J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes: An 8-year follow-up of relatively lean Japanese individuals

J-shaped relationship between waist circumference and subsequent risk for type 2 diabetes: an 8-year follow-up of relatively lean Japanese

Running title: Waist circumference and diabetes in Japanese

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Abstract

Aims

This study investigated the relationship between waist circumference and the subsequent incidence of type 2 diabetes and the association with insulin resistance and beta-cell function in relatively lean Japanese.

Methods

The study participants were 3,992 employees (2,533 men and 1,459 women, 35-55 years old) of a metal-products factory in Japan. The incidence of diabetes was surveyed in annual medical examinations during an 8-year follow-up. We calculated age- and sex-adjusted hazard ratios (HRs) according to the sex-specific quintile of waist circumference at baseline. Differences in baseline insulin resistance (HOMA-IR) and beta-cell function (HOMA-B) were compared between participants who developed diabetes and those who did not.

Results

During the follow-up, 218 participants developed diabetes. Age- and sex-adjusted HRs across the quintiles of waist circumference were 1.78, 1.00 (reference), 1.59, 3.11, and 3.30, respectively (p for trend, <0.0001). The HR for the lowest quintile was significantly higher than that for the second quintile. Among participants with waist circumference of the lowest quintile, HOMA-B was lower in those who developed diabetes than in those who did not (geometric mean, interquartile range; 33.1, 24.1-45.0 vs. 54.3, 37.9-74.6; $p < 0.001$), but HOMA-IR did not differ between these groups.

Conclusions

There was a J-shaped relationship between waist circumference and subsequent risk for type 2 diabetes in relatively lean Japanese; lower beta-cell function may also increase

the risk of diabetes in very lean Japanese.

Key Words

Incidence, type 2 diabetes, waist circumference, insulin resistance, insulin secretion, Asian

Abbreviations

BMI, body mass index; HbA1c, glycolated hemoglobin; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-B, homeostasis model assessment of beta-cell function; OGTT, oral glucose tolerance test; HR hazard ratio

Introduction

Obesity increases the risk for type 2 diabetes (1-7), with previous reports indicating a linear association between the degree of obesity and the incidence of type 2 diabetes in Western populations (1-5). Although the prevalence of obesity is much lower in Asian countries than in Western countries, the prevalence of type 2 diabetes has been reported to be similar (8) suggesting that the association between obesity and diabetes may be different in Asian countries compared with Western countries.

One possible reason for the high frequency of type 2 diabetes in Asians is the presence of prominent abdominal fat in Asians compared with Caucasians with a similar body mass index (BMI) (9, 10); however, few studies have evaluated the association between waist circumference and diabetic risk in Asians (11). Waist circumference might be a useful predictor for diabetes in Asians with high abdominal fat.

In addition to obesity, impairment of early-phase insulin secretion and low pancreatic beta-cell mass may play important roles in the development of type 2 diabetes in lean Asians (12-15). Decreased beta-cell function can cause hyperglycemia prior to the onset of obesity. It is possible that not only obese people with insulin resistance but also lean people with lower beta-cell function are at high risk for developing type 2 diabetes. Recently, a J-curve association between BMI and the incidence of diabetes was reported in older Japanese adults (16). This report suggested that older Japanese people with low BMI would also be at higher risk for developing diabetes. However, there have been few prospective studies investigating the relationship of waist circumference to future development of diabetes in lean Asian people with observation

of beta-cell function and insulin resistance.

In this large-scale, 8-year prospective study of relatively lean Japanese men and women, we investigated the relationship between anthropometric indices (BMI and waist circumference) and the subsequent risk for developing type 2 diabetes. The objectives of this study were: 1) to investigate whether waist circumference is associated with the future risk of diabetes, 2) to determine whether the relationship is linear or J-shaped, and 3) to investigate how this relationship is influenced by insulin resistance and beta-cell function.

Research Design and Methods

The participants were employees of a factory that produces zippers and aluminum sashes in Toyama Prefecture, Japan. Detailed information on the study population has been described (17-19). The Industrial Safety and Health Law in Japan requires employers to conduct annual health examinations of all employees. A survey of the incidence of diabetes mellitus was performed during the annual medical examinations between 1996 and 2004. At the baseline examination in 1996, 4,274 (90%) of 4,757 employees aged 35-55 years received health examinations. Of these 4,274 potential participants, 282 (6.6%) were excluded: 199 were diabetic or had high fasting plasma glucose (≥7.0 mmol/L) at the time of the baseline examination, 16 had missing data in baseline anthropometric indices, and 67 did not participate in consecutive follow-up annual health examinations. The final study population consisted of 3,992 employees (2,533 men and 1,459 women).

