Family history of diabetes, lifestyle factors, and the 7-year incident risk of type 2 diabetes mellitus in middle-aged Japanese men and women

Masaru Sakurai[1,2]*, Koshi Nakamura[1], Katsuyuki Miura[3], Toshinari Takamura[4], Katsushi Yoshita[5], Satoshi Sasaki[6], Shin-ya Nagasawa[1], Yuko Morikawa[1], Masao Ishizaki[7], Teruhiko Kido[8], Yuchi Naruse[9], Yasushi Suwazono[10], Hideaki Nakagawa[1]

ABSTRACT

Aims/Introduction: This cohort study of middle-aged Japanese participants investigated the relationship between family history of diabetes, the incident risk of type 2 diabetes and the interaction of these variables with other factors.

Materials and Methods: Study participants were 3,517 employees (2,037 men and 1,480 women) of a metal products factory in Japan. Baseline health examinations included questions about medical history, physical examination, anthropometric measurements, questions about lifestyle factors, such as smoking, alcohol consumption and habitual exercise, and a self-administered diet history questionnaire. Family history of diabetes was defined as having at least one-first-degree relative with diabetes. The incidence of diabetes was determined in annual medical examinations over a 7-year period. Hazard ratios (HRs) for type 2 diabetes were estimated by Cox proportional hazards analysis.

Results: Of the 3,517 participants, 630 (18%) had a family history of diabetes mellitus. During the study, 228 participants developed diabetes. The age and sex-adjusted HR for type 2 diabetes in participants with a family history of diabetes was 1.82 (95% confidence interval 1.36–2.43) as compared with those without a family history of diabetes. HRs did not change after adjustment for body mass index and lifestyle factors. We found no interactions with body mass index, insulin resistance, pancreatic β-cell function or lifestyle factors.

Conclusions: Family history of diabetes was associated with the incident risk of diabetes, and these associations were independent of other risk factors, such as obesity, insulin resistance, and lifestyle factors in Japanese men and women. (J Diabetes Invest doi: 10.1111/jdi.12033, 2013)

KEY WORDS: Cohort study, Epidemiology, Family history

INTRODUCTION

The prevalence of type 2 diabetes mellitus is similar in Asian and Western countries, even though the prevalence of obesity is lower in Asia[1]. The high incidence of diabetes in the relatively lean Asian population might be explained, in part, by a difference in fat distribution[2,3] and lower pancreatic β-cell function as compared with Western populations, rather than by insulin resistance[4–8]. One well-known risk factor for diabetes is family history. Family history of diabetes can include environmental in addition to genetic risk factors[9]. Obesity[10–14] and some lifestyle factors, such as alcohol consumption[14–16] and diet[15], were reported to be associated with a family history of diabetes, and these non-genetic factors explain a substantial part of the association between family history and risk of type 2 diabetes[15–17]. However, these reports were from Western countries, and it is not clear whether the association between family history and risk of diabetes involves interactions with obesity, insulin resistance and lifestyle factors in relatively lean Asian people.

In the present cohort study of middle-aged Japanese men and women, we examined the association between family history of diabetes and the 7-year incident risk of type 2 diabetes mellitus. We also evaluated the influence of interactions

Departments of [1]Epidemiology and Public Health, and [7]Social and Environmental Medicine, Kanazawa Medical University, Ishikawa, [3]Department of Health Science, Shiga University of Medical Science, [4]Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Science, [8]School of Health Sciences, College of Medical, Pharmaceutical and Health Sciences, Kanazawa University, Kanazawa, [5]Department of Food Science and Nutrition, Graduate School of Human Life Science, Osaka City University, Osaka, [6]Department of Social and Preventive Epidemiology, School of Public Health, the University of Tokyo, Tokyo, [9]Department of Community and Geriatric Nursing, Toyama University, Toyama, [10]Department of Occupation and Environmental Medicine, Graduate School of Medicine, Chiba University, Chiba, Japan, and [2]Department of Preventive Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA
*Corresponding author. Masaru Sakurai Tel.: +81-76-286-2211 Fax: +81-76-286-3728
E-mail address: m-sakura@kanazawa-med.ac.jp
Received 25 September 2012; revised 26 October 2012; accepted 11 November 2012

involving obesity, insulin resistance and lifestyle-related risk factors on this relationship.

