Risk and population attributable fraction of metabolic syndrome and impaired fasting glucose for the incidence of type 2 diabetes mellitus among middle-aged Japanese individuals: Aichi Worker’s Cohort Study

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Impaired fasting glucose, Metabolic syndrome, Population attributable fraction and type 2 diabetes mellitus

ABSTRACT
Aims/Introduction: The Japanese government started a nationwide screening program for metabolic syndrome (MetS) to prevent cardiovascular diseases and diabetes mellitus. Although impaired fasting glucose (IFG) is a strong predictor for type 2 diabetes mellitus, the program does not follow up IFG in non-MetS individuals. This study aimed to examine the risk and the population attributable fraction (PAF) of MetS and IFG for incidence of type 2 diabetes mellitus.

Materials and Methods: Japanese workers (3,417 men and 714 women) aged 40–64 years without a history of diabetes were prospectively followed. MetS was defined as either abdominal obesity plus two or more metabolic risk factors, or being overweight in the case of normal waist circumference plus three or more metabolic risk factors. IFG was defined as fasting blood glucose 100–125 mg/dL.

Results: During a mean 6.3 years, 240 type 2 diabetes mellitus cases were identified. Compared with those without MetS and IFG, the multivariable-adjusted hazard ratios (95% confidence interval) of non-MetS individuals with IFG, MetS individuals without IFG and MetS individuals with IFG for type 2 diabetes mellitus were 4.9 (3.4–7.1), 2.4 (1.6–3.5) and 8.3 (5.9–11.5), respectively. The corresponding PAFs for type 2 diabetes mellitus incidence were 15.6, 9.1 and 29.7%, respectively.

Conclusions: IFG represented a higher risk and PAF than MetS for type 2 diabetes mellitus incidence in middle-aged Japanese individuals. The coexistence of MetS and IFG showed the highest risk and PAF for type 2 diabetes mellitus incidence. The current Japanese MetS screening program should be reconsidered to follow up non-MetS individuals with IFG.

INTRODUCTION
The increasing trend of type 2 diabetes mellitus is one of the most significant public health threats in Japan and the world. Modifying lifestyles to prevent metabolic syndrome (MetS), a likely precursor of type 2 diabetes mellitus, could be an effective approach. The Japanese government started an annual screening program for MetS among people aged ≥40 years in 2008. All public health insurers are obliged to carry out the MetS screening and provide the identified MetS individuals with health education support. In this program, MetS is defined as either abdominal obesity plus two or more metabolic risk factors, or being overweight in the case of normal waist circumference plus three or more metabolic risk factors (Table 1). This program...
aims to improve abdominal obesity by modifying lifestyles, and eventually to prevent cardiovascular diseases and type 2 diabetes mellitus\(^9,10\). However, the current program does not include non-MetS individuals with impaired fasting glucose (IFG) as targets for the health education support. Although IFG is a well-known predictor of type 2 diabetes mellitus incidence\(^11-15\), and type 2 diabetes mellitus is often preventable through lifestyle modification of IFG individuals\(^16,17\), to our knowledge, no previous studies estimated the contribution of MetS compared with IFG for predicting type 2 diabetes mellitus incidence.

The present study aimed to estimate the risk and population attributable fraction (PAF) of MetS and IFG for the incidence of type 2 diabetes mellitus in middle-aged Japanese individuals.

**METHODS**

**Study population**

The Aichi Worker’s Cohort Study, established in 1997, is an ongoing prospective study of cardiovascular disease and diabetes mellitus, targeting civil servants in Aichi Prefecture, located in central Japan\(^18,19\). The study targeted 8,989 participants (6,885 men and 2,104 women) aged 19–64 years. The following participants were excluded from the analysis: (i) 679 prevalent type 2 diabetes mellitus cases at baseline; (ii) 3,284 with missing values for baseline height, weight, waist circumference, fasting blood glucose (FBG), triglycerides or smoking status; and (iii) 895 aged <40 years. Finally, 4,131 participants (3,417 men and 714 women) remained for analysis.

**Data collection and variables**

Baseline data were collected by annual mandatory health check-ups and self-administrated questionnaires in 2005 and 2007. The baseline health checkup data included: bodyweight measured to the nearest 0.1 kg; height measured to the nearest 0.1 cm; body mass index (BMI) computed as bodyweight (kg) divided by height squared (m\(^2\)); waist circumference measured at the umbilical level to the nearest 0.1 cm; blood pressure obtained in the seated position; blood samples drawn after at least eight hours of fasting; and physicians’ interview records\(^20\).