The baseline health examination included a medical history, physical examination, anthropometric measurements (waist circumference and BMI), and the determination of fasting plasma glucose, fasting insulin, glycolated hemoglobin (HbA1c) and serum lipid levels. Height was measured, without shoes, to the nearest 0.1 cm using a stadiometer. Weight was measured, with participants wearing only light clothing and no shoes, to the nearest 0.1 kg using a standard scale. BMI was calculated as weight/height^2 (kg/m^2). Waist circumference was determined to the nearest 0.5 cm by measuring from a point above the iliac crests and below the lowest rib margin, during minimal respiration in a standing position. Blood pressure was measured once with a mercury sphygmomanometer after the subjects had rested for five minutes in a seated position.

Trained staff took all of the measurements.

Plasma glucose levels were measured enzymatically (Abbott glucose UV test; Abbott Laboratories, Chicago, IL, USA), and plasma insulin levels were determined by radioimmunoassay (Shionogi Co., Tokyo, Japan). HbAlc was measured by high-velocity liquid chromatography using a fully automated hemoglobin Alc analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan). Total cholesterol and triglycerides were measured by enzyme assay. HDL-cholesterol was measured by direct method. Insulin resistance was calculated by the homeostasis model assessment (HOMA) method, using the formula: HOMA-IR = fasting insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5 (20). The HOMA of beta-cell function (HOMA-B) was calculated using the following formula: HOMA-B = 20 × fasting insulin (μU/mL)/[fasting plasma glucose (mmol/L) - 3.5] (20).

Participants with HbA1c >6.0% received a 75-g oral glucose tolerance test (OGTT). According to the definition of American Diabetes Association (21) and Japanese Diabetes Society (22), the diagnosis of diabetes is confirmed by at least one of the following observations: 1) fasting plasma glucose concentration ≥7.0 mmol/L (126 mg/dL), 2) 2-h glucose level ≥11.1 mmol/L (200 mg/dL) in a 75-g OGTT, or 3) treatment with insulin or an oral hypoglycemic agent.

A questionnaire was used to identify voluntary health-related behaviors such as alcohol consumption, smoking, and habitual exercise. Participants were classified as either nondrinkers or active drinkers. Active drinkers were further divided into occasional

(less than 5 days/week), light (greater than 5 days/week and average amounts less than 40 g ethanol/day for men and 20 g/day for women), or moderate/heavy (greater than 5 days/week and average amounts of more than 40 g ethanol/day for men and 20 g/day for women) drinkers. Data were also collected concerning smoking habits (never, ex-smoker, or current smoker) and frequency of exercise (no, weak, moderate, or strong). Exercise was defined as the participation in any physical activity such as jogging, bicycling, swimming, or tennis that was performed long enough to sweat. A self-administered questionnaire was also used to collect information about a medical history of hypertension, dyslipidemia, diabetes, and the use of antidiabetic medication. High blood pressure and dyslipidemia were defined by the Japanese criteria of metabolic syndrome (23): high blood pressure was defined as a systolic blood pressure ≥130 mmHg or a diastolic blood pressure ≥85 mmHg; dyslipidemia was defined as serum triglycerides ≥1.7mmol/L or HDL-cholesterol ≤1.0 mmol/L.

We calculated the incidence rates and hazard ratios (HRs) of diabetes according to the sex-specific quintile of waist circumference and BMI. The Cox proportional hazard model was used to calculate age- and sex-adjusted HRs and multivariate-adjusted HRs. In the multivariate-adjusted model, HRs were adjusted simultaneously for potential confounders including age, sex, family history of diabetes, smoking habits, alcohol use, and exercise frequency. In each category of quintile of waist circumference or BMI, the geometric means and 95% CI of HOMA-IR and HOMA-B were calculated and were compared between those who developed type 2 diabetes and those who did not using a *t*-test. Statistical analysis was conducted with the Statistical Package for the Social Sciences (SPSS version 12.0J; Tokyo, Japan).

Results

The baseline characteristics of the study participants are presented in Table 1. At the baseline examinations, the participants had a mean age of 44.4 years for both men and women, a mean BMI of 23.2 kg/m^2 for men and 22.6 kg/m^2 for women, and a mean waist circumference of 80.4 cm for men and 72.4 cm for women. During the 8-year follow-up (27,861 person-years), we documented 218 incident cases of diabetes (175 men and 43 women). Among these, 172 were diagnosed with diabetes based on high fasting plasma glucose levels, 40 were diagnosed according to a 75-g OGTT, and six had been treated with hypoglycemic medications.