METHODS

Participants

The study participants were employees of a factory that produces zippers and aluminum sashes in Toyama Prefecture, Japan. Detailed information on the study population has been reported previously[8,18–20]. The Industrial Safety and Health Law in Japan requires employers to provide annual health examinations for all employees. A test for diabetes mellitus was carried out during annual medical examinations between 2003 and 2010. In 2003, 3,776 employees (2,243 men and 1,533 women) aged 35–55 years underwent health examinations and responded to a dietary survey. Of these 3,776 potential participants, 259 (10%) were excluded for the following reasons: 193 had diabetes or high levels of fasting plasma glucose (FPG; ≥126 mg/dL) or glycated hemoglobin (HbA_{1c}; ≥6.5%) at the time of the baseline examination; 14 had a total daily energy intake of ≤ 500 kcal or ≥5,000 kcal; and 52 did not participate in consecutive annual follow-up health examinations. The remaining 3,517 participants (2,037 men and 1,480 women) were included in the present study.

Data Collection

The annual health examination included medical history, a physical examination, anthropometric measurements, and measurements of FPG, fasting insulin, HbA_{1c} 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. Body mass index (BMI) was calculated as weight / height^2 (kg/m^2). Blood pressure was measured twice using an automatic manometer (BP 103i; Nippon Colin, Komaki, Japan) after a 5-min rest in a seated position. All measurements were carried out by trained staff.

Plasma glucose levels were measured enzymatically using a glucose ultraviolet test (Abbott Laboratories, Chicago, IL, USA), and plasma insulin levels were determined by radioimmunoassay (Shionogi, Tokyo, Japan). HbA_{1c} was measured by high-velocity liquid chromatography using a fully automated hemoglobin A1c analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan). Quality control of the HbA_{1c} measurements was carried out using the standard certified by the Japan Diabetes Society (JDS), and HbA_{1c} values were converted to National Glycohemoglobin Standardization Program (NGSP) values using the formula provided by the JDS: HbA_{1c} (NGSP) (%) = 1.02 × HbA_{1c} (JDS) (%) + 0.25[21]. All present analyses used the HbA_{1c} values by the NGSP methods. Total cholesterol and triglycerides were measured using an enzymatic assay. High-density lipoprotein (HDL) cholesterol was measured using direct methods. Insulin resistance was calculated by the homeostasis model assessment (HOMA) method using the following formula: HOMA of insulin resistance (HOMA-IR) = fasting insulin (μU/mL) × FPG (mg/dL) / 405[22]. HOMA of pancreatic β-cell function (HOMA-B)[22] was calculated using the formula: HOMA-B = 20 × fasting insulin (μU/mL) / (FPG [mg/dL] / 18 − 3.5).

A questionnaire was used to collect information about smoking, alcohol consumption, habitual exercise, family history of diabetes, medical history of hypertension, dyslipidemia, diabetes and the use of antidiabetic medication. The presence of high FPG was defined by the JDS criteria[23], and the presence of hypertension and dyslipidemia were defined by the Japanese criteria for the metabolic syndrome[24]. High FPG was defined as FPG levels ≥110 mg/dL; hypertension was defined as systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or use of antihypertensive medications; and dyslipidemia was defined as serum triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL, or use of cholesterol-lowering medications. Hypercholesterolemia was defined as a serum total cholesterol ≥220 mg/dL or use of cholesterol-lowering medications. Participants were asked to report in the questionnaire whether any of their first-degree relatives (father, mother and/or siblings) had ever had diabetes. Total energy intake (kcal/day) was assessed using a self-administered diet history questionnaire (DHQ)[25]. The DHQ was developed for epidemiological studies in Japan to estimate the dietary intakes of macronutrients and micronutrients. Estimates of dietary intakes of 147 food and beverage items, energy, and nutrients were calculated using an ad hoc computer algorithm developed for the DHQ and based on the Standard Tables of Food Composition in Japan[26]. A detailed description of the methods used to calculate dietary intakes and the validity of the DHQ have been reported previously[25,27,28].

Participants were categorized as non-manual workers or manual workers according to their occupation. Non-manual workers consisted of managers, engineers and clerks, whereas the remaining individuals (laborers, and other workers including guards, gardeners, employees at the shop of the branch factory, and individuals engaged in managing dormitories and catering) were considered manual workers.

Diagnosis of Diabetes

FPG and HbA_{1c} were measured during the annual medical examinations. According to the definition of the American Diabetes Association[29] and the JDS[23], the diagnosis of diabetes was confirmed by at least one of the following observations: (i) a FPG concentration ≥126 mg/dL; (ii) a HbA_{1c} value ≥ 6.5%; and (iii) treatment with insulin or an oral hypoglycemic agent.