Metabolic syndrome was defined as: high waist circumference plus two or more risk factors including raised blood pressure or a positive history of hypertension, raised blood glucose, raised triglycerides, and/or lowered high-density lipoprotein cholesterol and smoking; or high BMI with normal waist circumference plus three or more of the above risk factors according to the Japanese MetS screening criteria, as shown in Table 1. IFG was defined as FBG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L)\(^21\). Alcohol intake (g/day) was estimated based on the type of alcohol, the amount of each type of alcohol and frequency of drinking, and it was categorized as 0, 1–20 and ≥20 g/day\(^22\). Current smoking status was dichotomized as non-current smoker or current smoker. Physically active individuals were identified as those who engaged in moderate or vigorous leisure-time exercise for a total of ≥60 min during ≥4 days per month.

**Ascertainment of incident type 2 diabetes mellitus**

Participants were followed up until the end of March 2013. The follow-up data were collected by annual mandatory health checkups and a biennially self-administered questionnaire survey on the medical histories of selected conditions including type 2 diabetes mellitus. Incident type 2 diabetes mellitus was defined by the following criteria: (i) FBG ≥126 mg/dL (7.0 mmol/L) or glycated hemoglobin ≥6.5% (48 mmol/mol)\(^21\); (ii) use of antidiabetic drugs; and (iii) self-reported diabetes. The participants who reported a type 2 diabetes mellitus history were requested to provide the detailed contact information of their attending physicians, and their medical records were confirmed with the physicians.

The person-years of the follow up were calculated from baseline to the date of censoring, ascertainment of the incidence of type 2 diabetes mellitus or the end of the follow up, whichever came first. Participants were censored when they died or retired from the workplace, except for those who agreed to provide their health history information to the researchers after their retirement.

The study protocol was approved by the Bioethics Review Committee of Nagoya University School of Medicine, Nagoya, Japan (approval number: 2007-0504). All participants gave written informed consent. The participants’ medical records were confirmed with the attending physicians after the participants’ written consents were obtained.

**Statistical analysis**

The characteristics of participants according to the combination of MetS and IFG were reported in means and 95% confidence limits.
RESULTS

Baseline characteristics of the participants are shown in Table 2. The mean age of the participants was 50.0 years (50.2 years in men and 49.5 years in women). Participants who developed type 2 diabetes mellitus were significantly older in age, and had higher waist circumference, BMI, systolic and/or diastolic blood pressure, triglycerides, and FBG than those who did not develop type 2 diabetes mellitus. Current smokers and those with hypertension were more likely to develop type 2 diabetes mellitus. Alcohol intake and regular physical activities did not differ between the two groups. The detailed characteristics of the participants with or without MetS and/or IFG are shown in Table S1.

During a mean 6.3-year follow-up period (interquartile range 6.1–7.3 years), 240 participants developed type 2 diabetes mellitus. Compared with non-MetS, significantly higher adjusted HRs and PAF of MetS for type 2 diabetes mellitus incidence were observed. Similarly, adjusted HRs and PAF of IFG for type 2 diabetes mellitus incidence were significantly higher than those without IFG. Furthermore, the PAF and HR point estimates of IFG for type 2 diabetes mellitus development were higher than those of MetS (Table 3).

Table 4 shows that the association with type 2 diabetes mellitus was stronger for non-MetS individuals with IFG than MetS individuals without IFG. Similarly, PAF of non-MetS individuals with IFG was higher than MetS individuals without IFG. The highest adjusted HR and PAF were observed for MetS individuals with IFG.

We obtained similar findings when we analyzed the data using the MetS criteria defined by the Joint Interim Statement in 200923 (Table S2 and S3).

Table 2 | Baseline characteristics of the participants according to the occurrence of type 2 diabetes during the follow up or not, 2005–2007

