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

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Original article

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

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Short running title: Family history, lifestyle and diabetes

ABSTRACT

Aims/Introduction: This cohort study of middle-aged Japanese participants investigated the relationship among 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 a 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%CI 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 (HOMA-IR), pancreatic beta-cell function (HOMA-B), 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.

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 may be explained, in part, by a difference in fat distribution[2,3] and lower pancreatic beta- 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 may 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 this 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 involving obesity, insulin resistance, and lifestyle-related risk factors on this relationship.

PARTICIPANTS AND 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, 19, 20] The Industrial Safety and Health Law in Japan requires that employers provide annual health examinations for all employees. A test for diabetes mellitus was conducted 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 (HbA1c) (≥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, 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. 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-minutes rest in a seated position. All measurements were performed by trained staff.

Plasma glucose levels were measured enzymatically using a glucose UV test (Abbott

Laboratories, Chicago, IL, USA), and plasma insulin levels were determined by radioimmunoassay (Shionogi Co., Tokyo, Japan). HbA1c was measured by high-velocity liquid chromatography using a fully automated hemoglobin A1c analyzer (Kyoto Daiichi Kagaku, Kyoto, Japan). Quality control of the HbA1c measurements was performed using the standard certified by the Japan Diabetes Society (JDS), and HbA1c values were converted to National Glycohemoglobin Standardization Program (NGSP) values using the formula provided by the JDS: HbA1c (NGSP) (%) = 1.02 × HbA1c (JDS) (%) + 0.25.[21] All present analyses adopted the HbA1c 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-IR = fasting insulin (μU/mL) × FPG (mg/dL) / 405.[22] HOMA of pancreatic beta-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 anti-hypertensive 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 HbA1c 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: 1) a FPG concentration ≥126 mg/dL; 2) an HbA1c value ≥6.5%; and 3) 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 performed sequentially as follows: 1) for age and sex (Model 1); 2) for age, sex, and BMI (Model 2); 3) for family history of diabetes (no, yes), smoking status (never smoker, ex-smoker, or current smoker), alcohol consumption determined by the DHQ (nondrinker, occasional drinker, consumption <20 g/day, consumption ≥20 g/day), and 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); 4) for total energy intake (kcal/day) (Model 4); and 5) 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 conducted using the Japanese version of the Statistical Package for the Social Sciences (SPSS version 17.0; Tokyo, Japan). A *p*-value of <0.05 was deemed to indicate statistical significance.

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

RESULTS

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. Degree of obesity, variables for glucose metabolism and insulin resistance, pancreatic beta-cell function, and lifestyle 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 HbA1c levels, and 23 were based on both high FPG and high HbA1c 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%CI 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 beta-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

This cohort study of middle-aged Japanese workers investigated the association between family history of diabetes and the incident risk of type 2 diabetes. The results indicate 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 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] 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 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 our 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 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 may 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. 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, may 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 may jointly increase the risk of diabetes.[40, 41] However, these studies did not evaluate the interaction between physical activity and family history. Our 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 our 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 may have a greater influence on their children's eating habits and other lifestyle behaviors because they may 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 this study are its prospective cohort design and large sample size as compared with other Asian studies. Moreover, 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 andHbA1c. This study has several limitations. First, the family history of diabetes was self-reported and was evaluated only once, at the baseline examination. This may have

caused misclassification errors. A family history of diabetes was observed in 18% of our 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 may prevent some individuals from working. Thus, the prevalence of obesity or the incidence of diabetes may 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 may have provided more information about abdominal fat accumulation and insulin resistance than was provided by BMI measurements. Fourth, oral glucose tolerance tests were not performed, 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, 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 be useful for the primary prevention of type 2 diabetes also in the relatively lean Asian population.

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The authors declare no conflict of interest.

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

	No family history	Family history	P†
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 (mmHg)	117.7 ± 18.8	116.3 ± 17.0	0.087
Diastolic blood pressure (mmHg)	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 for analyses of variance for continuous variables and chi-square test for categorical variables.

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)

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 HOMA-IR.

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 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	No family history	1,884	7.6	1.00 (reference)	
smoker	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	No family history	1,349	7.5	1.00 (reference)	
drinker	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)	
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.