Impact of metabolic syndrome on the incidence of type 2 diabetes in middle-aged Japanese individuals with impaired insulin secretion: the Saku study

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Abstract

Aims To assess the impact of metabolic syndrome (MetS) on the incidence of type 2 diabetes in middle-aged Japanese individuals with impaired insulin secretion (IIS).

Methods This cohort study included 1,702 individuals aged 40–59 without diabetes at baseline who underwent a comprehensive medical check-up between April 2008 and March 2009 at Saku Central Hospital. Participants were classified according to their IIS and insulin resistance (IR) status [normal, isolated IR (i-IR), or isolated IIS (i-IIS)] and MetS (presence or absence). They were followed up until March 2014. Type 2 diabetes was defined based on fasting and 2-h post-load plasma glucose concentrations and by the receipt of medical treatment for diabetes.

Results During 7,572 person-years of follow-up, 92 individuals developed type 2 diabetes. The incidence rates (/1,000 person-years) for type 2 diabetes in the normal without MetS, normal with MetS, i-IR without MetS, i-IR

with MetS, i-IIS without MetS, and i-IIS with MetS groups were 5.3, 3.7, 11.3, 24.7, 16.7, and 59.5, respectively. The multivariable-adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs) for type 2 diabetes in the normal with MetS, i-IR with MetS, and i-IIS with MetS groups, relative to the normal without MetS group, were 0.52 (0.12–2.25), 3.78 (1.93–7.42), and 7.94 (3.96–15.91), respectively. Additionally, a positive association of MetS with type 2 diabetes was observed in the i-IIS group [HR (95 % CI) 3.56 (1.88–6.73)] but not in the normal and i-IR groups.

Conclusions The prevention of MetS is important, particularly in individuals with low insulin secretion.

Keywords Metabolic syndrome · Impaired insulin secretion · Type 2 diabetes · Middle age

Introduction

The prevalence of type 2 diabetes is rapidly increasing worldwide, posing a global health problem [1]. In particular, Asia is the major site of a rapidly emerging diabetes epidemic [2, 3]. Although impaired insulin secretion (IIS) and insulin resistance (IR) are the main pathophysiological components of type 2 diabetes [4, 5], the contributions of these factors are believed to differ among races. Recently, Asians have been reported to show lower insulin secretion and higher insulin sensitivity than Caucasians [6–8]. We recently reported that the population-attributable fraction (50.6 %) of type 2 diabetes onset due to isolated IIS (i-IIS) was higher than that (14.2 %) due to isolated IR (i-IR) in a Japanese population [9], whereas the reverse is true for Caucasians.

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One of the hallmarks of type 2 diabetes in Asian countries is the development of type 2 diabetes at a relatively early age, particularly in middle age [10]. In recent years, the prevalence of metabolic syndrome (MetS), a constellation of metabolic disorders, has also rapidly increased in Asians, as a result of changes in lifestyle factors such as dietary patterns and physical activity. MetS increases the risk of type 2 diabetes [11, 12], but the effect of MetS on the development of type 2 diabetes in individuals with a low reserve capacity of insulin secretion is unknown. We hypothesized that MetS has a strong influence on the development of type 2 diabetes in middle-aged individuals with a low reserve capacity of insulin secretion because of beta-cell exhaustion due to MetS. We accordingly assessed the impact of MetS on the incidence of type 2 diabetes in middle-aged Japanese individuals with IIS.