| Total (n = 4,131) | Non-type 2 diabetes (n = 3,891) | Type 2 diabetes (n = 240) | P-value |
|------------------|-------------------------------|--------------------------|---------|
| Men (%)          | 3,417 (82.7)                  | 3,204 (82.3)             | 213 (88.8) | <0.05 |
| Age (years)      | 50.0 (49.9–50.2)              | 50.0 (49.8–50.1)         | 51.2 (50.6–51.8) | <0.01 |
| Alcohol intake (g/day) | 14.8 (14.3–15.3) | 14.7 (14.2–15.2) | 15.7 (13.6–17.9) | 0.37 |
| 0                | 1,136 (27.5)                  | 1,079 (27.7)             | 57 (23.8) | 0.25 |
| 1–20             | 1,788 (43.3)                  | 1,685 (43.3)             | 103 (42.9) |         |
| ≥20              | 1,207 (29.2)                  | 1,127 (29.0)             | 80 (33.3) |         |
| Regular physical activities (yes) | 2,040 (49.4) | 1,918 (49.3) | 122 (50.8) | 0.64 |
| Waist circumference (cm) | 83.0 (82.8–83.3) | 82.8 (82.6–83.1) | 86.8 (85.7–87.8) | <0.01 |
| Body mass index (kg/m²) | 22.9 (22.9–23.0) | 22.8 (22.8–22.9) | 24.4 (24.0–24.8) | <0.01 |
| Systolic blood pressure (mmHg) | 125.2 (124.7–125.7) | 124.8 (124.3–125.3) | 131.2 (129.0–133.3) | <0.01 |
| Diastolic blood pressure (mmHg) | 78.9 (78.3–79.2) | 78.6 (78.2–79.0) | 82.9 (81.5–84.3) | <0.01 |
| Triglycerides (mg/dL)† | 102.7 (101.0–104.4) | 101.4 (99.7–103.1) | 127.1 (118.6–136.3) | <0.01 |
| HDL-cholesterol (mg/dL)† | 57.8 (57.3–58.2) | 58.1 (57.6–58.5) | 53.1 (51.4–54.8) | <0.01 |
| Fasting blood glucose (mg/dL) | 92.7 (92.4–93.0) | 92.2 (91.9–92.4) | 101.3 (99.9–102.7) | <0.01 |
| History of hypertension (yes) | 1,471 (35.6) | 1,347 (34.6) | 124 (51.7) | <0.01 |
| Current smoking (yes) | 1,066 (25.8) | 987 (25.4) | 79 (32.9) | <0.01 |

Data are reported as the mean and the 95% confidence interval or number (%), unless otherwise specified. P-values are from analysis of variance for continuous variables, and the χ²-test for categorical variables. HDL-cholesterol, high-density lipoprotein cholesterol; IFG, impaired fasting glucose; MetS, metabolic syndrome. †Geometric mean and 95% confidence interval.
Table 3 | Hazard ratios and population attributable fractions of metabolic syndrome or impaired fasting glucose for the incidence of type 2 diabetes mellitus, 2005–2013

|                | MetS (−) | MetS (+) |
|----------------|----------|----------|
| No. participants | 3,141    | 990      |
| No. incidences   | 121      | 119      |
| Person-years     | 19,767   | 5,883    |
| Crude incidence (/1,000 person-years) | 6.1 | 20.2 |
| Crude HR         | Ref      | 3.3 (2.6–4.2) |
| Age adjusted HR  | Ref      | 3.1 (2.4–4.0) |
| Adjusted HR† (%) | 33.4 (24.4–41.4) |

Hazard ratios and population attributable fractions; Ref, reference. †Adjusted models for analysis of metabolic syndrome (MetS) included the covariates of sex (men/women), age (years), alcohol intake (0, 1–20, ≥20 g/day) and regular physical activity (yes/no). For the analysis of impaired fasting glucose (IFG) further added covariates were current smoking (yes/no), body mass index ≥25 kg/m² (yes/no), and systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or history of hypertension (yes/no) and triglycerides ≥150 mg/dL and/or high-density lipoprotein cholesterol <40 mg/dL (yes/no).

Table 4 | Hazard ratios and population attributable fractions for the incidence of type 2 diabetes mellitus according to the combination of metabolic syndrome and impaired fasting glucose, 2005–2013

|                | MetS (−) | MetS (+) |
|----------------|----------|----------|
| No. participants | 2,761    | 380      |
| No. incidences   | 74       | 47       |
| Person-years     | 17,557   | 2,211    |
| Crude incidence (/1,000 person-years) | 42 | 21.3 |
| Crude HR         | Ref      | 5.0 (3.5–7.3) |
| Age adjusted HR  | Ref      | 4.9 (3.4–7.0) |
| Adjusted HR† (%) | 15.6 (10.1–20.7) |

HR, hazard ratio; PAF, population attributable fraction; Ref, reference. †Adjusted models include the covariates of sex (men/women), age (years), alcohol intake (0, 1–20, ≥20 g/day) and regular physical activity (yes/no).

Supplementary analyses using the Japanese MetS screening criteria without current smoking showed somewhat lower PAF (28.3%) compared with the one obtained in the original analysis (33.4%; Table S4). Similarly, PAFs of MetS individuals without IFG (5.8%) and MetS individuals with IFG (26.5%) were both lower than those in the original analysis (6.6 and 28.4%, respectively). Consequently, the PAF of non-MetS individuals with IFG became slightly higher (17.9%) than the original analysis (16.1%; Table S5).

**DISCUSSION**

The present study showed that IFG contributed to higher HR and PAF for developing type 2 diabetes mellitus than MetS, which would be subject to vigorous intervention in the MetS screening program in Japan. We reported for the first time that the risk and PAF of non-MetS individuals with IFG for type 2 diabetes mellitus was higher than MetS individuals without IFG in middle-aged Japanese individuals.