Statistical Analysis

Mean baseline values were compared between the participants with and without a family history of diabetes using Student's *t*-tests. Because fasting insulin, HOMA-IR and HOMA-B were log-normally distributed, log-transformed values were used for analyses. We calculated crude incidence rates and hazard ratios (HRs) for diabetes according to the family history of diabetes. The Cox proportional hazards model was used to calculate adjusted HRs. Adjustment for possible confounders was carried out sequentially as follows: (i) for age and sex (model 1); (ii) for age, sex and BMI (model 2); (iii) for family history of diabetes (no, yes), smoking status (never smoker, ex-smoker or current smoker), alcohol consumption determined by the DHQ (non-drinker, occasional drinker, consumption <20 g/day, consumption ≥20 g/day), habitual exercise (no, yes), occupational class (non-manual worker, manual worker), and presence of hypertension (no, yes), dyslipidemia (no, yes), and hypercholesterolemia (no, yes; model 3); (iv) for total energy intake (kcal/day; model 4); and (v) for HOMA-IR (model 5). Using the HR from model 5, the diabetes incidence fraction attributable to family history in this population was estimated. HRs for diabetes according to family history were calculated separately for males and females, different BMI categories (<22, 22–25 and ≥25 kg/m^2), different HOMA-IR and HOMA-B categories (tertiles), and other lifestyle factors. Interactions between family history and variables associated with obesity and lifestyle factors were also evaluated. Statistical analyses were carried out using the Japanese version of the Statistical Package for the Social Sciences (SPSS version 17.0; SPSS Japan Inc., Tokyo, Japan). A *P*-value of <0.05 was deemed to show statistical significance.

The present study was approved by the Institutional Review Committee for Ethical Issues of Kanazawa Medical University.

RESULTS

The mean age at baseline was 46.2 years and mean BMI was 23.0 kg/m^2. Of the 3,517 participants, 630 (18%) had a family history of diabetes mellitus. The participants' baseline characteristics according to family history of diabetes are shown in Table 1. The degree of obesity, variables for glucose metabolism and insulin resistance, pancreatic β-cell function, and lifestyle

Table 1 | Baseline characteristics of the 3,517 participants according to family history of diabetes

	No family history	Family history	*P*-value†
n	2,887	630	
Women (%)	41.7	43.9	0.303
Age (years)	46.3 ± 6.1	45.8 ± 6.0	0.051
Body mass index (kg/m^2)	23.0 ± 3.1	22.9 ± 3.1	0.634
Fasting plasma glucose (mg/dL)	91.1 ± 9.2	91.7 ± 9.4	0.121
Hemoglobin A1c (%)	5.3 ± 0.3	5.4 ± 0.4	0.078
Fasting insulin (μU/mL)	4.9 (3.0–7.0)	4.9 (3.3–7.0)	0.915
HOMA-IR	1.05 (0.70–1.60)	1.06 (0.70–1.60)	0.688
HOMA-B	66.6 (46.5–94.7)	65.0 (45.0–94.7)	0.344
Total cholesterol (mg/dL)	207.9 ± 33.4	207.1 ± 33.3	0.592
Triglycerides (mg/dL)	85.9 (56.0–126.0)	88.5 (58.0–128.0)	0.248
HDL-cholesterol (mg/dL)	62.4 ± 15.1	62.4 ± 16.5	0.993
Systolic blood pressure (mm Hg)	117.7 ± 18.8	116.3 ± 17.0	0.087
Diastolic blood pressure (mm Hg)	74.8 ± 13.4	73.9 ± 12.2	0.135
Total energy intake (kcal/day)	2,048 ± 600	2,036 ± 613	0.632
Smoking status (%)			0.084
Never smoker	56.8	52.0	
Ex-smoker	8.6	9.5	
Current smoker	34.6	38.5	
Alcohol consumption			0.340
Never	31.9	35.1	
Occasional	14.9	15.3	
Consumption <20 g/day	26.9	26.1	
Consumption ≥20 g/day	26.3	23.5	
Habitual exercise – yes (%)	24.0	27.0	0.113
Presence of metabolic abnormalities (%)			
High fasting plasma glucose	3.9	4.6	0.451
Hypertension	29.3	26.2	0.118
Dyslipidemia	24.4	25.3	0.666
Hypercholesterolemia	37.6	34.0	0.089
Occupational class (%)			0.038
Non-manual workers	25.4	29.4	
Manual workers	74.6	70.6	

Data are presented as *n*, mean ± standard deviation, geometric mean (interquartile range) or %.
†*P*-value for Student's t-test for continuous variables and χ^2-test for categorical variables.

factors, such as smoking status, alcohol consumption and total energy intake did not differ significantly according to family history of diabetes.

During the 7-year follow up (20,096 person-years, mean follow-up time 5.7 ± 1.7 years), we documented 228 cases of diabetes; 94 were diagnosed based on high FPG levels, 111 were based on high HbA_{1c} levels, and 23 were based on both high FPG and high HbA_{1c} levels.