Table 2 shows the baseline characteristics and incidence of diabetes according to the sex-specific quintiles of waist circumference. Participants with higher waist circumference tended to be older, and to have higher values of fasting plasma glucose, HbA1c, HOMA-IR, and HOMA-B, and higher prevalence of high blood pressure and dyslipidemia (p for trend < 0.001 for all). There was no significant difference in prevalence of family history of diabetes among the quintiles of waist circumference.

The crude incident rates (per 1,000 person-years) across the sex-specific quintiles of waist circumference at baseline were 6.3, 4.0, 6.0, 11.1, and 12.8, respectively (Table 2). The association between waist circumference and the incidence of diabetes was J-shaped. The age- and sex-adjusted HRs (Model 1) across the quintiles of waist circumference were 1.78, 1.00 (reference), 1.59, 3.11, and 3.30, respectively, and the HRs of the lowest, the fourth, and the highest quintile of waist circumference were significantly higher than that of the second quintile. Further adjustment for family

history of diabetes, alcohol intake, smoking, and physical activity (Model 2), and the presence of high blood pressure and dyslipidemia at baseline (Model 3) did not change the HRs. The association became slightly weaker after an additional adjustment for fasting plasma glucose at the baseline examination (Model 4). The results were similar for the association between baseline BMI and the incidence of diabetes (Table 3). The age- and sex-adjusted HRs across the quintiles of BMI were 1.40, 1.00 (reference), 1.21, 1.97, and 3.06, but the association was somewhat weaker than that for waist circumference. The HR for the lowest quintile was not significantly higher than that for the second quintile. Additional adjustments for potential confounders did not substantially change the HRs (Model 2-4). The results were similar when we analyzed excluding 21 participants who developed diabetes within one year of follow-up.

We evaluated the differences in the baseline insulin resistance and beta-cell function between the participants who developed diabetes and those who did not, and examined their association with obesity (Table 4). Among participants in the lowest and the second waist circumference quintile, HOMA-B was significantly lower in those who developed diabetes than in those who did not; however, there were no differences in HOMA-IR between these two groups. In contrast, among participants in the fourth and the highest quintile of waist circumference, HOMA-IR was significantly higher in those who developed diabetes than in those who did not, and no significant difference was observed in HOMA-B between these groups. These relationships were somewhat weaker for BMI.

Discussions

In this prospective cohort study of Japanese men and women, there was a J-shaped association between abdominal obesity and the incidence of type 2 diabetes. The risk of the lowest quintile of waist circumference was approximately 80% higher than that for the second quintile, indicating that very lean Japanese are also at high risk for developing diabetes. Among the lean participants, HOMA-B was lower in those who developed diabetes than in those who did not, but there was no difference in HOMA-IR between these two groups. These results suggest that lower beta-cell function increases the future risk for developing type 2 diabetes in lean Japanese with a very low waist circumference, whereas insulin resistance increases the risk in abdominally obese Japanese.

Previous studies have shown that waist circumference is associated with increased risk for diabetes, independently of BMI, and that waist circumference is a better predictor for diabetes than BMI (1, 2, 6). Waist circumference is regarded as a more useful marker for insulin resistance and metabolic abnormalities, because it is more closely associated with visceral adiposity, compared with BMI (24). Our results show that, in obese people, waist circumference was more strongly associated with the future risk for type 2 diabetes, compared with BMI, and that waist circumference could effectively predict the higher diabetic risk of obese people.

In contrast, previous studies using populations from Western countries have shown that the association between waist circumference and the incidence of type 2 diabetes was linear, not J-shaped (1-5). This discrepancy might have resulted from a difference in

the degree of obesity between Western and Asian populations. In our study, the upper limit of waist circumference in the lowest quintile was 73 cm for men and 65 cm for women, which was lower than that in previous studies (1-5). These previous studies might have been unable to detect a higher risk for developing diabetes in people with very low waist circumference.

