JDI Journal of Diabetes Investigation Open access
Official Journal of the Asian Association for the Study of Diabetes
ORIGINAL ARTICLE

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

Kayo Kaneko[1], Hiroshi Yatsuya[1,2]*, Yuanying Li[2], Mayu Uemura[1], Chifa Chiang[1], Yoshihisa Hirakawa[1], Atsuhiko Ota[2], Koji Tamakoshi[3], Atsuko Aoyama[1,4]

[1]Department of Public Health and Health Systems, Nagoya University Graduate School of Medicine, Nagoya, Japan, [2]Department of Public Health, Fujita Health University School of Medicine, Toyoake, Japan, [3]Department of Nursing, Nagoya University School of Health Sciences, Nagoya, Japan, and [4]Nagoya University of Arts and Sciences, Nissin, Japan

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

***Correspondence**
Hiroshi Yatsuya
Tel.: +81-562-93-2452
Fax: +81-562-93-3079
E-mail address:
yatsuya@gmail.com;
yatsuya@fujita-hu.ac.jp

J Diabetes Investig 2020; 11: 1163–1169

doi: 10.1111/jdi.13230

ABSTRACT

Aims/Introduction: The Japanese government started a nationwide screening program for metabolic syndrome (MetS) to prevent cardiovascular diseases and diabetes in 2008. 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[1–3]. Modifying lifestyles to prevent metabolic syndrome (MetS), a likely precursor of type 2 diabetes mellitus, could be an effective approach[4–6]. The Japanese government started an annual screening program for MetS among people aged ≥40 years in 2008[7,8]. 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)[7]. This program

Received 11 September 2019; revised 13 January 2020; accepted 3 February 2020

Table 1 | Japanese metabolic syndrome criteria for the national screening program

Pre-requirement
Waist circumference: men ≥85 cm; women ≥90 cm
and/or
Body mass index: ≥25 kg/m^2
Risk factors
1. Systolic blood pressure ≥130 and/or diastolic blood pressure ≥85 mmHg
2. Fasting blood glucose ≥100 mg/dL and/or HbA_{1c} ≥5.6% (38 mmol/mol)
3. Triglycerides ≥150 mg/dL and/or high-density lipoprotein cholesterol <40 mg/dL
4. Current smoking[†]
Definition of metabolic syndrome
High waist circumference plus two or more risk factors
or
High body mass index (in case of normal waist circumference) plus three or more risk factors

[†]Current smoking is counted as a risk factor, in case of simultaneous presence with at least one of the other risk factors. HbA_{1c}, glycated hemoglobin

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 checkups 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[7]. 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

intervals (CIs) for the continuous variable with normal distribution. As the distributions were skewed in triglycerides and high-density lipoprotein cholesterol, geometric means and 95% CIs were presented. The differences of continuous data were tested by analysis of variance. Categorical variables were described as frequency (%) and were analyzed by χ^2-tests.

Cox proportional hazards models were carried out to estimate the hazard ratios (HRs) and 95% CIs of MetS and IFG for the incidence of type 2 diabetes mellitus. For the analysis of the combination of MetS and IFG, four categories were created as follows: (i) non-MetS individuals without IFG; (ii) non-MetS individuals with IFG; (iii) MetS individuals without IFG; and (iv) MetS individuals with IFG. The multivariable models were adjusted for sex (male/female), age (years), alcohol intake (0, 1–20, ≥20 g/day)[22] and regular physical activity (yes/no). The analysis of IFG additionally included current smoking (yes/no)[23], BMI ≥25 kg/m^2 (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) as the covariates. The PAFs were calculated to express the proportion of type 2 diabetes mellitus that is attributed to MetS and IFG[24].

Supplementary analyses that used MetS criteria defined by the Joint Interim Statement in 2009[25], in which obesity is not a prerequisite, and the Japanese MetS screening criteria, but without current smoking criterion, were carried out, respectively.

Two-tailed $P < 0.05$ was considered statistically significant. Statistical analyses were carried out using IBM SPSS statistics for Windows software, version 25.0 (IBM Corporation, Tokyo, Japan).

