Impact of impaired insulin secretion and insulin resistance on the incidence of diabetes in a Japanese cohort. Reply to Yamauchi K and Aizawa T [letter]

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Abbreviations

FPG	Fasting plasma glucose
HOMA-IR	HOMA of insulin resistance
i-IIS	Isolated impaired insulin secretion
IIS	Impaired insulin secretion
i-IR	Isolated insulin resistance
IR	Insulin resistance
PAF	Population-attributable fraction

To the Editor: We appreciate the comments from Dr Yamauchi and Dr Aizawa [1] on our recent publication in

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Diabetologia [2]. We sincerely respond to their concerns as follows.

Pathophysiological risk and population-based risk of impaired insulin secretion (IIS) and insulin resistance (IR) First of all, our investigation was an epidemiological study to clarify the population-based risk, and our results only suggest a certain pathophysiological mechanism as a target of future experimental and clinical research. Our study simply showed predicted values for the incidence of type 2 diabetes for certain clinical findings, such as isolated impaired insulin secretion (i-IIS) or isolated insulin resistance (i-IR) as defined in our paper, measured on a single occasion. In an additional analysis conducted for the present letter, the multivariable-adjusted HR for the incidence of type 2 diabetes was 1.69 (95% CI 1.17, 2.42) in the i-IIS group compared with the i-IR group after adjustment for age, sex, family history of diabetes, current smoking, alcohol consumption and exercise. After adjustment for the above-mentioned variables and BMI, waist circumference, body fat, systolic BP, HDL-cholesterol, $\log_e$ -transformed triacylglycerol, $\log_e$ -transformed γ -glutamyltransferase, uric acid, high-sensitive C-reactive protein and fasting plasma glucose (FPG), the multivariable-adjusted HR for the incidence of type 2 diabetes was 3.25 (95% CI 2.15, 4.90) in the i-IIS group compared with the i-IR group.

Estimation of IR As mentioned by Yamauchi and Aizawa [1], estimation of IR by calculating the HOMA-IR, which primarily reflects hepatic IR [3], was one of the major limitations of our study. We are planning to measure serum insulin concentrations at 0 (fasting), 30, 60 and 120 min using standard 75 g OGTTs, and we will estimate the risk of whole body IR in the near future.

Table 1 Incidence rates, HRs and PAFs for the development of type 2 diabetes, according to baseline IIS and IR status: additional analysis

Variable	Normal (<i>n</i> =1,550)	i-IIS (<i>n</i> =900)	i-IR (<i>n</i> =505)	IIS plus IR (<i>n</i> =104)
Incident cases (<i>n</i> /person-years)	24/5,447	126/3,032	39/1,748	30/326
Incidence rate (/1,000 person-years)	4.4	41.6	22.3	92.0
HR (95% CI)				
Model 1 [2]	1.0	8.27 (5.33, 12.83)	4.90 (2.94, 8.17)	16.93 (9.80, 29.25)
Model 2	1.0	6.19 (3.95, 9.70)	1.91 (1.18, 3.29)	4.39 (2.43, 7.93)
PAF (95% CI) ^a , %				
Model 1 [2]	–	50.6 (46.7, 53.0)	14.2 (11.8, 15.6)	12.9 (12.3, 13.2)
Model 2	–	48.2 (43.0, 51.6)	8.5 (2.8, 12.4)	10.6 (8.1, 12.0)

Normal, insulinogenic index >51.7, HOMA-IR ≤1.6; i-IIS, insulinogenic index ≤51.7, HOMA-IR ≤1.6; i-IR, insulinogenic index >51.7, HOMA-IR >1.6; IIS plus IR, insulinogenic index ≤51.7, HOMA-IR >1.6

Model 1, adjusted for age, sex, family history of diabetes (yes or no), current smoking (yes or no), alcohol consumption (0 g/week, 1–139 g/week or ≥140 g/week) and exercise (0 min/week, 1–119 min/week or ≥120 min/week)

Model 2, adjusted for all factors in Model 1 plus BMI, waist circumference, body fat, systolic BP, HDL-cholesterol, log_e-transformed triacylglycerol, log_e-transformed γ-glutamyltransferase, uric acid, high-sensitive C-reactive protein and FPG

^a PAF (%) was calculated using multivariable-adjusted HR (Models 1 or 2)

Other confounding factors in the Cox model The results of additional analysis are shown in Table 1. Age, sex, family history of diabetes, current smoking, alcohol consumption and exercise were included in Model 1 [2]; and BMI, waist circumference, body fat, systolic BP, HDL-cholesterol, log_e-transformed triacylglycerol, log_e-transformed γ-glutamyltransferase, uric acid, high-sensitive C-reactive protein and FPG were included in Model 2. The results in Model 2 in Table 1 indicate that i-IIS and i-IR are pathophysiological risk factors for type 2 diabetes after full adjustment, and the PAF (48.2%) of type 2 diabetes onset due to i-IIS was similarly high.

We did not adjust for BMI, waist circumference, FPG, etc. for two reasons. First, IR is a syndrome associated with the clustering of metabolic disorders, including obesity, hypertension, lipid abnormalities and atherosclerotic cardiovascular disease [4]. Obesity, in particular, would tend to lead to type 2 diabetes, mainly through IR [5]. Therefore, adjustment for metabolic disorders, especially BMI and waist circumference, may be an over-adjustment. This may result in an underestimation of the risks of IR on type 2 diabetes. Second, we assessed the population-based risk of the state of being insulin resistant (i.e. individuals with IR have high BMI, waist circumference, FPG, etc.) on the incidence of type 2 diabetes.

Minimum value of the insulinogenic index Yamauchi and Aizawa mention that negative values cannot be used to calculate the insulinogenic index. However, there were no negative values and the minimum insulinogenic index in the individuals

eligible for our analysis was 2.8 pmol/mmol. Accordingly, no-one was excluded from the analysis for this reason.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement All authors contributed to drafting or critical revision of the letter. All authors approved the final version of the letter.

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