Materials and methods

Study participants

The details of this study have been described previously [9, 13, 14]. The cohort included 2,250 individuals aged 40–59 years who underwent a baseline comprehensive medical check-up over two days and one night between April 2008 and March 2009 at Saku Central Hospital. Of these, 1,989 did not have diabetes at baseline, based on the following three criteria: (1) no history of diabetes, as determined by interviews conducted by physicians; (2) fasting plasma glucose (FPG) concentration <7.0 mmol/L; and (3) 2-h post-load plasma glucose (PG) concentration <11.1 mmol/L. Among these individuals, we excluded 38 with a past or present history of cardiovascular disease, such as coronary heart disease and stroke, and 3 who had missing data. We also excluded 77 individuals with both IIS and IR because of the small sample size. Of the 1,871 remaining individuals, 1,702 (91.0 %) underwent at least one follow-up examination by the end of March 2014 and were eligible for our analysis. The study protocol was in accordance with the Declaration of Helsinki, and was approved by the Ethics Committee of Saku Central Hospital and Shiga University of Medical Science. An opt-out consent procedure was implemented.

Data collection

All participants were fasted overnight, and had a standard 75 g oral glucose tolerance test (OGTT). Blood samples were obtained at 0 (fasting), 30, 60, and 120 min, with PG measured on all four occasions and serum insulin concentrations measured at 0 and 30 min in the clinical laboratory of Saku Central Hospital. Serum insulin

concentrations were measured using a chemiluminescence enzyme immunoassay (Lumipulse Presto Insulin, Fujirebio, Tokyo, Japan). Blood glucose, high-density lipoprotein (HDL) cholesterol, and serum triacylglycerol concentrations were measured by enzymatic methods. Weight, height, waist circumference, and body fat percentage were measured in the morning in the fasting state. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Waist circumference was measured around the abdomen at the level of the navel at the late expiratory phase in the standing position with a tape measure. Body fat percentage was evaluated by the bioelectric impedance method with an automatic scale. Blood pressure (BP) was measured twice in each participant by trained nurses using an automatic sphygmomanometer with the participants in the sitting position after resting for at least 5 min, and the mean value for each participant was recorded. Each check-up also included standard questionnaires on demographic characteristics, medical history, family history and health-related habits. Smoking status was categorized as nonsmoker, ex-smoker, or current smoker. Alcohol consumption was categorized as 0 g/week, 1–139 g/week, or ≥ 140 g/week. Exercise was categorized as ≥ 2 times/week (≥ 30 min each) or <2 times/week.

Definition of IIS and IR status

Details of the definitions of IIS and IR status have been provided previously [9]. To evaluate IIS, the insulinogenic index was calculated using the formula: $\text{insulinogenic index} = (\text{insulin}_{30} [\text{pmol/L}] - \text{insulin}_0 [\text{pmol/L}]) / (\text{glucose}_{30} [\text{mmol/L}] - \text{glucose}_0 [\text{mmol/L}])$ [15]. To evaluate IR, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated by the formula: $\text{HOMA-IR} = \text{insulin}_0 (\mu\text{U/ml}) \times \text{glucose}_0 (\text{mmol/L}) / 22.5$ [16]. IIS and IR status were defined as follows: normal as insulinogenic index >51.7 pmol/mmol (40.0 $\mu\text{U/mg}$) and HOMA-IR ≤ 1.6 ; i-IR as insulinogenic index >51.7 pmol/mmol and HOMA-IR >1.6 ; and i-IIS as insulinogenic index ≤ 51.7 pmol/mmol and HOMA-IR ≤ 1.6 [9, 17, 18].

Definition of MetS

MetS was defined based on the joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity [19]. MetS was diagnosed when a participant showed three or more of the following components: (1) elevated waist circumference (≥ 90 cm for men and ≥ 80 cm for women); (2)

elevated triacylglycerol (≥ 1.7 mmol/L or drug treatment for elevated triacylglycerol); (3) reduced HDL cholesterol (< 1.0 mmol/L for men and < 1.3 mmol/L for women or drug treatment for reduced HDL cholesterol); (4) elevated BP (systolic ≥ 130 and/or diastolic ≥ 85 mmHg or antihypertensive drug treatment); and (5) elevated FPG (≥ 5.6 mmol/L).

