)	0.99 (0.73–1.40)	1.06 (0.79–1.59)*	1.32 (0.99–1.85)*	1.48 (1.03–2.16)*
Lipid-lowering medication, n (%)	252 (12.0)	119 (9.3)	9 (7.9)	94 (18.7)*	30 (15.1)*
Hypertension, n (%)[b]	876 (41.8)	420 (32.9)	64 (56.1)*	268 (53.2)*	124 (62.3)*
Smoking habits, n (%)	432 (20.6)	270 (21.1)	36 (31.6)*	76 (15.1)*	50 (25.1)

Daily amounts of alcohol, g/day	0.7 (0.0–16.4)	0.8 (0.0–17.9)	8.6 (0.0–35.7)*	0.0 (0.0–9.5)*	1.3 (0.0–29.2)*
Alcohol consumption, n (%)					
No (0 g/day)	1010 (48.2)	614 (48.1)	42 (36.8)	259 (51.4)	95 (47.7)
Moderate (1–33 g/day)	781 (37.3)	478 (37.4)	39 (34.2)	202 (40.1)	62 (31.2)
Heavy (over 34 g/day)	303 (14.5)	185 (14.5)	33 (29.0)	43 (8.5)	42 (21.1)
Regular exercise, n (%)	265 (12.7)	164 (12.8)	9 (7.9)	63 (12.5)	29 (14.6)
Number of health examinations received during follow-up	5.39 (2.09)	5.46 (2.04)	5.46 (2.08)	5.32 (2.17)	5.10 (2.17)*

Insulinogenic index, HOMA-IR, disposition index (insulinogenic index/HOMA-IR), serum triacylglycerols and daily amounts of alcohol are shown as the median (IQR) due to the skewed distribution. All other values are given as mean (SD) or n (%)

Conversion factors for units were as follows: plasma glucose in mg/dl to mmol/l, × 0.0555; serum insulin in μU/ml to pmol/l, × 6.945; serum cholesterol (total and HDL) in mg/dl to mmol/l, × 0.0259; serum triacylglycerols in mg/dl to mmol/l, × 0.0113

[a] The status of IBF and IR were defined as IBF (−) and IR (−) for normal, IBF (+) and IR (−) for isolated IBF, IBF (−) and IR (+) for isolated IR, and IBF (+) and IR (+) for both IBF and IR, where IBF (+) and IR (+) were defined as disposition index (insulinogenic index/HOMA-IR) ≤28.5 and HOMA-IR ≥1.61, respectively

[b] Hypertension was defined as BP ≥140/90 mmHg, and/or use of anti-hypertensive agents

*$p<0.05$ vs normal

IR, insulin resistance

Table 2 Risk of the development of type 2 diabetes according to the status of IBF and insulin resistance in the overall population and in the subgroups according to BMI

Variable	Status of IBF and IR[a]				*p* for interaction[b]
	Normal	Isolated IBF	Isolated IR	Both IBF and IR	
Overall					
No. of events/PYs at risk	77/7955	43/576	61/3026	91/979	
Crude incidence (per 100 PYs)	0.97	7.46	2.02	9.30	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	6.89 (4.73, 10.05)**	2.11 (1.51, 2.95)**	9.87 (7.27, 13.41)**	0.13
Multivariable-adjusted[c]	1.00 (reference)	6.30 (4.30, 9.23)**	1.88 (1.30, 2.70)**	8.03 (5.66, 11.38)**	0.13
PAF (95% CI), %	–	13.3 (8.7, 17.7)	10.5 (4.0, 16.6)	29.3 (23.0, 35.1)	
BMI <25.0 kg/m^2					
No. of events/PYs at risk	69/7081	34/448	30/1721	34/420	
Crude incidence (per 100 PYs)	0.97	7.59	1.74	8.10	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	6.87 (4.54, 10.41)**	1.86 (1.21, 2.85)**	8.97 (5.93, 13.59)**	0.28
Multivariable-adjusted[c]	1.00 (reference)	6.53 (4.28, 9.96)**	1.84 (1.17, 2.89)**	7.91 (5.10, 12.27)**	0.21
PAF (95% CI), %	–	17.2 (10.6, 23.4)	8.2 (1.1, 14.8)	17.8 (11.2, 23.9)	
BMI ≥25.0 kg/m^2					
No. of events/PYs at risk	8/875	9/129	31/1305	57/559	
Crude incidence (per 100 PYs)	0.91	7.00	2.38	10.20	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	7.30 (2.80, 19.06)**	2.67 (1.23, 5.81)*	11.65 (5.53, 24.52)**	0.34
Multivariable-adjusted[c]	1.00 (reference)	7.29 (2.78, 19.10)**	2.26 (1.03, 4.95)*	9.28 (4.36, 19.77)**	0.29
PAF (95% CI), %	–	7.4 (1.7, 12.7)	16.5 (1.8, 28.9)	48.4 (35.7, 58.7)	