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 2009[25] (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/m^2)	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 (78.5–79.2)	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 χ^2-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 (+)	IFG (–)	IFG (+)
No. participants	3,141	990	3,354	777
No. incidences	121	119	112	128
Person-years	19,767	5,883	21,237	4,413
Crude incidence (/1,000 person-years)	6.1	20.2	5.3	29.0
Crude HR	Ref	3.3 (2.6–4.2)	Ref	5.5 (4.2–7.1)
Age adjusted HR		3.1 (2.4–4.0)		5.2 (4.0–6.8)
Adjusted HR†		3.1 (2.3–4.0)		4.5 (3.4–5.8)
Adjusted PAF† (%)		33.4 (24.4–41.4)		41.4 (32.8–48.8)

HR, hazard ratio; PAF, population attributable fraction; 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/m^2 (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 (+)	
	IFG (–)	IFG (+)	IFG (–)	IFG (+)
No. participants	2,761	380	593	397
No. incidences	74	47	38	81
Person-years	17,557	2,211	3,681	2,202
Crude incidence (/1,000 person-years)	4.2	21.3	10.3	36.8
Crude HR	Ref	5.0 (3.5–7.3)	2.4 (1.7–3.6)	8.7 (6.3–11.9)
Age adjusted HR		4.9 (3.4–7.0)	2.4 (1.6–3.5)	8.2 (6.0–11.3)
Adjusted HR†		4.9 (3.4–7.1)	2.4 (1.6–3.5)	8.3 (5.9–11.5)
Adjusted PAF† (%)		15.6 (10.1–20.7)	9.1 (3.8–14.2)	29.7 (23.0–35.8)

HR, hazard ratio; IFG, impaired fasting blood glucose; MetS, metabolic syndrome; 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 (28.5%) 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[26,27] and in the USA[28]. This suggests that individuals having both MetS and IFG require the most intensive interventions to prevent type 2 diabetes mellitus[29]. As the previous study in the USA referred to the criteria of MetS in which obesity was not a prerequisite[30], 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[25].

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[31–33]. 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[23,34]. 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[26,27,35], 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%)[36,37]. 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[38]. As the prevalence of obesity and being overweight is higher in the white European population than the East Asian population[39], a higher prevalence of MetS might have led to the increased PAF for type 2 diabetes mellitus in the Finnish and Canadian studies.

The higher risk and PAF of IFG than MetS for type 2 diabetes mellitus incidence in the Japanese population might be partly due to the lower insulin secretion in East Asian populations than white European populations[40,41]. The presence of mild insulin resistance without obesity or visceral fat accumulation could lead to type 2 diabetes mellitus development in the East Asian population[42–45], and might contribute to the recent increase of diabetes prevalence[42,46].

The present findings imply that non-MetS individuals with IFG require vigorous interventions to prevent future type 2 diabetes mellitus development among the Japanese population. Health education support is an integral part of the Japanese MetS screening program[9,10], which is provided to MetS individuals only. As lifestyle modification, such as strengthening physical activities or improving dietary habits, are reported to be effective in preventing the progression of hyperglycemia to type 2 diabetes mellitus [16,17], such 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[47]. 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%)[48]. 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.

ACKNOWLEDGMENTS

The authors thank the participants and healthcare personnel of the local government office. This work was supported in part by MEXT/JSPS KAKENHI (grant numbers 13470087 and 17390185 to Professor Emeritus Hideaki Toyoshima; 17790384, 22390133, 23659346, 26293153 and 18H03057 to HY; 16590499, 18590594, 20590641, 23590787 and 15K08802 to KT; and 25893088 and 16K19278 to YL); Health and Labor Sciences research grants for Comprehensive Research on Cardiovascular and Life-Style Related Diseases (H26-Junkankitou [Seisaku]-Ippan-001 and H29-Junkankitou [Seishuu]-Ippan-003) from the Ministry of Health, Labor and Welfare; and research grants from the Japan Atherosclerosis Prevention Fund (to HY), the Aichi Health Promotion Foundation (to HY) and the Uehara Memorial Fund (to HY).

DISCLOSURE

The authors declare no conflict of interest.

REFERENCES

1. Cho NH, Shaw JE, Karuranga S, *et al*. IDF Diabetes Atlas: Global estimates of diabetes prevalence for 2017 and projections for 2045. *Diabetes Res Clin Pract* 2018; 138: 271–281.
2. Charvat H, Goto A, Goto M, *et al*. Impact of population aging on trends in diabetes prevalence: a meta-regression analysis of 160,000 Japanese adults. *J Diabetes Investig* 2015; 6: 533–542.
3. Lau LH, Lew J, Borschmann K, *et al*. Prevalence of diabetes and its effects on stroke outcomes: a meta-analysis and literature review. *J Diabetes Investig* 2019; 10: 780–792.
4. Wang CY, Neil DL, Home P. 2020 vision – an overview of prospects for diabetes management and prevention in the next decade. *Diabetes Res Clin Pract* 2018; 143: 101–112.