Racial differences in the association between obesity and the risk for type 2 diabetes might also have influenced the results. Although the prevalence of obesity is much lower in Asia than in Western countries, the prevalence of type 2 diabetes is similar between the two regions (8), and type 2 diabetes occurs in Asians who are less obese (25, 26). In this study, range of waist circumference in the fourth quintile was 82.5-86.0cm for men and 74.0-80.0cm for women; these values were somewhat lower than the cutoff points of waist circumference proposed by the Japan Medical Association (85cm for men and 90cm for women) (23) and also by IDF (90cm for men and 80cm for women) (27). However, multivariate-adjusted hazard ratios for diabetes in the fourth quintile were significantly higher than those in the second quintile. The participants with high-normal waist circumference would be also at high risk for diabetes even though they were not diagnosed as having abdominal obesity. The definition of abdominal obesity in Asian should be carefully considered from the aspects not only to identify the people with CVD risk factors as proposed by several previous reports (28-32), but also to detect people at higher risk of future diabetes. It has also been reported that the incidence of type 2 diabetes was significantly higher in Asian women than in non-Hispanic White women after adjustment for BMI (33). Some factors beyond obesity, including genetics, may also cause the higher risk for type

2 diabetes seen in Asian populations.

More Asians have prominent abdominal obesity, compared with those in Western countries with a similar BMI (9, 10), indicating that Asians may have a higher predisposition to insulin resistance and thus may be at higher risk for developing diabetes at a lower BMI, compared with people of European descent. Furthermore, not only insulin resistance but also impaired beta-cell function have been reported to play important roles in the development of type 2 diabetes in Asians (14, 34). We have shown that lower beta-cell function may increase the risk for developing diabetes in lean Japanese. Lower beta-cell function may cause hyperglycemia or marked insulin resistance in the absence of abdominal obesity in these very lean participants.

A study conducted in a relatively lean Taiwanese population found that waist circumference for men and BMI for women were strongly associated with the incidence of diabetes (11); however, the shape of the relationship could not be determined because the data were analyzed using linear logistic regression analysis. Recently, a J-curve association between BMI and the incidence of diabetes was reported in Japanese men and women, aged 60-79 years (16). It was concluded that aging was a high risk factor for developing diabetes, because it is associated with a decline in beta-cell function (35, 36); however, our results suggest that younger and leaner individuals with decreased beta-cell function may also be at increased risk for developing diabetes mellitus.

The strength of our study lies in its relatively large sample size compared with those of other Asian studies. Many previous cohort studies used information collected from

self-administered questionnaires, whereas our conclusions are based on more reliable data obtained from medical examinations and from determinations of fasting blood glucose and insulin levels, HOMA-IR, and HOMA-B. However, our study sample included only people who were employed. As poor health may exclude some individuals from working, the prevalence of obesity and the incidence of diabetes may be lower in our sample population than in the general Japanese population. Another limitation of this study was that the classification of diabetes was not exactly evaluated in all participants with diabetes. Some lean people with diabetes may not be type 2 diabetes, but type 1 diabetes or secondary diabetes. However, the participants with incident diabetes in this study were diagnosed in annual medical check-up with relatively mild diabetes (mean HbA1c at diagnosis was 5.9% and was not different among the quintile of waist circumference). Furthermore, the results were similar when we evaluated the risk of diabetes in participants excluding those who developed diabetes within one year of follow-up, who could have other diseases which may influence anthropometric variables and glucose tolerance. Therefore, most of participants who developed diabetes in this study would be type 2 diabetes.

In conclusion, although the absolute incident risk of diabetes is higher in obese people, leaner Japanese with a smaller waist circumference would also be at high risk for developing type 2 diabetes. Moreover, lower beta-cell function, but not insulin resistance, may increase the future risk of type 2 diabetes. Greater attention should be given to very lean Asians, in addition to obese Asians, for the primary prevention of type 2 diabetes.

Declaration of Competing Interests: Nothing to declare.

References

1. Carey VJ, Walters EE, Colditz GA, Solomon CG, Willett WC, Rosner BA, et al. Body fat distribution and risk of non-insulin-dependent diabetes mellitus in women. The Nurses' Health Study. Am J Epidemiol 1997;145:614-619.

2. Wei M, Gaskill SP, Haffner SM, Stern MP. Waist circumference as the best predictor of noninsulin dependent diabetes mellitus (NIDDM) compared to body mass index, waist/hip ratio and other anthropometric measurements in Mexican Americans: a 7-year prospective study. Obes Res 1997;5:16-23.

3. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Arch Intern Med 2000;160:2117-2128.

4. Wang Y, Rimm EB, Stampfer MJ, Willett WC, Hu FB. Comparison of abdominal adiposity and overall obesity in predicting risk of type 2 diabetes among men. Am J Clin Nutr 2005;81:555-563.

5. Meisinger C, Doring A, Thorand B, Heier M, Lowel H. Body fat distribution and risk of type 2 diabetes in the general population: are there differences between men and women? The MONICA/KORA Augsburg cohort study. Am J Clin Nutr 2006; 84:483-489.

