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Associations between dietary intakes of iron, copper and zinc with risk of type 2 diabetes mellitus: A large population-based prospective cohort study

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Short Title: Iron, copper and zinc intakes and type 2 diabetes.

Abstract

Background and aims: Abnormal homeostasis of iron, copper and zinc has been included in the pathogenesis of type 2 diabetes mellitus (T2DM). However, the evidence of associations between dietary intakes of these elements and T2DM is limited. We thought to examine the association between dietary intakes of iron, copper and zinc with risk of T2DM in Japanese population.

Methods: A prospective study encompassing 16,160 healthy Japanese men and women aged 40-65 years in whom the associations between dietary intakes of iron, copper and zinc, determined by a validated self-administered food frequency questionnaire, with risk of 5-year cumulative incidence of validated physician-diagnosed T2DM, were evaluated by logistic regression model.

Results: We ascertained 396 self-reported new cases of diabetes within 5-year period. Dietary intakes of iron (total and nonheme but not heme iron) and copper were positively associated with risk of T2DM; the multivariable OR in the highest versus lowest quartiles of intakes were 1.32 (1.04, 1.70; *P*-trend=0.03) and 1.55 (1.13, 2.02; *P*-trend=0.003), respectively. These associations were more evident in the high risk group; older, overweight, smokers and those with family history of diabetes. The dietary intake of zinc was inversely associated with risk of T2DM; the multivariable OR was 0.64 (0.54, 1.00; *P*-trend=0.003), and such association was evident among younger subjects (age 40-55years) only.

Conclusions: Dietary intakes of iron and copper were associated with a higher risk, while dietary intake of zinc was associated with a reduced risk of T2DM in Japanese population.

Keywords Cohort study; copper; iron; Japanese; type 2 diabetes mellitus; zinc.

1. Introduction

Globally, about 415 million people suffer from diabetes mellitus and this number is expected to increase to 642 million by 2040 (1). Type 2 diabetes (T2DM) accounts for 90% of all cases of diabetes (1). A rapid increase in diabetes prevalence was seen in Japan during the past two decades (2). To curb the trajectory of T2DM burden worldwide, concerted efforts to prevent diabetes are thus desirable.

Recognizing that genetic pool evolution is slow, the surge in T2DM burden in recent decades has been attributed to environmental determinants including declining diet quality (3). Lifestyle interventions, with overall diet modifications, have proven to be effective in reducing diabetes risk (2,4). Although, dietary trace elements like iron, copper, and zinc are major elements that work as cofactors of numerous enzymes (5), they can be toxic in excessive amounts via production of free radicals (5); one of the mechanisms for development of diabetes and diabetic complications is abnormal homeostasis of trace elements (5-9).

Epidemiological studies showed the associations of iron and serum ferritin (10-11), copper (6,12) and zinc (13,14) with insulin resistance and sensitivity; however, no study so far has examined the association between dietary intake of copper and risk of T2DM. Moreover, among the few studies that investigated the associations between dietary intakes of iron (15-21) and zinc (22-25) with T2DM, none of them were in Japanese population, whom dietary intakes of such trace elements did not meet the recommendation (26).

Our hypothesis is that, higher dietary intakes iron and copper may be positively associated, while higher intake of zinc may be inversely associated with risk of T2DM, among Japanese population.

2. Subjects and Methods

2.1. Study Population

The Japanese Ministry of Education, Sports and Science has sponsored a large prospective study; the Japan Collaborative Cohort Study for Evaluation of Cancer Risk (JACC Study) which was launched in 1988 to 1990 with 110,585 subjects (n= 46,395 men and 64,190 women) aged 40-79 years from 45 Japanese communities. After subjects or community leaders have given informed consents, subjects completed a self-administered questionnaire inquiring about their medical histories and habits. Details for JACC study protocol were described previously (27). The protocol of this investigation has been approved by the ethics committees of Hokkaido and Osaka Universities.

Of the subjects, 43,255 (16,926 males and 26,329 females) at baseline 40-65 years, with no prior history of diabetes, cancer or cardiovascular diseases gave valid responses on dietary iron, copper and zinc intakes. Of these subjects, those with missing information for history of diabetes and non-respondents to the 5-year questionnaire survey were excluded. Accordingly, 16,160 subjects (5,955 males and 10,205 females) were included in the study (See supplemental figure 1).