Table 2 presents the risk of type 2 diabetes in different categories of a family history of diabetes. After adjustment for age and sex (model 1), the HR for type 2 diabetes in participants with any family history of diabetes was 1.82 (95% confidence interval 1.36–2.43) compared with participants without a family history of diabetes. The HR did not change after further adjustment for BMI (model 2), other lifestyle factors (model 3, 4) and HOMA-IR (model 5). The overall fraction of diabetes incidence attributable to family history in this population was 13.1%.

We found no differences in age, BMI and other lifestyle factors among family-history categories (data not shown); however, the HR for participants with a maternal history of diabetes was the highest among those with a family history of diabetes in first-degree relatives (Table 2).

We found no interactions between family history of diabetes and sex, degree of obesity, degree of insulin resistance and pancreatic β-cell function, lifestyle factors, presence of other chronic diseases, total energy intake, and occupational class in the context of incidence of type 2 diabetes (Table 3).

DISCUSSION

The present cohort study of middle-aged Japanese workers investigated the association between a family history of diabetes and the incident risk of type 2 diabetes. The results show that participants with a family history of diabetes had an 80% greater risk of incident diabetes compared with those without a family history of diabetes. These associations were independent of other risk factors, such as obesity, insulin resistance, dietary and lifestyle factors, and the presence of other chronic diseases. Additionally, 13% of the incident diabetes in this population was explained by a family history of diabetes. Among individuals with a family of history of diabetes, the risk of diabetes was highest among those with a maternal history of diabetes.

Similar to previous studies in Western countries[9,13,15,16,30–34], a family history of diabetes was significantly associated with the risk of diabetes in Japanese individuals. Family history of diabetes includes environmental factors in addition to genetic factors[9]. Obesity[10–14] and lifestyle factors, such as alcohol consumption[14–16] and diet[15], have been reported to be associated with a family history of diabetes, and these non-genetic factors explain a substantial part of the association between family history and the risk for type 2 diabetes[14,15,17]. However, these reports were from Western countries, and it is not clear to what extent obesity and lifestyle can explain the association between family history and the risk of diabetes in relatively lean Asian people with different lifestyles.

Family history of diabetes was not associated with BMI and insulin resistance in the present study participants, and the association between family history and the risk for diabetes did not change after adjustment for BMI and HOMA-IR. These results differ from those reported in previous studies in Western countries[14,15,17]. A previous study from Asia showed that a positive family history was associated with higher obesity levels and HOMA-IR[35]. However, the study was cross-sectional and

Table 2 | Incidence rate and adjusted hazard ratio for type 2 diabetes during the 7-year follow up according to family history of diabetes in 3,517 Japanese men and women

	No family history	Family history	Father only	Mother only	Sibling only	≥2 family members
n	2,887	630	299	181	75	75
Cases	166	62	20	25	8	9
Person-years of follow up	16,465	3,631	1,765	1,027	402	437
Incidence rate (/1,000 person-years)	10.1	17.1	11.3	24.3	19.9	20.6
Hazard ratio (95% CI)						
Model 1	1 (reference)	1.82 (1.36–2.43)	1.26 (0.79–2.01)	2.60 (1.71–3.97)	1.76 (0.86–3.58)	1.98 (1.01–3.87)
Model 2	1 (reference)	1.81 (1.36–2.43)	1.21 (0.76–1.93)	2.75 (1.80–4.19)	1.91 (0.94–3.90)	1.85 (0.95–3.62)
Model 3	1 (reference)	1.78 (1.32–2.37)	1.21 (0.76–1.93)	2.56 (1.67–3.92)	2.06 (1.01–4.20)	1.95 (0.99–3.82)
Model 4	1 (reference)	1.78 (1.33–2.38)	1.21 (0.76–1.93)	2.56 (1.67–3.92)	2.05 (1.00–4.18)	1.95 (0.99–3.81)
Model 5	1 (reference)	1.84 (1.36–2.47)	1.29 (0.80–2.08)	2.56 (1.67–3.92)	1.95 (0.95–4.00)	1.98 (1.01–3.91)

CI, confidence interval;
Model 1, adjusted for age and sex;
Model 2, adjusted for age, sex and body mass index;
Model 3, adjusted for Model 2 variables plus smoking, alcohol consumption, habitual exercise, occupational class, and presence of hypertension, dyslipidemia and hypercholesterolemia;
Model 4, adjusted for Model 3 variables plus total energy intake;
Model 5, adjusted for Model 4 variables plus homeostasis model assessment for insulin resistance.