6. The Diabetes Prevention Program Research Group. Relationship of body size and shape to the development of diabetes in the diabetes prevention program. Obesity 2006;14:2107-2117.

7. Colditz GA, Willett WC, Stampfer MJ, Manson JE, Hennekens CH, Arky RA, et al. Weight as a risk factor for clinical diabetes in women. Am J Epidemiol 1990;132:501-513.

8. Yoon KH, Lee JH, Kim JW, Cho JH, Choi YH, Ko SH, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006;368:1681-1688.

9. Park YW, Allison DB, Heymsfield SB, Gallagher D. Larger amounts of visceral adipose tissue in Asian Americans. Obes Res 2001;9:381-387.

10. He Q, Horlick M, Thornton J, Wang J, Pierson Jr RN, Heshka S, et al. Sex and race differences in fat distribution among Asian, African-American, and Caucasian prepubertal children. J Clin Endocrinol Metab 2002;87:2164-2170.

11. Wang SL, Pan WH, Hwu CM, Ho LT, Lo CH, Lin SL, et al. Incidence of NIDDM and the effects of gender, obesity and hyperinsulinaemia in Taiwan. Diabetologia 1997;40:1431-1438.

12. Chen KW, Boyko EJ, Bergstrom RW, Leonetti DL, Newell-Morris L, Wahl PW, et al. Earlier appearance of impaired insulin secretion than of visceral adiposity in the pathogenesis of NIDDM. 5-Year follow-up of initially nondiabetic Japanese-American men. Diabetes Care 1995;18:747-753.

13. Matsumoto K, Miyake S, Yano M, Ueki Y, Yamaguchi Y, Akazawa S, et al. Glucose tolerance, insulin secretion, and insulin sensitivity in nonobese and obese Japanese subjects. Diabetes Care 1997;20:1562-1568.

14. Yoshinaga H, Kosaka. Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulin-dependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. Diabetes Res Clin Pract 1999;44:129-136.

15. Fukushima M, Suzuki H, Seino Y. Insulin secretion capacity in the development from normal glucose tolerance to type 2 diabetes. Diabetes Res Clin Pract 2004;66 Suppl 1:S37-43.

16. Sairenchi T, Iso H, Irie F, Fukasawa N, Ota H, Muto T. Underweight as a predictor of diabetes mellitus in older adults: A large cohort study. Diabetes Care 2008;31:583-584.

17. Morikawa Y, Nakagawa H, Ishizaki M, Tabata M, Nishijo M, Miura K, et al. Ten-year follow-up study on the relation between the development of non-insulin-dependent diabetes mellitus and occupation. Am J Ind Med 1997;31:80-84.

18. Ishizaki M, Yamada Y, Morikawa Y, Noborisaka Y, Ishida M, Miura K, et al. The relationship between waist-to-hip ratio and occupational status and life-style factors among middle-aged male and female Japanese workers. Occup Med (Lond) 1999;49:177-182.

19. Sakurai M, Miura K, Takamura T, Ota T, Ishizaki M, Morikawa Y, et al. Gender differences in the association between anthropometric indices of obesity and blood pressure in Japanese. Hypertens Res 2006;29:75-80.

20. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412-419.

21. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183-1197.

22. Kuzuya T, Nakagawa S, Satoh J, Kanazawa Y, Iwamoto Y, Kobayashi M, et al.; Committee of the Japan Diabetes Society on the diagnostic criteria of diabetes mellitus. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Diabetes Res Clin Pract 2002;55:65-85.

23.The Examination Committee of Criteria for Metabolic Syndrome. Definition and Criteria of Metabolic Syndrome. J Jpn Soc Int Med 2005;94:794-809 (in Japanese).

24. Shen W, Punyanitya M, Wang Z, Gallagher D, St-Onge MP, Albu J, Heymsfield SB, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. J Appl Physiol 2004;97:2333-2338.

25. Ko GT, Chan JC, Cockram CS, Woo J. Prediction of hypertension, diabetes, dyslipidaemia or albuminuria using simple anthropometric indexes in Hong Kong Chinese. Int J Obes Relat Metab Disord 1999;23:1136-1142.

26. Sone H, Ito H, Ohashi Y, Akanuma Y, Yamada N. Obesity and type 2 diabetes in Japanese patients. Lancet 2003;361:85.

27. Arberti KG, Zimmet P, Shaw J for the IDF Epidemiology Task Force Consensus Group. The metabolic syndrome—a new worldwide definition. Lancet 2005;366:1059–62.