a The status of IBF and IR were defined as IBF (−) and IR (−) for normal, IBF (+) and IR (−) for isolated IBF, IBF (−) and IR (+) for isolated IR, and IBF (+) and IR (+) for both IBF and IR, where IBF (+) and IR (+) were defined as disposition index (insulinogenic index/HOMA-IR) $\leq$28.5 and HOMA-IR $\geq$1.61, respectively

b p for interaction was tested using relevant Cox model including isolated IBF, isolated IR and their multiplicative interaction term

c Adjusted for age, sex, BMI (<18.5, 18.5–24.9, $\geq$25.0 kg/m^2), family history of diabetes, hypertension, serum total cholesterol, serum HDL-cholesterol, serum triacylglycerols (log-transformed), use of lipid-lowering medication, current smoking, alcohol consumption and regular exercise in the overall analysis. BMI was excluded in the subgroup analysis of BMI

* p<0.01, ** p<0.001 vs reference

IR, insulin resistance; PYs, person-years

Table 3 Risk of the development of type 2 diabetes according to the status of IBF and insulin resistance among individuals with and without prediabetes

Variable	Status of IBF and IR[a]				*p* for interaction[b]
	Normal	Isolated IBF	Isolated IR	Both IBF and IR	
Normal glucose tolerance					
No. of events/PYs at risk	27/6716	10/240	17/1986	9/249	
Crude incidence (per 100 PYs)	0.40	4.17	0.86	3.62	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	9.57 (4.59, 19.96)**	2.18 (1.19, 4.01)*	9.71 (4.55, 20.72)**	0.17
Multivariable-adjusted[c]	1.00 (reference)	9.40 (4.39, 20.14)**	2.31 (1.18, 4.53)*	10.52 (4.62, 23.93)**	0.21
PAF (95% CI), %	-	14.2 (4.4, 22.9)	15.3 (0.7, 27.7)	12.9 (3.7, 21.3)	
Prediabetes					
No. of events/PYs at risk	50/1239	33/336	44/1039	82/730	
Crude incidence (per 100 PYs)	4.03	9.81	4.23	11.23	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	2.33 (1.50, 3.63)**	1.09 (0.72, 1.63)	2.88 (2.01, 4.13)**	0.66
Multivariable-adjusted[c]	1.00 (reference)	2.15 (1.37, 3.38)**	1.00 (0.65, 1.55)	2.51 (1.68, 3.76)**	0.62
PAF (95% CI), %	-	8.4 (2.6, 14.0)	0.0 (−9.5, 8.7)	23.6 (13.5, 32.5)	

[a] The status of IBF and IR were defined as IBF (−) and IR (−) for normal, IBF (+) and IR (−) for isolated IBF, IBF (−) and IR (+) for isolated IR, and IBF (+) and IR (+) for both IBF and IR, where IBF (+) and IR (+) were defined as disposition index (insulinogenic index/HOMA-IR) ≤ 28.5 and HOMA-IR ≥ 1.61, respectively

[b] *p* for interaction was tested using the relevant Cox model including isolated IBF, isolated IR and their multiplicative interaction term

[c] Adjusted for age, sex, BMI (<18.5, 18.5–24.9, ≥ 25.0 kg/m^2), family history of diabetes, hypertension, serum total cholesterol, serum HDL-cholesterol, serum triacylglycerols (log-transformed), use of lipid-lowering medication, current smoking, alcohol consumption and regular exercise in the overall analysis.