Table 3 | Interactions between obesity, insulin resistance, lifestyle factors and family history of diabetes in the context of the incidence of diabetes in 3,517 Japanese men and women

	Family history	*n*	Incidence rate (/1,000 person-years)	Adjusted-HR (95% CI)†	*P*-value for interaction
Sex					0.344
Men	No family history	1,682	13.5	1.00 (reference)	
	Family history	355	23.1	1.62 (1.14–2.28)	
Women	No family history	1,202	5.6	1.00 (reference)	
	Family history	278	10.7	2.39 (1.36–4.22)	
Body mass index (kg/m^2)					0.687
<22	No family history	1,165	4.5	1.00 (reference)	
	Family history	262	6.4	1.75 (0.84–3.62)	
22.0–24.9	No family history	1,032	10.2	1.00 (reference)	
	Family history	223	19.8	1.83 (1.13–2.97)	
≥25	No family history	687	19.9	1.00 (reference)	
	Family history	148	34.1	1.81 (1.16–2.81)	
Fasting plasma glucose (mg/dL)					0.212
<110	No family history	2,773	6.8	1.00 (reference)	
	Family history	601	12.2	1.87 (1.31–2.67)	
110–125	No family history	114	123.6	1.00 (reference)	
	Family history	29	180.3	1.54 (0.88–2.70)	
HOMA-IR (tertiles)					0.478
<0.9	No family history	990	5.2	1.00 (reference)	
	Family history	214	11.2	2.26 (1.17–4.36)	
0.9–1.4	No family history	950	8.2	1.00 (reference)	
	Family history	203	15.0	1.96 (1.12–3.43)	
≥1.5	No family history	808	19.2	1.00 (reference)	
	Family history	179	30.3	1.56 (1.03–2.38)	
HOMA-B (tertiles)					0.495
< 53.0	No family history	906	15.4	1.00 (reference)	
	Family history	203	24.2	1.54 (0.98–2.42)	
53.0–83.5	No family history	939	8.8	1.00 (reference)	
	Family history	197	17.9	2.09 (1.24–3.50)	
≥83.6	No family history	906	6.8	1.00 (reference)	
	Family history	196	12.1	1.99 (1.06–3.76)	
Smoking status					0.584
Never/former smoker	No family history	1,884	7.6	1.00 (reference)	
	Family history	389	13.5	2.00 (1.32-3.05)	
Current smoker	No family history	997	14.8	1.00 (reference)	
	Family history	244	23.8	1.59 (1.06–2.40)	
Alcohol drinking					0.060
Never/occasional drinker	No family history	1,349	7.5	1.00 (reference)	
	Family history	319	16.0	2.74 (1.75–4.29)	
Regular drinker	No family history	1,535	12.4	1.00 (reference)	
	Family history	314	18.7	1.44 (0.97–2.15)	
Habitual exercise					0.288
No	No family history	2,192	10.0	1.00 (reference)	
	Family history	462	15.6	1.55 (1.09–2.20)	
Yes	No family history	692	10.3	1.00 (reference)	
	Family history	171	22.1	2.47 (1.43–4.27)	
Presence of metabolic abnormalities‡					0.835
No	No family history	1,196	4.1	1.00 (reference)	
	Family history	285	8.1	1.99 (1.05–3.78)	
Yes	No family history	1,691	14.7	1.00 (reference)	
	Family history	345	25.2	1.73 (1.24–2.41)	

Table 3 | (*Continued*)

	Family history	*n*	Incidence rate (/1,000 person-years)	Adjusted-HR (95% CI)†	*P*-value for interaction
Total energy intake (kcal/day, tertiles)					0.526
<1,744	No family history	963	9.3	1.00 (reference)	
	Family history	216	9.4	1.48 (0.78–2.81)	
1,745-2,194	No family history	952	8.8	1.00 (reference)	
	Family history	217	21.0	2.19 (1.34–3.59)	
≥2,195	No family history	969	12.0	1.00 (reference)	
	Family history	200	22.1	1.75 (1.10–2.80)	
Occupational class					0.485
Non-manual worker	No family history	732	5.4	1.00 (reference)	
	Family history	185	11.0	2.21 (1.05–4.67)	
Manual worker	No family history	2,155	11.5	1.00 (reference)	
	Family history	445	19.4	1.69 (1.23–2.33)	

†Adjusted for age, sex, body mass index, smoking, alcohol consumption, habitual exercise, and presence of hypertension, dyslipidemia and hypercholesterolemia.
‡Metabolic abnormalities included hypertension, dyslipidemia and hypercholesterolemia.
HOMA-B, homeostasis model assessment for pancreatic β-cell function; HOMA-IR, homeostasis model assessment for insulin resistance.

could not evaluate how these factors affect each other and the association between family history and risk for diabetes. Our prospective observations suggest that the association is not confounded by the presence of obesity and insulin resistance. Among relatively lean Asian people, not only obesity and insulin resistance, but also impaired insulin secretion is thought to be an important risk factor for diabetes[5–8]. Associations between family history of diabetes and obesity/insulin resistance, and the interaction between these factors and incidence of diabetes might differ from those identified in Western people. Similarly, family history was not associated with HOMA-B. HOMA-IR and HOMA-B are calculated using fasting plasma insulin and glucose levels. A family history of diabetes was reported to be associated with insulin response after glucose load[36–39], and postprandial glucose metabolism, rather than fasting glucose/insulin regulation, might be strongly associated with the family history-related incidence of diabetes in Asian people.