28. Hara K, Matsushita Y, Horikoshi M, Yoshiike N, Yokoyama T, Tanaka H, et al. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. Diabetes Care 2006;29:1123–4.

29. Ohkubo T, Kikuya M, Asayama K. A proposal for the cutoff point of waist circumference for the diagnosis of metabolic syndrome in the Japanese population. Diabetes Care 2006;29:1986–7.

30. Matoba Y, Inoguchi T, Nasu S, Suzuki S, Yanase T, Nawata H, et al. Optimal cut points of waist circumference for the clinical diagnosis of metabolic syndrome in the Japanese population. Diabetes Care 2008;31:590-2.

31. Oka R, Kobayashi J, Yagi K, Tanii H, Miyamoto S, Asano A, et al. Reassessment of the cutoff values of waist circumference and visceral fat area for identifying Japanese subjects at risk for the metabolic syndrome. Diabetes Res Clin Pract 2008; 79: 474-81.

32. Narisawa S, Nakamura K, Kato K, Yamada K, Sasaki J, Yamamoto M. Appropriate

waist circumference cutoff values for persons with multiple cardiovascular risk factors in Japan: a large cross-sectional study. J Epidemiol 2008;18:37-42.

33. Shai I, Jiang R, Manson JE, Stampfer MJ, Willett WC, Colditz GA, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 2006;29:1585-1590.

34. Kadowaki T, Yoshinaga H. Risk factors for the development of non-insulin-dependent diabetes mellitus (NIDDM) in Japan. Diabetes Res Clin Pract 1994;24 Suppl:S123-127.

35. Iozzo P, Beck-Nielsen H, Laakso M, Smith U, Yki-Jarvinen H, Ferrannini E. Independent influence of age on basal insulin secretion in nondiabetic humans. European Group for the Study of Insulin Resistance. J Clin Endocrinol Metab 1999;84:863-868.

36. Basu R, Breda E, Oberg AL, Powell CC, Dalla Man C, Basu A, et al. Mechanism of the age-associated deterioration in glucose tolerance: contribution of alterations in insulin secretion, action, and clearance. Diabetes 2003;52:1738-1748.

Table 1. Baseline characteristics of study participants

Characteristic	Total	Men	Women
Participants (n)	3,992	2,533	1,459
Age (y)	44.4 ± 5.8	44.4 ± 5.9	44.4 ± 5.7
Waist circumference (cm)	77.2 ± 8.8	80.0 ± 7.6	72.4 ± 8.8
Body mass index (kg/m^2)	23.0 ± 2.9	23.2 ± 2.7	22.6 ± 3.2
Fasting plasma glucose (mmol/l)	4.99 ± 0.49	5.04 ± 0.50	4.90 ± 0.45
Fasting insulin (μU/ml)	5.6 ± 4.3	5.7 ± 4.8	5.4 ± 3.3
HbA1c (%)	5.0 ± 0.4	5.0 ± 0.4	4.9 ± 0.4
HOMA-IR*	1.04 (0.69-1.50)	1.04 (0.67-1.55)	1.03 (0.76-1.43)
HOMA-B*	67.2 (47.0-95.3)	64.5 (43.2-93.3)	72.0 (51.4-98.2)
Systolic blood pressure (mmHg)	119.4 ± 14.1	121.8 ± 14.0	115.3 ± 13.4
Diastolic blood pressure (mmHg)	74.8 ± 10.6	76.8 ± 10.5	71.5 ± 9.9
Total cholesterol (mmol/L)	5.31 ± 0.87	5.30 ± 0.86	5.34 ± 0.89
HDL cholesterol (mmol/L)	1.52 ± 0.40	1.43 ± 0.39	1.67 ± 0.38
Triglycerides (mmol/L)*	1.01 (0.69-1.42)	1.19 (0.80-1.67)	0.77 (0.56-0.99)
Family history of diabetes (%)	11.9	12.8	10.5
Smoking (%)			
Never	53.7	28.7	96.9
Ex-smoker	7.4	11.5	0.5
Current smoker	38.9	59.8	2.6
Alcohol drinking (%)			
Nondrinker	43.8	21.5	82.6
Occasional drinker	2.5	2.2	3.0
Light drinker	41.0	56.9	13.2
Moderate/heavy drinker	12.7	19.3	1.2
Habitual exercise (%)			
No	70.9	66.5	78.3
Weak	17.1	19.5	13.2
Moderate	8.8	9.9	6.9
Strong	3.2	4.1	1.6
Prevalence of high blood pressure† (%)	29.5	36.0	18.2
Prevalence of dyslipidemia† (%)	21.3	29.7	6.8

Values are means ± standard deviation or %.