5. Honda T, Kishimoto H, Mukai N, *et al*. Objectively measured sedentary time and diabetes mellitus in a general Japanese population: the Hisayama Study. *J Diabetes Investig* 2019; 10: 809–816.
6. Grundy SM. Metabolic syndrome update. *Trends Cardiovasc Med* 2016; 26: 364–373.
7. Yamagishi K, Iso H. The criteria for metabolic syndrome and the national health screening and education system in Japan. *Epidemiol Health* 2017; 39: e2017003.
8. Ikeda N, Saito E, Kondo N, *et al*. What has made the population of Japan healthy? *Lancet* 2011; 378: 1094–1105.
9. Tsushita K, Hosler AS, Miura K, *et al*. Rationale and descriptive analysis of specific health guidance: the nationwide lifestyle intervention program targeting metabolic syndrome in Japan. *J Atheroscler Thromb* 2018; 25: 308–322.
10. Nakao YM, Miyamoto Y, Ueshima K, *et al*. Effectiveness of nationwide screening and lifestyle intervention for abdominal obesity and cardiometabolic risks in Japan: the metabolic syndrome and comprehensive lifestyle intervention study on nationwide database in Japan (MetS ACTION-J study). *PLoS ONE* 2018; 13: e0190862.
11. Nichols GA, Hillier TA, Brown JB. Normal fasting plasma glucose and risk of type 2 diabetes diagnosis. *Am J Med*. 2008; 121: 519–524.
12. Grundy SM. Pre-diabetes, metabolic syndrome, and cardiovascular risk. *J Am Coll Cardiol* 2012; 59: 635–643.
13. Chen GY, Cao HX, Li F, *et al*. New risk-scoring system including non-alcoholic fatty liver disease for predicting incident type2 diabetes in East China: Shanghai Baosteel Cohort. *J Diabetes Investig* 2016; 7: 206–211.
14. Heianza Y, Hara S, Arase Y, *et al*. HbA1c 5.7–6.4% and impaired fasting plasma glucose for diagnosis of prediabetes and risk of progression to diabetes in Japan (TOPICS 3): a longitudinal cohort study. *Lancet* 2011; 378: 147–155.
15. Hong JL, McNeill AM, He J, *et al*. Identification of impaired fasting glucose, healthcare utilization and progression to diabetes in the UK using the Clinical Practice Research Datalink (CPRD). *Pharmacoepidemiol Drug Saf* 2016; 25: 1375–1386.
16. Zhang X, Imperatore G, Thomas W, *et al*. Effect of lifestyle interventions on glucose regulation among adults without impaired glucose tolerance or diabetes: a systematic review and meta-analysis. *Diabetes Res Clin Pract* 2017; 123: 149–164.
17. Gong QH, Kang JF, Ying YY, *et al*. Lifestyle interventions for adults with impaired glucose tolerance: a systematic review and meta-analysis of the effects on glycemic control. *Intern Med* 2015; 54: 303–310.
18. Yatsuya H, Tamakoshi K, Yoshida T, *et al*. Association between weight fluctuation and fasting insulin concentration in Japanese men. *Int J Obes Relat Metab Disord* 2003; 27: 478–483.
19. Kaneko K, Yatsuya H, Li Y, *et al*. Association of gamma-glutamyl transferase and alanine aminotransferase with type 2 diabetes mellitus incidence in middle-aged Japanese men: 12-year follow up. *J Diabetes Investig* 2019; 10: 837–845.
20. Li Y, Yatsuya H, Iso H, *et al*. Incidence of metabolic syndrome according to combinations of lifestyle factors among middle-aged Japanese male workers. *Prev Med* 2010; 51: 118–122.
21. American Diabetes A. Standards of medical care in diabetes–2014. *Diabetes Care* 2014; 37(Suppl 1): S14–S80.
22. Tsugane S, Fahey MT, Sasaki S, *et al*. Alcohol consumption and all-cause and cancer mortality among middle-aged Japanese men: seven-year follow-up of the JPHC study Cohort I. Japan Public Health Center. *Am J Epidemiol* 1999; 150: 1201–1207.
23. Hilawe EH, Yatsuya H, Li Y, *et al*. Smoking and diabetes: is the association mediated by adiponectin, leptin, or C-reactive protein? *J Epidemiol* 2015; 25: 99–109.
24. Greenland S. Re: "Confidence limits made easy: interval estimation using a substitution method". *Am J Epidemiol* 1999; 149: 884; author reply 885-886.
25. Alberti KG, Eckel RH, Grundy SM, *et al*. Harmonizing the metabolic syndrome: a 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. *Circulation* 2009; 120: 1640–1645.
26. Kurotani K, Miyamoto T, Kochi T, *et al*. Metabolic syndrome components and diabetes incidence according to the presence or absence of impaired fasting glucose: The Japan Epidemiology Collaboration on Occupational Health Study. *J Epidemiol* 2017; 27: 408–412.
27. Mukai N, Doi Y, Ninomiya T, *et al*. Impact of metabolic syndrome compared with impaired fasting glucose on the development of type 2 diabetes in a general Japanese population: the Hisayama study. *Diabetes Care* 2009; 32: 2288–2293.
28. Wilson PW, D'Agostino RB, Parise H, *et al*. Metabolic syndrome as a precursor of cardiovascular disease and type 2 diabetes mellitus. *Circulation* 2005; 112: 3066–3072.
29. Chen ZK, Wu SL, Huang JH, *et al*. Metabolic syndrome increases cardiovascular risk in a population with prediabetes: a prospective study in a cohort of Chinese adults. *J Diabetes Investig* 2019; 10: 673–679.
30. Grundy SM, Brewer HB Jr, Cleeman JI, *et al*. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Circulation* 2004; 109: 433–438.
31. Saito I, Iso H, Kokubo Y, *et al*. Metabolic syndrome and all-cause and cardiovascular disease mortality: Japan Public