Two previous studies of Asian populations suggested that insufficient physical activity and family history of diabetes might jointly increase the risk of diabetes[40,41]. However, these studies did not evaluate the interaction between physical activity and family history. The present study found no significant interaction between habitual exercise and family history of diabetes, and family history was associated with an increased risk of diabetes independent of habitual exercise.

Among individuals with a family history of diabetes in different first-degree relatives, those with a maternal history of diabetes had the highest risk of diabetes in the present study. A greater risk from maternal diabetes compared with paternal diabetes has been reported in some previous studies[13,16,30,32], but not in all studies[9,15,33,42]. The explanations for this greater importance of maternal diabetes have included the following: genomic imprinting (i.e. the differential expression of inherited susceptibility genes in the paternal or maternal generation[43]); mutations in mitochondrial DNA, which are maternally inherited[44]; and metabolic programming during intrauterine exposure[45]. Furthermore, mothers might have a greater influence on their children's eating habits and other lifestyle behaviors, because they might spend more time with their children during childhood and in later life as compared with fathers. However, excess maternal transmission of type 2 diabetes was not observed in a hospital-based cross-sectional study from Korea[42]. Our prospective study suggests that Asian individuals with a maternal history of diabetes have a greater risk of type 2 diabetes. Because these associations were similar after adjustment for lifestyle factors, genetic background appears to have strongly affected the maternal transmission of diabetes.

The strengths of the present study were its prospective cohort design and large sample size as compared with other Asian studies. Furthermore, several previous cohort studies used information about incident diabetes collected from self-administered questionnaires, whereas our conclusions are based on more reliable data obtained from annual examinations and determination of fasting blood glucose and HbA_{1c}. The present study had several limitations. First, the family history of diabetes was self-reported and was evaluated only once, at the baseline examination. This might have caused misclassification errors. A family history of diabetes was observed in 18% of the present study participants; this percentage was similar to those in previous studies of Asian people (10–20%)[40–42], and any misclassification does not therefore appear to have been excessive. Second, the sample included only people who were employed. Poor health can prevent some individuals from working. Thus, the prevalence of obesity or the incidence of diabetes might be lower in our sample than in the general Japanese population.

However, in previous population-based cohort studies in Japan, the number of incident cases of diabetes was reported to be 67 in a group of 926 men followed for 9 years[46], and 65 in a group of 827 men and women followed for 9–10 years[47], these rates seem to be similar to that in our workplace cohort. Third, we did not measure waist circumference at baseline, which might have provided more information about abdominal fat accumulation and insulin resistance than was provided by BMI measurements. Fourth, oral glucose tolerance tests were not carried out, and we cannot evaluate the interaction between family history and glucose/insulin levels after glucose load in the context of diabetes incidence. A further limitation is that we did not determine whether the diabetes that developed was type 1 or type 2. However, the study participants were middle-aged men and, as the condition was detected in an annual medical check-up and was relatively mild, it is most likely that the cases were type 2 diabetes.

In conclusion, a family history of diabetes was significantly associated with the incident risk of diabetes in Japanese men and women, and this association was independent of interactions with obesity and lifestyle factors. Although family history of diabetes is an unmodifiable risk factor, detection and early intervention in these high-risk people would also be useful for the primary prevention of type 2 diabetes in the relatively lean Asian population.

ACKNOWLEDGMENTS

This research was supported by a Grant-in-Aid from the Ministry of Health, Labor, and Welfare, Health and Labor Sciences research grants, Japan (H18-Junkankitou [Seishuu]-Ippan-012, H19-Junkankitou [Seishuu]-Ippan-012, H19- Junkankitou [Seishuu]-Ippan- 021, H20-Junkankitou [Seishuu]-Ippan-013, H22- Junkankitou [Seishuu]-Ippan-005, H23-Junkankitou [Seishuu]-Ippan-005); and the Japan Arteriosclerosis Prevention Fund. The authors declare no conflict of interest.