*Values are geometric means (interquartile range).

†High blood pressure and dyslipidemia were defined by Japanese criteria of metabolic syndrome.

Table 2. Age- and sex-adjusted and multivariate-adjusted hazard ratios for the incidence of type 2 diabetes according to sex-specific quintile of waist circumference

	Waist circumference quintile				
Parameter	Q1	Q2	Q3	Q4	Q5
Range of waist circumference, men (cm)	51.0-73.0	73.5-78.0	78.5-82.0	82.5-86.0	86.5-110.0
Range of waist circumference, women (cm)	54.0-65.0	65.5-69.0	69.5-73.5	74.0-80.0	80.5-120.0
Participants (n)	852	803	820	765	752
Age (y)	43.7 ± 5.7	44.3 ± 5.7	44.4 ± 5.9	44.7 ± 5.8	45.0 ± 5.9
Fasting plasma glucose (mmol/L)	4.90 ± 0.49	4.93 ± 0.46	4.99 ± 0.46	5.05 ± 0.52	5.09 ± 0.49
HbA1c (%)	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.1 ± 0.4
Fasting insulin (μU/mL)	4.1 ± 3.9	4.7 ± 3.4	5.3 ± 3.3	6.3 ± 4.0	7.7 ± 5.7
HOMA-IR*	0.75 (0.54-1.05)	0.88 (0.61-1.24)	1.04 (0.72-1.46)	1.22 (0.86-1.67)	1.48 (1.07-2.06)
HOMA-B*	53.4 (37.9-75.0)	60.2 (41.5-83.5)	66.8 (48.0-90.0)	75.0 (53.3-106.7)	87.9 (63.5-120.0)
Family history of diabetes (%)	10.7	11.7	13.3	10.2	13.8
Prevalence of high blood pressure† (%)	21.5	24.8	28.4	35.6	38.7
Prevalence of dyslipidemia† (%)	7.9	14.8	21.5	26.0	38.7
Total person-years	6,143	5,787	5,689	5,242	5,000
Incident cases (n)	39	23	34	58	64
Rate per 1,000 person-years	6.3	4.0	6.0	11.1	12.8
Adjusted hazard ratio (95%CI) (Model 1)	1.78 (1.06-2.98)	1.00 (reference)	1.59 (0.94-2.71)	3.11 (1.92-5.04)	3.30 (2.05-5.31)
Adjusted hazard ratio (95%CI) (Model 2)	1.81 (1.08-3.04)	1.00 (reference)	1.62 (0.95-2.76)	3.27 (2.01-5.31)	3.37 (2.09-5.43)
Adjusted hazard ratio (95%CI) (Model 3)	1.90 (1.13-3.19)	1.00 (reference)	1.50 (0.88-2.56)	2.82 (1.73-4.61)	2.72 (1.67-4.42)
Adjusted hazard ratio (95%CI) (Model 4)	1.62 (0.96-2.72)	1.00 (reference)	1.18 (0.69-2.01)	2.10 (1.28-3.46)	2.03 (1.24-3.33)

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, family history of diabetes, smoking, alcohol drinking, and habitual exercise; Model 3, adjusted for variables used in Model 2 and presence of hypertension and hyperlipidemia at baseline; Model 4, adjusted for variables used in Model 3 and fasting plasma glucose level.

*Values are geometric means (interquartile range).

†High blood pressure and dyslipidemia were defined by Japanese criteria of metabolic syndrome.

Table 3. Age- and sex-adjusted and multivariate-adjusted hazard ratios for incidence of type 2 diabetes according to sex-specific quintile of body mass index