Definition of type 2 diabetes incidence and follow-up

Type 2 diabetes was defined using the 1999 WHO criteria [20], including FPG ≥ 7.0 mmol/L and/or 2-h post-load PG ≥ 11.1 mmol/L, or receiving medical treatment for type 2 diabetes. All 1,702 participants were followed up annually at Saku Central Hospital with comprehensive medical check-ups over 2 days and one night, including the 75 g OGTT, until they developed type 2 diabetes or until March 2014. Individuals not examined during the follow-up were censored on the date of their last examination.

Statistical analysis

Participants in the study were classified into six groups according to the combination of IIS and IR status (normal, i-IR, or i-IIS) and MetS (presence or absence). To compare baseline characteristics among the six groups, an analysis of covariance with adjustments for age and sex was used for normally distributed continuous variables and a chi-squared test was used for dichotomous variables.

Cox proportional hazards regression was used to estimate the multivariable-adjusted hazard ratios (HRs) and 95 % confidence intervals (CIs) for the incidence of type 2 diabetes among the six groups. The normal without MetS group was used as the reference group in analyses. Data were adjusted for age, sex, family history of diabetes (yes or no), smoking status (nonsmoker, ex-smoker, or current smoker), alcohol consumption (0 g/week, 1–139 g/week, or ≥ 140 g/week), and exercise (≥ 2 times/week or < 2 times/week). The assumptions required for proportional hazards were met and assessed with log–log plots.

Additionally, participants were stratified into three groups: normal, i-IR, and i-IIS groups. In each group, Cox proportional hazards models were used to estimate the multivariable-adjusted HRs and 95 % CIs for the incidence of type 2 diabetes, according to presence or absence of MetS. Data were adjusted for age, sex, family history of diabetes (yes or no), smoking status (nonsmoker, ex-smoker, or current smoker), alcohol consumption (0 g/week, 1–139 g/week, or ≥ 140 g/week), and exercise (≥ 2 times/week or < 2 times/week). To test the interaction between the three groups and MetS, an interaction term was added to model. In addition, we conducted sex- and age-specific analyses.

We also conducted the same analysis using criteria for MetS defined by the Japanese Society of Internal Medicine [21].

All data were analyzed with Stata (version 14; Stata Corp LP, College Station, TX, USA) and SPSS (version 23; SPSS Japan, Tokyo, Japan) statistical software. All reported *p* values are two-tailed; those < 0.05 were considered statistically significant.

Results

At baseline, the mean age of the 1,702 participants was 52.8 years. Among them, 490 individuals (28.8 %) were classified as i-IIS. Prevalence of MetS was 20.1 % ($n = 342$). Table 1 shows the baseline characteristics according to the combination of IIS and IR status (normal, i-IR, or i-IIS) and presence or absence of MetS. Age, sex, current smoking status, alcohol consumption, BMI, and body fat differed significantly among the six groups.

The median follow-up was 5 years (total person-years 7,572), during which 92 individuals developed type 2 diabetes, including ten defined as having diabetes as they were receiving medical treatment for this disease. Table 2 shows incidence rates and multivariable-adjusted HRs for the incidence of type 2 diabetes according to the combination of IIS and IR status (normal, i-IR, or i-IIS) and presence or absence of MetS. Figure 1 shows the diabetes-free survival curves. The incidence rates (/1,000 person-years) for the development of type 2 diabetes in the normal without MetS, normal with MetS, i-IR without MetS, i-IR with MetS, i-IIS without MetS, and i-IIS with MetS groups were 5.3, 3.7, 11.3, 24.7, 16.7, and 59.5, respectively. After adjusting for age, sex, family history of diabetes, smoking status, alcohol consumption, and exercise, the multivariable-adjusted HRs (95 % CIs) for the development of type 2 diabetes in the normal with MetS, i-IR with MetS, and i-IIS with MetS groups, relative to the normal without MetS group, were 0.52 (0.12–2.25), 3.78 (1.93–7.42), and 7.94 (3.96–15.91), respectively. These results were not altered when we added BMI and body fat as covariates in a Cox proportional hazards regression.