REFERENCES

1. Yoon KH, Lee JH, Kim JW, *et al.* Epidemic obesity and type 2 diabetes in Asia. *Lancet* 2006; 368: 1681–1688.
2. Park YW, Allison DB, Heymsfield SB, *et al.* Larger amounts of visceral adipose tissue in Asian Americans. *Obes Res* 2001; 9: 381–387.
3. He Q, Horlick M, Thornton J, *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.
4. Chen KW, Boyko EJ, Bergstrom RW, *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.
5. Matsumoto K, Miyake S, Yano M, *et al.* Glucose tolerance, insulin secretion, and insulin sensitivity in non-obese and obese Japanese subjects. *Diabetes Care* 1997; 20: 156–158.
6. Yoshinaga H, Kosaka K. Heterogeneous relationship of early insulin response and fasting insulin level with development of non-insulindependent diabetes mellitus in non-diabetic Japanese subjects with or without obesity. *Diabetes Res Clin Pract* 1999; 44: 129–136.
7. 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: S37–S43.
8. Sakurai M, Miura K, Takamura T, *et al.* J-shaped relationship between waist circumference and subsequent risk for Type 2 diabetes: an 8-year follow-up of relatively lean Japanese individuals. *Diabet Med* 2009; 26: 753–759.
9. Meigs JB, Shrader P, Sullivan LM, *et al.* Genotype score in addition to common risk factors for prediction of type 2 diabetes. *N Engl J Med* 2008; 359: 2208–2219.
10. Lapidus L, Bengtsson C, Lissner L, *et al.* Family history of diabetes in relation to different types of obesity and change of obesity during 12-yr period. *Results from prospective population study of women in Goteborg, Sweden. Diabetes Care* 1992; 15: 1455–1458.
11. Rice T, Bouchard C, Perusse L, *et al.* Familial clustering of multiple measures of adiposity and fat distribution in the Québec Family Study: a trivariate analysis of percent body fat, body mass index, and trunk-to-extremity skinfold ratio. *Int J Obes Relat Metab Disord* 1995; 19: 902–908.
12. Haffner SM, Miettinen H, Stern MP. Insulin secretion and resistance in nondiabetic Mexican Americans and non-Hispanic whites with a parental history of diabetes. *J Clin Endocrinol Metab* 1996; 81: 1846–1851.
13. Groop L, Forsblom C, Lehtovirta M, *et al.* Metabolic consequences of a family history of NIDDM (the Botnia study): evidence for sex-specific parental effects. *Diabetes* 1996; 45: 1585–1593.
14. van Dam RM, Boer JM, Feskens EJ, *et al.* Parental history of diabetes modifies the association between abdominal adiposity and hyperglycemia. *Diabetes Care* 2001; 24: 1454–1459.
15. van't Riet E, Dekker JM, Sun Q, *et al.* Role of adiposity and lifestyle in the relationship between family history of diabetes and 20-year incidence of type 2 diabetes in U.S. women. *Diabetes Care* 2010; 33: 763–767.
16. Abbasi A, Corpeleijn E, van der Schouw YT, *et al.* Maternal and paternal transmission of type 2 diabetes: influence of diet, lifestyle and adiposity. *J Intern Med* 2011; 270: 388–396.
17. Valdez R, Yoon PW, Liu T, *et al.* Family history and prevalence of diabetes in the U.S. population: the 6-year results from the National Health and Nutrition Examination Survey (1999-2004). *Diabetes Care* 2007; 30: 2517–2522.
18. Nakashima M, Sakurai M, Nakamura K, *et al.* Dietary glycemic index, glycemic load and blood lipid levels in middle-aged Japanese men and women. *J Atheroscler Thromb* 2010; 17: 1082–1095.