Health Center-based Prospective (JPHC) Study. *Circ J* 2009; 73: 878–884.
32. Noda H, Iso H, Saito I, *et al*. The impact of the metabolic syndrome and its components on the incidence of ischemic heart disease and stroke: the Japan public health center-based study. *Hypertens Res* 2009; 32: 289–298.
33. Irie F, Iso H, Noda H, *et al*. Associations between metabolic syndrome and mortality from cardiovascular disease in Japanese general population, findings on overweight and non-overweight individuals. Ibaraki Prefectural Health Study. *Circ J* 2009; 73: 1635–1642.
34. Kato A, Li Y, Ota A, *et al*. Smoking results in accumulation of ectopic fat in the liver. *Diabetes Metab Syndr Obes* 2019; 12: 1075–1080.
35. Nakanishi N, Nishina K, Okamoto M, *et al*. Clustering of components of the metabolic syndrome and risk for development of type 2 diabetes in Japanese male office workers. *Diabetes Res Clin Pract* 2004; 63: 185–194.
36. Laaksonen MA, Knekt P, Rissanen H, *et al*. The relative importance of modifiable potential risk factors of type 2 diabetes: a meta-analysis of two cohorts. *Eur J Epidemiol* 2010; 25: 115–124.
37. Naicker K, Manuel D, Overland S, *et al*. Population attributable fractions for Type 2 diabetes: an examination of multiple risk factors including symptoms of depression and anxiety. *Diabetol Metab Syndr* 2018; 10: 84.
38. Alberti KG, Zimmet P, Shaw J. Metabolic syndrome – a new world-wide definition. A consensus statement from the international diabetes federation. *Diabet Med* 2006; 23: 469–480.
39. Ng M, Fleming T, Robinson M, *et al*. Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; 384: 766–781.
40. Kodama K, Tojjar D, Yamada S, *et al*. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. *Diabetes Care* 2013; 36: 1789–1796.
41. Yokoi N, Kanamori M, Horikawa Y, *et al*. Association studies of variants in the genes involved in pancreatic beta-cell function in type 2 diabetes in Japanese subjects. *Diabetes* 2006; 55: 2379–2386.
42. Chan JC, Malik V, Jia W, *et al*. Diabetes in Asia: epidemiology, risk factors, and pathophysiology. *JAMA* 2009; 301: 2129–2140.
43. Chan JC, Yeung R, Luk A. The Asian diabetes phenotypes: challenges and opportunities. *Diabetes Res Clin Pract* 2014; 105: 135–139.
44. King GL, McNeely MJ, Thorpe LE, *et al*. Understanding and addressing unique needs of diabetes in Asian Americans, native Hawaiians, and Pacific Islanders. *Diabetes Care* 2012; 35: 1181–1188.
45. Ma RC, Chan JC. Type 2 diabetes in East Asians: similarities and differences with populations in Europe and the United States. *Ann N Y Acad Sci* 2013; 1281: 64–91.
46. Ramachandran A, Ma RC, Snehalatha C. Diabetes in Asia. *Lancet* 2010; 375: 408–418.
47. Nathan DM, Davidson MB, DeFronzo RA, *et al*. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007; 30: 753–759.
48. Martinez-Larrad MT, Corbaton-Anchuelo A, Fernandez-Perez C, *et al*. Metabolic syndrome, glucose tolerance categories and the cardiovascular risk in Spanish population. *Diabetes Res Clin Pract* 2016; 114: 23–31.

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.