2.2. Dietary Assessment

Via a 40-items food frequency questionnaire (FFQ), the past year intakes of foods and drinks without specifying portion size were collected. The possible responses for the frequency of intake for each item were rarely, 1-2 times/month, 1-2 times/week, 3-4 times/week, and almost every day (27). These frequencies were then multiplied by 0, 0.38, 1.5, 3.5, and 7.0/week, respectively to obtain the intake of each food item. Dietary intakes of iron, copper and zinc- from various foods and drinks without any amounts from nutritional supplements- were obtained by multiplying the iron, copper

and zinc content from each food by the subject's frequency scores followed by summing all the food items. A validation study that used 1-year period intakes from four 3-days weighted dietary records in 85 subjects as a reference was used to estimate each portion size and to obtain data on validity of the FFQ-estimated intakes (27). The Spearman rank correlation coefficients for iron, copper and zinc intakes between the FFQ and DRs were 0.46, 53 and 0.27, respectively (27). The FFQ estimated intakes (mean ± SD) were (6.8 ± 2.1 mg/day) for iron, (0.97 ± 0.24 mg/day) for copper and (6.5 ± 1.5 mg/day) for zinc, while the DR estimated intakes were (9.4 ± 2.0 mg/day) for iron, (1.33 ± 0.27 mg/day) for copper and (8.8 ± 1.6 mg/day) for zinc. The FFQ was also used to assess heme and non heme iron intakes; the details of estimations and methods used were discussed in details previously (28).

2.3. Assessment of Diabetic Status

Subjects who reported having diabetes newly diagnosed by physicians on the 5-year questionnaire survey were considered to have incident diabetes. The validity of self-reporting physician diagnosed diabetes was assessed by comparing the self-reported data with treatment status and laboratory findings in a sample of 1230 men and 1837 women (29). As the criteria of the American Diabetic Association (30) were established after the diagnosis were made; treatment with oral hypoglycaemic or insulin or elevated serum glucose levels (fasting levels ≥ 7.8 mmol/L or randomly measured levels of ≥ 11.1 mmol/L) were the diagnostic criteria. Accordingly, the sensitivity of self-reporting was 70% for men and 75% for women and the specificity was 95% for men and 98% for women (29).

2.4. Statistical Analysis

The residual method was used to calculate the calorie-adjusted dietary intakes (31) of iron, copper, and zinc. Calorie-adjusted intakes were then modeled as four

categorical (quartiles) variables in the main analysis. The $\chi 2$-test and analysis of covariance were used to assess the significance of differences in proportions and mean values of subjects' baseline characteristics across quartiles of iron, copper and zinc intakes. Because the precise dates of diabetes onset were unknown, the outcome was the 5-year cumulative incidence of diabetes without calculating person-years. Associations between intakes of iron, copper and zinc with risk of T2DM, and the respective odds ratios (OR) and 95% confidence intervals (CI) in each quartile of intake were assessed by multiple logistic regression modeling that adjusted for age and sex in the first model. The second model was further adjusted for non-dietary factors including: family history of diabetes (yes, no); past history of hypertension (yes, no); smoking status (never, former smoker, current smoker of 1-19 and ≥20 cigarettes/day); body mass index (BMI) (quartiles); walking hours (almost no, daily 0.5, 0.6-0.9, and ≥1 hour) and exercise hours (almost no, weekly 1-2 , 3-4 and ≥5 hours). The third model was further adjusted for dietary factors including: alcohol intake (never, former and current daily drinker of 0.1-22.9, 23.0-45.9, 46.0-68.9, and ≥69.0 g ethanol); green tea intake in cups (<once/week, 1-6 /week, 1-2 /day, 3-5 /day, and ≥6 /day); coffee intake in cups (<once/week, 1-6 /week, 1-2 /day, and ≥3 /day); total energy intake (quartiles) and energy-adjusted intakes for magnesium and total carbohydrate (quartiles), while, on the last model we further adjusted for energy-adjusted intakes (quartiles) of iron, copper and zinc mutually. The median intake value (mg/day) for each quartile was used as a continuous variable to assess the trend across increasing groups of each element intake.

Stratification by age (40-54 or 55-65 years), sex, smoking status (current smokers and non-current smokers), family history of diabetes (yes or no), BMI (<25 or ≥25 kg/m²), alcohol intake (<23 or ≥23 g ethanol/day; the median intake) and

energy-adjusted magnesium intake (<230.7 or ≥230.7 mg/day; the median intake) were done. An interaction term generated by multiplying the median value of iron, copper and zinc intakes (mg/day) by (dichotomous) stratifying variables was added to the model to assess interactions. Two-tailed statistical tests were performed and a p-value <0.05 was considered statistically significant. SAS 9.4 software (SAS Institute Inc., Cary, NC, USA) was used.