19. Sakurai M, Nakamura K, Miura K, *et al.* Dietary glycemic index and risk of type 2 diabetes in middle-aged Japanese men. *Metabolism* 2012; 61: 47–55.
20. Sakurai M, Nakamura K, Miura K, *et al.* Self-reported speed of eating and 7-year risk of type 2 diabetes mellitus in middle-aged Japanese men. *Metabolism* 2012; 61: 1566–1571.
21. Kashiwagi A, Kasuga M, Araki E, *et al.* International clinical harmonization of glycated hemoglobin in Japan: from Japan Diabetes Society to National Glycohemoglobin Standardization Program values. *J Diabetes Invest* 2012; 3: 39–40.
22. Matthews DR, Hosker JP, Rudenski AS, *et al.* Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; 28: 412–419.
23. The Committee of the Japan Diabetes Society on the Diagnosis of Diabetes Mellitus. Report of the committee on the classification and diagnostic criteria of diabetes mellitus. *J Diabetes Invest* 2010; 1: 212–228.
24. Japan Medical Association Examination Committee of Criteria for Metabolic Syndrome. Definition and criteria of metabolic syndrome. *J Jpn Soc Int Med* 2005; 94: 794–809 (Japanese).
25. Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: a relative validation of the test-version by comparison with 3-day diet record in women. *J Epidemiol* 1998; 8: 203–215.
26. Science and Technology Agency. Standard tables of food composition in Japan, 5th edn. Printing Bureau of the Ministry of Finance, Tokyo, 2005 (Japanese).
27. Sasaki S, Ushio F, Amano K, *et al.* Serum biomarker-based validation of a self- administered diet history questionnaire for Japanese subjects. *J Nutr Sci Vitaminol* 2000; 46: 285–296.
28. Okubo H, Sasaki S, Rafamantanantsoa HH, *et al.* Validation of self-reported energy intake by a self-administered diet history questionnaire using the doubly labeled water method in 140 Japanese adults. *Eur J Clin Nutr* 2008; 62: 1343–1350.
29. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*1997;20: 1183–1197.
30. Karter AJ, Rowell SE, Ackerson LM, *et al.* Excess maternal transmission of type 2 diabetes. *The Northern California Kaiser Permanente Diabetes Registry. Diabetes Care* 1999; 22: 938–943.
31. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. *Diabetes* 2000; 49: 2201–2207.
32. Vaag A, Lehtovirta M, Thye-Rönn P, *et al.* Metabolic impact of a family history of Type 2 diabetes Results from a European multicentre study (EGIR). *Diabet Med* 2001; 18: 533–540.
33. Wilson PW, Meigs JB, Sullivan L, *et al.* Prediction of incident diabetes mellitus in middle-aged adults: the Framingham Offspring Study. *Arch Intern Med* 2007; 167: 1068–1074.
34. Magliano DJ, Barr EL, Zimmet PZ, *et al.* Glucose indices, health behaviors, and incidence of diabetes in Australia: the Australian Diabetes, Obesity and Lifestyle Study. *Diabetes Care* 2008; 31: 267–272.
35. Tan JT, Tan LS, Chia KS, *et al.* A family history of type 2 diabetes is associated with glucose intolerance and obesity-related traits with evidence of excess maternal transmission for obesity-related traits in a South East Asian population. *Diabetes Res Clin Pract* 2008; 82: 268–275.
36. Kadowaki T, Miyake Y, Hagura R, *et al.* Risk factors for worsening to diabetes in subjects with impaired glucose tolerance. *Diabetologia* 1984; 26: 44–49.
37. van Haeften TW, Dubbeldam S, Zonderland ML, *et al.* Insulin secretion in normal glucose-tolerant relatives of type 2 diabetic subjects Assessments using hyperglycemic glucose clamps and oral glucose tolerance tests. *Diabetes Care* 1998; 21: 278–282.
38. Jensen CC, Cnop M, Hull RL, *et al.* Beta-cell function is a major contributor to oral glucose tolerance in high-risk relatives of four ethnic groups in the U.S. *Diabetes* 2002; 51: 2170–2178.
39. Emerson P, Van Haeften TW, Pimenta W, *et al.* Different pathophysiology of impaired glucose tolerance in first-degree relatives of individuals with type 2 diabetes mellitus. *Metabolism* 2009; 58: 602–607.
40. Xu F, Wang Y, Ware RS, *et al.* Joint Impact of Physical Activity and Family History on the Development of Diabetes Among Urban Adults in Mainland China: a Pooled Analysis of Community-Based Prospective Cohort Studies. *Asia Pac J Public Health* 2012, (in press). doi: 10.1177/1010539512443700.
41. Xu F, Wang Y, Ware RS, *et al.* Physical activity, family history of diabetes and risk of developing hyperglycaemia and diabetes among adults in Mainland China. *Diabet Med* 2012; 29: 593–599.
42. Kim DJ, Cho NH, Noh JH, *et al.* Lack of excess maternal transmission of type 2 diabetes in a Korean population. *Diabetes Res Clin Pract* 2004; 65: 117–124.
43. Rampersaud E, Mitchell BD, Naj AC, *et al.* Investigating parent of origin effects in studies of type 2 diabetes and obesity. *Curr Diabetes Rev* 2008; 4: 329–339.
44. Maassen JA, Janssen GM, t' Hart LM. Molecular mechanisms of mitochondrial diabetes (MIDD). *Ann Med* 2005; 37: 213–221.
45. Fetita LS, Sobngwi E, Serradas P, *et al.* Consequences of fetal exposure to maternal diabetes in offspring. *J Clin Endocrinol Metab* 2006; 91: 3718–3724.
46. Doi Y, Kiyohara Y, Kubo M, *et al.* Elevated C-reactive protein is a predictor of the development of diabetes in a general Japanese population: the Hisayama Study. *Diabetes Care* 2005; 28: 2497–2500.
47. Ohnishi H, Saitoh S, Takagi S, *et al.* Incidence of type 2 diabetes in individuals with central obesity in a rural Japanese population: the Tanno and Sobetsu study. *Diabetes Care* 2006; 29: 1128–1129.