Figure 2 shows multivariable-adjusted HRs for the incidence of type 2 diabetes in those with MetS compared with those without MetS in the normal, i-IR, and i-IIS groups. After adjusting for age, sex, family history of diabetes, smoking status, alcohol consumption, and exercise, a positive association of MetS with type 2 diabetes was observed in the i-IIS group [HR (95 % CI) 3.56 (1.88–6.73)], but not in the normal and i-IR groups [HRs (95 % CIs) 0.52 (0.08–1.65) and 1.90 (0.80–4.50), respectively] (*p* for interaction < 0.001). These results were not altered when we added BMI and body fat as

Table 1 Baseline characteristics according to the combination of IIS and IR status (normal, i-IR, or i-IIS) and presence or absence of MetS between April 2008 and March 2009

	Normal		I-IR		I-IIS		<i>p</i> value
	MetS (−)	MetS (+)	MetS (−)	MetS (+)	MetS (−)	MetS (+)	
<i>n</i>	780	119	157	156	423	67	
Insulinogenic index, pmol/mmol ^a	104.7 (73.7–162.5)	91.8 (68.5–152.5)	113.7 (82.1–171.3)	112.4 (82.7–175.1)	34.9 (24.6–45.2)	34.9 (23.3–43.9)	
HOMA-IR	0.87 (0.83–0.91)	1.15 (1.05–1.25)	2.26 (2.17–2.35)	2.47 (2.39–2.56)	0.73 (0.68–0.78)	1.02 (0.89–1.16)	
Elevated waist circumference, %	26.2	72.3	43.9	80.8	14.9	64.2	
Elevated triacylglycerol, %	9.5	78.2	22.9	70.5	8.0	79.1	
Reduced HDL cholesterol, %	5.5	62.2	11.5	51.3	5.0	50.7	
Elevated blood pressure, %	18.8	65.5	20.4	56.4	20.1	80.6	
Elevated fasting glucose, %	23.8	53.8	51.6	83.3	35.5	80.6	
Age, years	52.2 (51.8–52.5)	54.2 (53.3–55.1)	52.4 (51.6–53.2)	53.8 (53.0–54.6)	53.0 (52.5–53.5)	55.2 (53.9–56.4)	<0.001
Men, %	47.2	54.6	65.6	64.1	61.0	77.6	<0.001
Family history of diabetes, %	13.3	16.8	12.1	15.4	19.4	16.4	0.098
Current smoker, %	15.8	19.3	23.6	22.4	24.1	37.3	<0.001
Alcohol consumption (ethanol), ≥140 g/week, %	25.9	27.7	31.8	28.8	39.7	62.7	<0.001
Exercise, ≥2 times/week, %	15.6	15.1	12.7	15.4	18.7	20.9	0.451
BMI, kg/m ²	22.3 (22.1–22.5)	24.4 (24.0–24.9)	24.8 (24.4–25.1)	26.3 (25.9–26.7)	21.6 (21.4–21.9)	24.2 (23.6–24.8)	<0.001
Body fat, %	23.6 (23.3–24.0)	27.4 (26.5–28.2)	28.3 (27.6–29.1)	30.8 (30.0–31.5)	22.4 (21.9–22.8)	27.0 (25.9–28.2)	<0.001

Dichotomous data are reported as %

Normally distributed continuous data are reported as the age- and sex-adjusted mean (95 % confidence interval)

Elevated waist circumference, ≥90 cm for men and ≥80 cm for women

Elevated triacylglycerol, ≥1.7 mmol/L or drug treatment for elevated triacylglycerol

Reduced HDL cholesterol, <1.0 mmol/L for men and <1.3 mmol/L for women or drug treatment for reduced HDL cholesterol

Elevated blood pressure, systolic ≥130 and/or diastolic ≥85 mmHg or antihypertensive drug treatment

Elevated fasting glucose, ≥5.6 mmol/L

i-IR isolated insulin resistance, *i-IIS* isolated impaired insulin secretion, *MetS* metabolic syndrome, *HOMA-IR* homoeostasis model assessment of insulin resistance, *HDL* high-density lipoprotein