* *p*<0.01, ** *p*<0.001 vs reference

IR, insulin resistance; PYs, person-years

Figure legends

Fig. 1 PAFs for the development of type 2 diabetes according to baseline IBF and insulin resistance status in the overall population (**a**) or in subgroups stratified by BMI levels (**b**). The PAFs for diabetes were calculated using the proportion of total cases in the population arising from the cases exposed to a risk factor and the multivariable-adjusted HRs of each group compared with the group without IBF and insulin resistance, where the HRs were adjusted for age, sex, BMI (<18.5, 18.5–24.9, ≥25.0 kg/m^2), family history of diabetes, hypertension, serum total cholesterol, serum HDL-cholesterol, serum triacylglycerols (log-transformed), use of lipid-lowering medication, current smoking, alcohol consumption and regular exercise in the overall analysis. BMI was excluded in the subgroup analysis of BMI. The status of IBF and insulin resistance were defined as IBF (−) and IR (−) for normal, IBF (+) and IR (−) for isolated IBF, IBF (−) and IR (+) for isolated IR, and IBF (+) and IR (+) for both IBF and IR, where IBF (+) and IR (+) were defined as disposition index (insulinogenic index/HOMA-IR) ≤28.5 and HOMA-IR ≥1.61, respectively.

IR, insulin resistance

a

Population attributable fraction (%)

Isolated IBF	Isolated IR	Both IBF and IR
n 114	504	199

Overall

b

Population attributable fraction (%)

Isolated IBF	Isolated IR	Both IBF and IR	Isolated IBF	Isolated IR	Both IBF and IR
n 89	286	83	25	218	116

BMI<25.0 kg/m^2 BMI≥25.0 kg/m^2
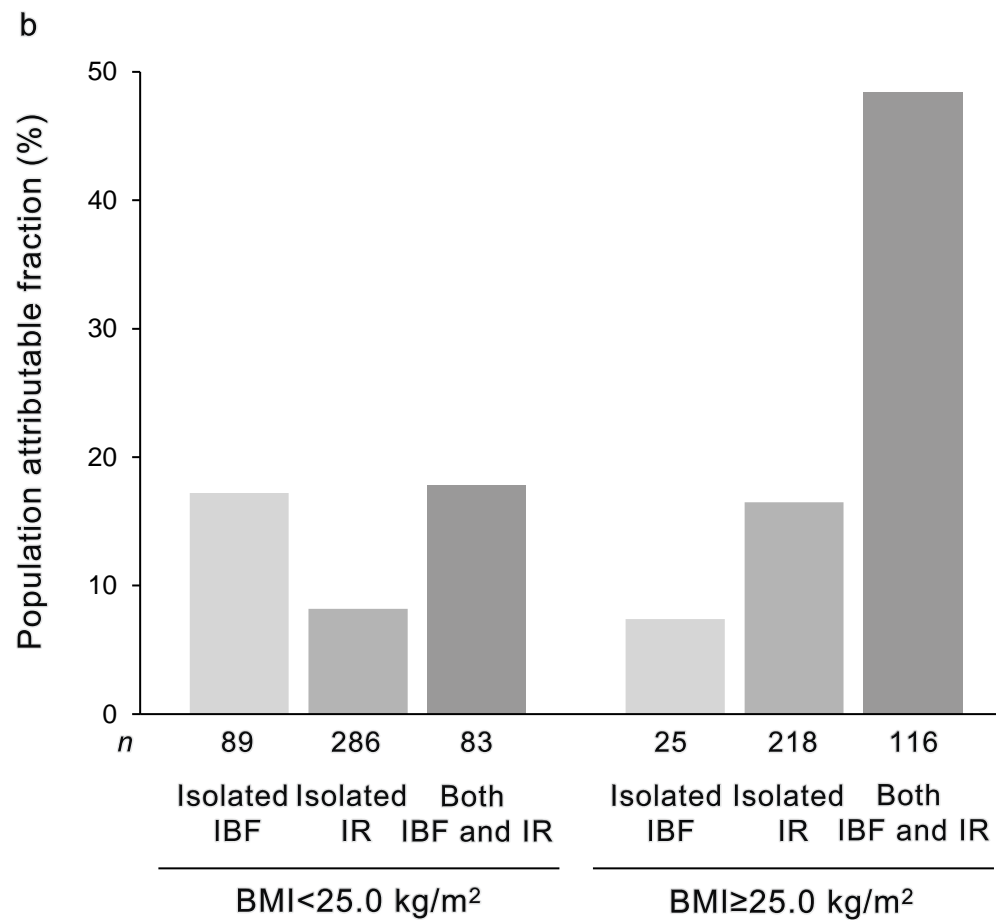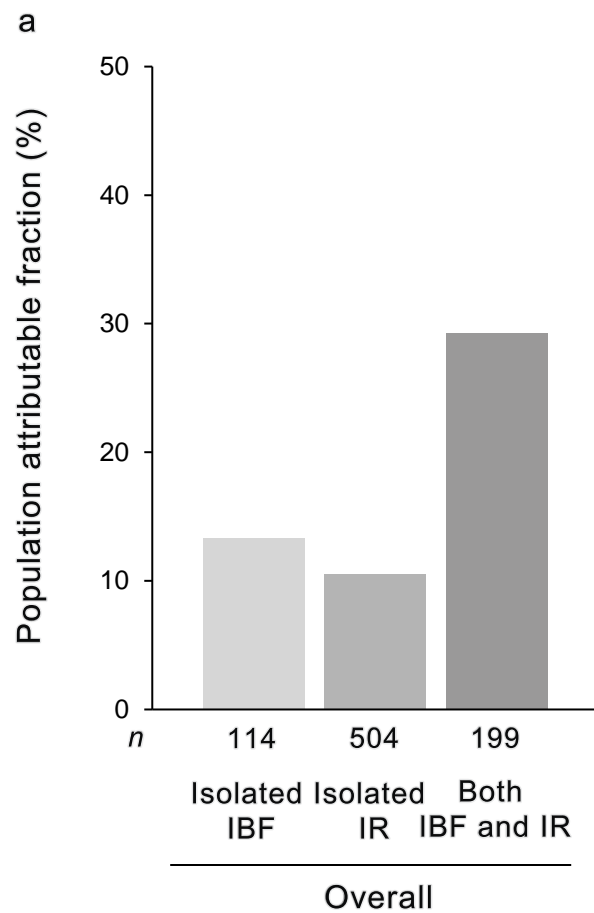
Electronic supplementary material (ESM)