HR or PAF for type 2 diabetes mellitus incidence was highest in MetS individuals with IFG. This finding was consistent with previous studies in Japan and in the USA. This suggests that individuals having both MetS and IFG require the most intensive interventions to prevent type 2 diabetes mellitus. As the previous study in the USA referred to the criteria of MetS in which obesity was not a prerequisite, the results might not be exactly comparable. However, we also obtained similar results when we analyzed the data using the Joint Interim Statement criteria of MetS, which does not pre-require the presence of obesity for the diagnosis.

The MetS criteria used in the Japanese screening program was sometimes criticized for the pre-requirement of abdominal or general obesity, which might decrease the effectiveness of screening to prevent cardiovascular diseases. However, the present study showed that the risk and PAF of MetS for type 2 diabetes mellitus incidence did not greatly differ when we used the MetS criteria without the pre-requirement of obesity. In contrast, the exclusion of current smoking from the Japanese MetS screening criteria might have attenuated the PAF of MetS for type 2 diabetes mellitus incidence to a certain degree. This might be due to the relatively high prevalence of cigarette...
smoking and its firm association with type 2 diabetes mellitus incidence. Although smoking prevalence is gradually decreasing, the inclusion of smoking status as a criterion to identify high-risk individuals for type 2 diabetes mellitus would be relevant and might be related to an improvement of the effectiveness of the screening system.

The adjusted HR for type 2 diabetes mellitus incidence in non-MetS individuals with IFG was higher than in MetS individuals without IFG. Several previous studies in Japan reported similar results, although PAF of MetS was 33.4% for type 2 diabetes mellitus incidence, which was lower than the findings in Finland (62%) and Canada (49%). The PAF of MetS for type 2 diabetes mellitus was higher than that of IFG in the Finnish study. The Finnish and Canadian studies used MetS criteria defined as a pre-requirement of abdominal or general obesity plus two or more metabolic abnormalities. As the prevalence of obesity and being overweight is higher in the white European population than the East Asian population, a higher prevalence of MetS might have led to the increased PAF for type 2 diabetes mellitus in the Finnish and Canadian studies.

The present study did not obtain data on impaired glucose tolerance (IGT), it is a component of prediabetes and is known to present a high risk of progressing to type 2 diabetes mellitus. Several interventions should be provided to non-MetS individuals with IFG as well. Although the present study did not obtain data on impaired glucose tolerance (IGT), it is a component of prediabetes and is known to present a high risk of progressing to type 2 diabetes mellitus. It is characterized by peripheral (muscle) insulin resistance and late-phase insulin response deficit during glucose challenge. In a community sample of Spanish adults aged 35–74 years, the prevalence of isolated IGT was 5.0%, which was much less than that of IFG (19.9%), and includes both IFG only (16.6%), and IFG and IGT together (3.3%). In that study, the prevalence of MetS in IGT patients (31.5%) was found to be noticeably smaller than that in IFG only (57.1%) or IFG and IGT (66.1%). Taken together, a smaller, but certain proportion of individuals who have high type 2 diabetes mellitus risk would not be detected by MetS screening and fasting blood examination. Strategies for interventions and the preceding identification of IGT patients should be studied in future research.

This is the first prospective cohort study that evaluated the contribution of MetS and IFG to develop type 2 diabetes mellitus among Japanese adults. However, there were several potential limitations. First, IGT could not be considered, as the inclusion of such data was not mandatory in the annual health checkup dataset. Second, the present study could not exclude the effect of the national intervention program introduced since 2008. Third, the study population was limited to middle-aged Japanese workers, thus much larger studies of the general population would be required to confirm the findings.

In conclusion, IFG represented a higher risk and PAF than MetS for type 2 diabetes mellitus incidence in middle-aged Japanese workers. Furthermore, the coexistence of MetS and IFG represented the highest risk and PAF for type 2 diabetes mellitus incidence. The Japanese MetS screening program should include non-MetS individuals with IFG in health education support interventions.

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DISCLOSURE

The authors declare no conflict of interest.

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**Supporting Information**

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Table S1** | Baseline characteristics of the participants according to the combination of metabolic syndrome and impaired fasting glucose.

**Table S2** | Hazard ratios and population attributable fractions of metabolic syndrome identified by the Joint Interim Statement for incidence of type 2 diabetes mellitus.

**Table S3** | Hazard ratios and population attributable fractions for the incidence of type 2 diabetes mellitus according to the combination of metabolic syndrome identified by the Joint Interim Statement and impaired fasting glucose.

**Table S4** | Hazard ratios and population attributable fractions of metabolic syndrome identified by Japanese criteria without “current smoking” for the incidence of type 2 diabetes mellitus.

**Table S5** | Hazard ratios and population attributable fractions for the incidence of type 2 diabetes mellitus according to the combination of metabolic syndrome identified by Japanese criteria without “current smoking” and impaired fasting glucose.