^a Non-normally distributed continuous data are reported as the median (25th–75th percentile)

covariates in a Cox proportional hazards regression. These results were not altered by sex-specific analysis (Fig. 2). Similar results were obtained after analyzing 1,305 individuals aged 50–59 years (Fig. 2). We did not analyze the 397 individuals aged 40–49 years because of the small number of incident cases. Similar results were observed for the analysis of 1,466 individuals with 2-h post-load PG <7.8 mmol/L. Additionally, we examined the characteristics of the 16 individuals who developed type 2 diabetes and the 51 individuals who did not develop type 2 diabetes in the i-IIS with MetS group (Table S1 in the Electronic supplementary material, ESM). Components of the MetS, BMI, and HOMA-IR did not differ significantly between the two groups, but those who developed type 2 diabetes had lower insulinogenic indices at both the

baseline and final examinations than those who did not develop diabetes.

We conducted the same analysis using the Japanese criteria for MetS (Table 3) [21]. The incidence rates (/1,000 person-years) for the development of type 2 diabetes in the normal without MetS, normal with MetS, i-IR without MetS, i-IR with MetS, i-IIS without MetS, and i-IIS with MetS groups were 4.6, 16.3, 15.7, 26.1, 19.6, and 60.2, respectively. After adjusting for age, sex, family history of diabetes, smoking status, alcohol consumption, and exercise, the multivariable-adjusted HRs (95 % CIs) for the development of type 2 diabetes in the normal with MetS, i-IR with MetS, and i-IIS with MetS groups, relative to the normal without MetS group, were 2.15 (0.62–7.50), 4.69 (1.92–11.45), and 9.45 (3.88–23.02), respectively. Additionally, a positive association of MetS with

Table 2 Incidence rates and multivariable-adjusted hazard ratios for the incidence of type 2 diabetes according to the combination of IIS and IR status (normal, i-IR, or i-IIS) and presence or absence of MetS

	Normal		I-IR		I-IIS	
	MetS (−)	MetS (+)	MetS (−)	MetS (+)	MetS (−)	MetS (+)
<i>n</i>	780	119	157	156	423	67
Person-years	3,554	539	705	649	1,856	269
Incident cases (<i>n</i>)	19	2	8	16	31	16
Incidence rate (/1000 person-years)	5.3	3.7	11.3	24.7	16.7	59.5
Hazard ratio (95 % CI)						
Model 1	1.0	0.59 (0.14–2.55)	1.91 (0.83–4.38)	3.77 (1.92–7.38)	2.79 (1.57–4.96)	8.90 (4.51–17.57)
Model 2	1.0	0.52 (0.12–2.25)	2.01 (0.87–4.61)	3.78 (1.93–7.42)	2.48 (1.39–4.43)	7.94 (3.96–15.91)

Model 1: adjusted for age and sex

Model 2: adjusted for age, sex, family history of diabetes (yes or no), smoking status (nonsmoker, ex-smoker, or current smoker), alcohol consumption (0 g/week, 1–139 g/week, or ≥ 140 g/week), and exercise (≥ 2 times/week or < 2 times/week)

i-IR isolated insulin resistance, *i-IIS* isolated impaired insulin secretion, *MetS* metabolic syndrome

Fig. 1 Diabetes-free survival curves according to the combination of IIS and IR status (normal, i-IR, or i-IIS) and presence or absence of MetS. Adjusted for age, sex, family history of diabetes (yes or no), smoking status (nonsmoker, ex-smoker, or current smoker), alcohol consumption (0 g/week, 1–139 g/week, or ≥ 140 g/week), and exercise (≥ 2 times/week or < 2 times/week). *i-IR* isolated insulin resistance, *i-IIS* isolated impaired insulin secretion, *MetS* metabolic syndrome

type 2 diabetes was observed in the i-IIS group [HR (95 % CI) 2.82 (1.24–6.42)] and not in the normal and i-IR groups [HRs (95 % CIs) 1.17 (0.31–4.38) and 2.20 (0.84–5.77), respectively]. We obtained similar results using universal criteria for MetS (cutoff points for waist circumference were 85 cm for men and 90 cm for women) (Table S2 in the ESM) [19].