Comparison of the contributions of impaired beta-cell function and insulin resistance to the development of type 2 diabetes in a Japanese community: the Hisayama Study

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Daigo Yoshida, Naoko Mukai, Udai Nakamura, Takanari Kitazono, Toshiharu Ninomiya

ESM Table 1 Cut-off criterion, sensitivity, specificity, and Youden's index of each index of beta cell function or insulin resistance

Index	Cut-off value[a]	Sensitivity, %	Specificity, %	Youden's index, %
Disposition index (insulinogenic index/HOMA-IR)	28.5	85.09	88.24	73.33
Disposition index (InsAUC/GluAUC×Matsuda index)	342.0	90.05	91.60	81.64
Matsuda index	12.9	67.39	63.87	31.25

[a] The cut-off values of the disposition index and Matsuda index were determined as the point maximizing the Youden index [=max (sensitivity + specificity − 1)] on the receiver operating characteristic curve that optimizes the discriminatory ability for the risk of incident diabetes

ESM Table 2 The sensitivity analyses for the risk of the development of type 2 diabetes according to the status of IBF defined by InsAUC/GluAUC×Matsuda index and insulin resistance defined by the Matsuda index

	Status of IBF and IR[a]				p for interaction[b]
	Normal (n=1316)	Isolated IBF (n=96)	Isolated IR (n=572)	Both IBF and IR (n=110)	
Disposition index (InsAUC/GluAUC×Matsuda index)	596.5 (480.1, 751.2)	302.7 (281.9, 323.0)	508.2 (433.8, 636.4)	305.7 (279.0, 323.3)	
InsAUC/GluAUC	28.5 (22.2, 37.2)	16.9 (12.1, 20.2)	57.2 (45.1, 74.2)	35.5 (29.9, 44.3)	
Matsuda index	20.8 (16.4, 27.3)	18.0 (14.8, 24.2)	9.6 (7.7, 11.3)	8.2 (6.4, 10.0)	
Risk of diabetes					
Overall					
No. of events/PYs at risk	79/8186	51/412	77/3457	65/481	
Crude incidence (per 100 PYs)	0.97	12.38	2.23	13.52	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	11.73 (8.19, 16.80)**	2.25 (1.64, 3.08)**	14.76 (10.59, 20.59)**	0.02
Multivariable-adjusted[c]	1.00 (reference)	10.36 (7.15-15.01)**	2.00 (1.42, 2.80)**	11.91 (8.20, 17.31)**	0.03
PAF (95% CI), %	-	16.9 (12.0, 21.6)	14.2 (6.8, 20.9)	21.9 (16.5, 26.9)	
Body mass index <25.0 kg/m²					
No. of events/PYs at risk	69/7167	37/297	41/2035	20/171	
Crude incidence (per 100 PYs)	0.96	12.45	2.02	11.72	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	11.08 (7.33, 16.75)**	2.02 (1.37, 2.98)**	12.90 (7.79, 21.35)**	0.11
Multivariable-adjusted[c]	1.00 (reference)	10.48 (6.82, 16.09)**	2.02 (1.35, 3.04)**	10.78 (6.39, 18.19)**	0.06
PAF (95% CI), %	-	20.0 (13.3, 26.3)	12.4 (4.1, 20.0)	10.9 (5.7, 15.7)	
Body mass index ≥25.0 kg/m²					
No. of events/PYs at risk	10/1019	14/115	36/1423	45/310	