	Body mass index quintile				
Parameter	Q1	Q2	Q3	Q4	Q5
Range of body mass index, men (kg/m^2)	15.8-20.9	21.0-22.4	22.5-23.8	23.9-25.4	25.5-33.9
Range of body mass index, women (kg/m^2)	15.2-19.9	20.0-21.4	21.5-22.8	22.9-24.9	25.0-41.3
Participants (n)	807	813	790	799	783
Age (y)	43.5 ± 5.6	44.1 ± 5.9	44.7 ± 5.8	44.8 ± 5.8	44.9 ± 5.9
Fasting plasma glucose (mmol/L)	4.91 ± 0.50	4.94 ± 0.47	4.98 ± 0.49	5.03 ± 0.48	5.09 ± 0.49
HbA1c (%)	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.0 ± 0.4	5.1 ± 0.4
Fasting insulin (μU/mL)	4.0 ± 3.0	4.7 ± 3.7	5.5 ± 4.0	6.1 ± 4.9	7.7 ± 4.7
HOMA-IR*	0.75 (0.54-1.06)	0.88 (0.63-1.20)	1.04 (0.74-1.48)	1.16 (0.82-1.61)	1.51 (1.08-2.11)
HOMA-B*	53.1 (37.2-72.0)	59.3 (41.5-83.1)	68.1 (49.1-94.7)	72.2 (51.4-98.5)	89.2 (65.5-120.0)
Family history of diabetes (%)	11.6	12.1	10.6	10.5	14.8
Prevalence of high blood pressure† (%)	22.4	23.5	28.4	32.7	41.0
Prevalence of dyslipidemia† (%)	9.4	15.1	19.0	26.3	37.4
Total person-years	5,781	5,836	5,492	5,518	5,234
Incident cases (n)	36	27	31	50	74
Rate per 1,000 person-years	6.2	4.6	5.6	9.1	14.1
Adjusted hazard ratio (95%CI) (Model 1)	1.40 (0.85-2.30)	1.00 (reference)	1.21 (0.72-2.03)	1.97 (1.23-3.14)	3.06 (1.97-4.75)
Adjusted hazard ratio (95%CI) (Model 2)	1.36 (0.82-2.24)	1.00 (reference)	1.23 (0.74-2.07)	2.02 (1.26-3.23)	3.00 (1.93-4.67)
Adjusted hazard ratio (95%CI) (Model 3)	1.42 (0.86-2.35)	1.00 (reference)	1.18 (0.70-1.98)	1.78 (1.11-2.85)	2.46 (1.57-3.86)
Adjusted hazard ratio (95%CI) (Model 4)	1.27 (0.77-2.10)	1.00 (reference)	1.03 (0.61-1.73)	1.59 (0.99-2.56)	2.06 (1.31-3.24)

Model 1, adjusted for age and sex; Model 2, adjusted for age, sex, family history of diabetes, smoking, alcohol drinking, and habitual exercise; Model 3, adjusted for variables used in Model 2 and presence of hypertension and hyperlipidemia at baseline; Model 4, adjusted for variables used in Model 3 and fasting plasma glucose level.

*Values are geometric means (interquartile range).

†High blood pressure and dyslipidemia were defined by Japanese criteria of metabolic syndrome.

Table 4. Difference in baseline insulin sensitivity (HOMA-R) and beta-cell function (HOMA-B) between subjects who developed type 2 diabetes and those who did not, across the sex-specific quintile of baseline waist circumference or body mass index

	HOMA-IR					HOMA-B				
	No diabetes		Incident diabetes		p*	No diabetes		Incident diabetes		p*
Waist circumference quintile										
Q1 (lowest)	0.75	(0.54-1.05)	0.79	(0.48-1.08)	0.561	54.8	(38.6-75.8)	31.7	(23.2-40.0)	<0.001
Q2	0.88	(0.62-1.24)	1.03	(0.76-1.35)	0.158	61.1	(42.4-85.0)	36.2	(25.7-51.4)	<0.001
Q3	1.03	(0.71-1.45)	1.23	(0.82-1.78)	0.041	67.4	(48.2-90.0)	54.0	(34.1-84.0)	0.053
Q4	1.20	(0.86-1.64)	1.59	(1.01-2.28)	0.003	76.4	(55.4-108.0)	60.1	(32.7-99.4)	0.025
Q5 (highest)	1.45	(1.30-2.02)	1.89	(1.34-2.57)	<0.001	88.9	(65.5-120.0)	78.1	(50.1-106.5)	0.070
Body mass index quintile										
Q1 (lowest)	0.75	(0.54-1.04)	0.83	(0.50-1.15)	0.268	54.3	(37.9-74.6)	33.1	(24.1-45.0)	<0.001
Q2	0.88	(0.63-1.20)	0.99	(0.71-1.33)	0.226	60.4	(42.4-83.1)	34.8	(23.2-51.4)	<0.001
Q3	1.04	(0.73-1.48)	1.15	(0.78-1.54)	0.322	68.9	(49.7-94.7)	50.0	(30.0-74.5)	0.001
Q4	1.15	(0.81-1.61)	1.31	(0.85-1.80)	0.111	73.3	(53.3-99.8)	56.9	(35.0-85.5)	0.038
Q5 (highest)	1.46	(1.04-2.04)	2.12	(1.54-2.95)	<0.001	90.2	(65.7-120.0)	80.0	(53.7-111.7)	0.087

Values are geometric means (interquartile range).

*t-test was used to compare geometric means.

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