Discussion

This community-based cohort study shows the risk of MetS for the incidence of type 2 diabetes in middle-aged Japanese individuals with IIS. Our main finding was that after adjusting for confounding factors, the HRs for type 2 diabetes were 3.78 in the i-IR with MetS group and 7.94 in the

i-IIS with MetS group relative to the normal without MetS group. Notably, individuals with MetS had an approximately 3.6-fold higher risk for type 2 diabetes onset than those without MetS in the i-IIS group, whereas a statistically significant association of MetS with type 2 diabetes was not observed in the normal and i-IR groups.

The combination of i-IIS and MetS increased the risk for type 2 diabetes in middle-aged Japanese individuals. Although whether i-IIS occurred before, after, or during the onset of MetS in this study is unclear, the median insulinogenic index before baseline [45.0 pmol/mmol between April 2003 and March 2004 ($n = 37$), 36.8 pmol/mmol between April 2005 and March 2006 ($n = 45$), and 34.3 pmol/mmol between April 2007 and March 2008 ($n = 46$) (data not shown)] of individuals with both i-IIS and MetS was not considerably different from that at baseline [34.9 pmol/mmol between April 2008 and March 2009 ($n = 67$)]. We inferred that individuals with both i-IIS and MetS in this study have had low insulin secretion for at least 5 years and that the present study was able to assess the impact of MetS on the incidence of type 2 diabetes in individuals with a low reserve capacity of insulin secretion. Our findings suggest that the prevention of MetS is important for the prevention of type 2 diabetes, particularly in those with a low reserve capacity of insulin secretion.

Notably, the prevalences of i-IIS in individuals aged 40–49 years and those aged 50–59 years were 23.9 % (approximately one-fourth) and 30.3 % (approximately one-third) in the present study (data not shown). We speculate that they have an increased risk for type 2 diabetes onset in the short term because 23.9 % (approximately one-fourth) of individuals with both i-IIS and MetS developed type 2 diabetes during the 5-year follow-up period. Previous studies have found that lifestyle

Fig. 2a–c Multivariable-adjusted hazard ratios for the incidence of type 2 diabetes according to presence or absence of MetS in the normal (a-1, 2, 3, and 4), i-IR (b-1, 2, 3, and 4), and i-IIS (c-1, 2, 3, and 4) groups. Adjusted for age, sex, family history of diabetes (yes or no), smoking status (nonsmoker, ex-smoker, or current smoker), alcohol consumption (0 g/week, 1–139 g/week, or ≥ 140 g/week), and exercise (≥ 2 times/week or < 2 times/week). *i-IR* isolated insulin resistance, *i-IIS* isolated impaired insulin secretion, *MetS* metabolic syndrome

intervention reduces the prevalence of MetS in the long term [22, 23]. Thus, lifestyle intervention for the prevention of MetS at earlier ages is essential.

In the present study, 31 (33.7 %) of the 92 incident cases were individuals who had i-IIS and who did not have MetS at baseline. Recent studies reported that individuals with a

Table 3 Incidence rates and multivariable-adjusted hazard ratios for the incidence of type 2 diabetes according to IIS and IR status (normal, i-IR, or i-IIS) and presence or absence of MetS: Japanese criteria for MetS