Crude incidence (per 100 PYs)	0.98	12.19	2.53	14.51	
HRs (95% CIs)					
Age- and sex-adjusted	1.00 (reference)	12.92 (5.73, 29.14)**	2.63 (1.31, 5.31)**	16.00 (8.01, 31.96)**	0.11
Multivariable-adjusted[c]	1.00 (reference)	11.10 (4.87, 25.28)**	2.25 (1.10, 4.58)*	13.11 (6.43, 26.73)**	0.18
PAF (95% CI), %	-	12.1 (5.2, 18.5)	19.0 (3.4, 32.2)	39.6 (28.5, 49.0)	
Normal glucose tolerance					
No. of events/PYs at risk	36/6943	5/83	19/2112	3/52	
Crude incidence (per 100 PYs)	0.52	6.01	0.90	5.79	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	10.26 (3.98, 26.44)**	1.68 (0.97, 2.94)	12.38 (3.75, 40.81)**	0.67
Multivariable-adjusted[c]	1.00 (reference)	11.03 (4.08, 29.85)**	1.58 (0.86, 2.91)	11.05 (3.16, 38.58)**	0.59
PAF (95% CI), %	-	7.2 (0.2, 13.7)	11.1 (−5.8, 25.3)	4.3 (−1.1, 9.5)	
Prediabetes					
No. of events/PYs at risk	43/1242	46/329	58/1345	62/429	
Crude incidence (per 100 PYs)	3.46	13.99	4.31	14.45	
HRs (95% CI)					
Age- and sex-adjusted	1.00 (reference)	3.98 (2.62, 6.06)**	1.28 (0.86, 1.90)	4.54 (3.05, 6.74)**	0.68
Multivariable-adjusted[c]	1.00 (reference)	3.70 (2.40, 5.68)**	1.22 (0.81, 1.85)	4.16 (2.68, 6.46)**	0.78
PAF (95% CI), %	-	16.1 (9.6, 22.1)	5.0 (−5.8, 14.7)	22.5 (15.0, 29.4)	

[a] The status of IBF and IR were defined as IBF (−) and IR (−) for normal, IBF (+) and IR (−) for isolated IBF, IBF (−) and IR (+) for isolated IR, and IBF (+) and IR (+) for both IBF and IR, where IBF (+) and IR (+) were defined as disposition index (InsAUC/GluAUC×Matsuda index) ≤ 342.0 and Matsuda index ≤ 12.9, respectively

[b] p for interaction was tested by using the relevant Cox model including isolated IBF, isolated IR and their multiplicative interaction term

[c] Adjusted for age, sex, body mass index (<18.5, 18.5–24.9, ≥ 25.0 kg/m^2), family history of diabetes, hypertension, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides (log-transformed), use of lipid-lowering medication, current smoking, alcohol consumption and regular exercise. Body mass index was excluded in the subgroup analysis of body mass index

*$p<0.01$, **$p<0.001$ vs. reference

IR, insulin resistance; PYs, person-years

ESM Table 3 The risk of the development of type 2 diabetes according to the levels of insulin secretion, insulin resistance, and beta cell function index