	Normal		I-IR		I-IIS	
	MetS (−)	MetS (+)	MetS (−)	MetS (+)	MetS (−)	MetS (+)
<i>n</i>	855	44	245	68	455	35
Person-years	3,909	184	1,086	268	1,992	133
Incident cases (<i>n</i>)	18	3	17	7	39	8
Incidence rate (/1000 person-years)	4.6	16.3	15.7	26.1	19.6	60.2
Hazard ratio (95 % CI)						
Model 1	1.0	2.15 (0.62–7.50)	3.12 (1.60–6.10)	4.69 (1.92–11.45)	3.47 (1.97–6.12)	9.45 (3.88–23.02)
Model 2	1.0	1.17 (0.31–4.38)				
Model 3			1.0	2.20 (0.84–5.77)		
Model 4					1.0	2.82 (1.24–6.42)

MetS was defined using the criteria of the Japanese Society of Internal Medicine

MetS was diagnosed when a participant had an elevated waist circumference (≥ 85 cm for men and ≥ 90 cm for women) plus at least two of the following components: (1) elevated triacylglycerol (≥ 1.7 mmol/L or drug treatment for elevated triacylglycerol) and/or reduced HDL cholesterol (< 1.0 mmol/L for both men and women or drug treatment for reduced HDL cholesterol), (2) elevated blood pressure (systolic ≥ 130 and/or diastolic ≥ 85 mmHg or antihypertensive drug treatment), and (3) elevated fasting plasma glucose (≥ 6.1 mmol/L)

Model 1: adjusted for age, sex, family history of diabetes (yes or no), smoking status (nonsmoker, ex-smoker, or current smoker), alcohol consumption (0 g/week, 1–139 g/week, or ≥ 140 g/week), and exercise (≥ 2 times/week or < 2 times/week)

Model 2: adjusted for all factors in model 1 among the normal group ($n = 899$)

Model 3: adjusted for all factors in model 1 among the i-IR group ($n = 313$)

Model 4: adjusted for all factors in model 1 among the i-IIS group ($n = 490$)

i-IR isolated insulin resistance, i-IIS isolated impaired insulin secretion, MetS metabolic syndrome

low reserve capacity of insulin secretion cannot compensate for minor increases in weight or minor decreases in insulin sensitivity and develop type 2 diabetes [24–26]. A minor increase in weight or decrease in insulin sensitivity may have been associated with type 2 diabetes onset in the i-IIS without MetS group. Further research on the mechanism of type 2 diabetes onset in individuals who have low insulin secretion and do not have MetS is needed to develop preventive measures for this group.

The strengths of the present study include its community-based cohort, which consisted of residents of many cities throughout Nagano Prefecture. Moreover, participants were screened for type 2 diabetes annually over a 5-year period using the 75 g OGTT, and the overnight fast prior to the 75 g OGTT was enforced by hospitalizing the participants the day prior to testing. This study, however, also had several limitations. First, the estimates of insulin secretion and IR were made using calculations based on the OGTT and not by the “gold standard” test, namely the glucose-clamp technique. However, performing a glucose clamp is not feasible in large-scale epidemiologic studies, and the proxy measures used in this study are reliable in large data sets. Second, the 75 g OGTT, which was used to define the baseline IIS and IR status, was measured only once. Third, there was a possibility of selection bias, as the participants in this study were

individuals who underwent routine comprehensive medical check-ups. Although these check-ups are generally expensive in Japan, those at Saku Central Hospital are relatively inexpensive or free because administrations and employers subsidize their costs. Consequently, many community residents undergo these examinations. Finally, individuals who did not undergo annual comprehensive medical check-ups after their baseline examinations were excluded from our analysis. As individuals who developed severe diseases or died during the follow-up period were not assessed, selection bias is possible.

In conclusion, to the best of our knowledge, this is the first report to suggest an impact of MetS on the development of type 2 diabetes in middle-aged Japanese individuals with a low reserve capacity of insulin secretion. Evaluating insulin secretion will be important for preventing type 2 diabetes in Asian countries. In addition, because dysfunction in insulin secretion has been reported in various populations in Asian countries [26–29], the prevention of MetS is important for preventing type 2 diabetes in Asians, particularly those with a low reserve capacity of insulin secretion.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later revisions. Informed consent or a substitute for it was obtained from all participants before they were included in the study.

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