The level of each parameter	No. of events/ PYs at risk	Crude incidence (per 100 PYs)	Age- and sex-adjusted		Multivariable-adjusted[c]	
			HRs (95% CI)	*p* for trend	HRs (95% CI)	*p* for trend
Insulinogenic index, pmol/mmoL[a]						
≤50.0	134/2991	4.48	5.40 (3.48, 8.37)**		6.12 (3.93, 9.54)**	
50.1–83.1	72/3081	2.34	2.97 (1.87, 4.73)**	<0.001	3.08 (1.93, 4.91)**	<0.001
83.2–147.8	42/3188	1.32	1.72 (1.04, 2.85)*		1.76 (1.07, 2.92)*	
≥147.9	24/3277	0.73	1.00 (reference)		1.00 (reference)	
InsAUC/GluAUC[b]						
≤23.8	98/2996	3.27	1.45 (1.06, 1.99)*		2.21 (1.57, 3.12)*	
23.9–33.8	58/3155	1.84	0.90 (0.63, 1.28)	0.01	1.22 (0.85, 1.75)	<0.001
33.9–48.1	51/3199	1.59	0.80 (0.56, 1.16)		0.89 (0.61, 1.28)	
≥48.2	65/3185	2.04	1.00 (reference)		1.00 (reference)	
HOMA-IR[a]						
≤0.83	32/2833	1.13	1.00 (reference)		1.00 (reference)	
0.84–1.18	40/2858	1.40	1.30 (0.81, 2.06)	<0.001	1.22 (0.77, 1.96)	<0.001
1.19–1.60	48/2841	1.69	1.53 (0.98, 2.40)		1.35 (0.85, 2.14)	
≥1.61	152/4005	3.80	3.51 (2.40, 5.14)**		2.66 (1.73, 4.09)**	
Matsuda index[b]						
≤11.2	115/2999	3.83	3.24 (2.24, 4.67)**		2.34 (1.55, 3.55)**	
11.3–16.2	74/3121	2.37	2.01 (1.36, 2.97)**	<0.001	1.71 (1.14, 2.58)*	<0.001
16.3–23.3	45/3231	1.39	1.19 (0.77, 1.84)		1.12 (0.72, 1.73)	
≥23.4	38/3185	1.19	1.00 (reference)		1.00 (reference)	
Disposition index (insulinogenic index/HOMA-IR)[b]						

≤36.3	178/2747	6.48	12.56 (7.50, 21.01)**		10.05 (5.95, 16.98)**	
36.4–63.3	54/3178	1.70	3.24 (1.85, 5.67)**	<0.001	2.91 (1.66, 5.10)**	<0.001
63.4–118.1	24/3288	0.73	1.46 (0.77, 2.74)		1.34 (0.71, 2.52)	
≥118.2	16/3322	0.48	1.00 (reference)		1.00 (reference)	

Disposition index (InsAUC/GluAUC×Matsuda index)[b]

≤430.9	182/2708	6.72	23.27 (11.87, 45.62)**		18.39 (9.30, 36.38)**	
431.0–540.7	59/3175	1.86	6.41 (3.17, 12.94)**	<0.001	5.57 (2.75, 11.29)**	<0.001
541.5–694.9	22/3309	0.66	2.35 (1.08, 5.11)*		2.13 (0.98, 4.63)	
≥695.1	9/3344	0.27	1.00 (reference)		1.00 (reference)	

[a] In the analyses, subjects without impaired insulin secretion (insulinogenic index of ≥50.1) were divided into tertiles, i.e., participants were divided into 4 categories based on their insulinogenic index: ≤50.0 pmol/mmoL (40.0 µU/mg), 50.1–83.1, 83.2–147.8, and ≥147.9. Insulin resistance was defined as HOMA-IR ≥1.61, and, similarly, subjects without insulin resistance (HOMA-IR ≤1.60) were divided by tertiles; i.e., participants were divided into 4 categories based on HOMA-IR as ≤0.83, 0.84–1.18, 1.19–1.60, and ≥1.61
[b] In the analysis, subjects were divided into 4 groups according to quartiles of InsAUC/GluAUC levels, Matsuda index, disposition index (insulinogenic index/HOMA-IR), and disposition index (InsAUC/GluAUC×Matsuda index) levels
[c] Adjusted for age, sex, body mass index (<18.5, 18.5–24.9, ≥25.0 kg/m^2), family history of diabetes, hypertension, serum total cholesterol, serum high-density lipoprotein cholesterol, serum triglycerides (log-transformed), use of lipid-lowering medication, current smoking, alcohol consumption and regular exercise
*$p<0.05$, **$p<0.01$ vs. reference
PYs, person-years