3. Results

Following 16,160 subjects (5,955 males and 10,205 females) aged 40-65 years for 5 years revealed a total of 396 subjects developed T2DM (2.5%); 200 (3.4%) among men and 196 (1.9%) among women (comparing women with men, $P < 0.001$). Compared with subjects who remained non-diabetic, those who turned diabetics were more likely to be hypertensive and to have a family history of diabetes. They were also older, with a higher BMI and more likely to smoke and to drink more alcohol (not shown in table).

Table 1 shows that subjects in the highest quartile of iron, copper and zinc intakes compared with those in the lowest quartile were older, with less ethanol intake and were less likely to smoke, to drink green tea daily and to have a familial history of diabetes; but were more likely to drink coffee and to have higher intakes of magnesium, iron, copper and zinc. In addition, subjects with high zinc intake were less likely to be hypertensives, and subjects with high copper intake had higher intakes of carbohydrate.

The OR for 5- year incident T2DM by intakes of iron, copper and zinc are given in Table 2. Increasing intakes of iron and copper were associated with an elevated risk of incident T2DM; whereas, increasing intake of zinc tended to reduce

the risk. Adjusting for non-dietary factors did not change these associations; while after adjusting for the dietary factors, the positive associations with iron and copper and the inverse association with zinc remained statistically significant. The multivariable OR (95% CI) for the highest versus the lowest quartile of intakes were 1.33 (1.05, 1.75; P-trend = 0.03) for iron, 1.55 (1.13, 2.02; P-trend = 0.002) for copper and 0.65 (0.57, 0.99; P-trend = 0.001) for zinc. Mutual adjustment for iron, copper and zinc did not affect the associations materially.

Table 3 shows the results of stratified analyses by age, sex, smoking status, family history of diabetes, BMI, ethanol intake and energy-adjusted magnesium intake. The positive associations between iron and copper intakes with risk of T2DM were observed in the high risk group (older subjects, subjects with family history of diabetes, current smokers and subjects with BMI $\geq$ 25 kg/m^2), and there were no interactions by sex, ethanol intake or magnesium intake (P-interaction >0.1). The inverse association of risk for T2DM with higher zinc intakes was evident among younger subjects, but there were no interactions with any other studied factors.

Supplemental table 1 shows the associations between heme and nonheme iron intakes with risk of T2DM. Heme iron intake was not associated with risk of T2DM; while nonheme iron showed the same positive association as that of total iron intake.

4. Discussion

Findings from this prospective cohort study showed that higher dietary intakes of iron and copper were associated with increased risk of T2DM, while higher dietary zinc intake was associated with the reduced risk in Japanese men and women. The associations of iron and copper intakes with diabetes risk appeared more evident for

those at high risk; older, overweight, smokers and those with family history of diabetes.

Although these major elements are important cofactors of numerous enzymes (5), and their abnormal homeostasis is associated with the development of T2DM and its complications; however, disturbed serum levels of these elements were found to be induced by conditions like insulin resistance and hyperglycemia (5-9). Thus, their serum levels can be both contributors to the development of T2DM and/or results of metabolic distress in T2DM. In the current study, however, we examined the associations of dietary intakes rather than serum levels of these elements with risk of T2DM.

Mechanisms by which iron, copper and zinc associate with risk of T2DM have been studied extensively (5-14); the summary of these mechanisms include: 1- Imbalance of these elements (elevated levels of iron and copper and decreased levels of zinc) might adversely affect the pancreatic islets. 2- Iron and copper facilitate the production of reactive oxygen species (ROS) that might decrease the insulin gene promoter activity. 3- Elevated iron levels decrease insulin secretion and increase insulin resistance by oxidizing lipids, proteins and nucleic acids. 4- Zinc is essential for insulin secretion and storage. 5-Zinc transporter (ZnT8) is a key protein for pancreatic B-cells function.

Almost half of the pervious evidence of association between iron intake and risk of T2M have come from Chinese populations (19-21), while the other half have come mostly from female gender (16-19) or from populations characterized by high BMI and high meat intake (15-19). In our study, total iron, represented mainly by non heme iron (the Spearman correlation coefficient between total iron and non heme iron in the current study was 0.99), was positively associated with T2DM. In previous

literature, there was no association between total iron intake and risk of T2DM (15,16,18), however, one Chinese study showed a positive association; the multivariable OR in the highest (mean, 40.2 mg/day) versus lowest (mean, 15.4 mg/day) quartile of total iron intake was 3.73 (1.50, 9.26; P=0.004); which was evident only for women, 5.53 (1.47, 20.44; P=0.012) but not for men, 1.73 (0.50, 6.01; P=0.39) (21). On the other hand, another study, in which total iron intake extensively reflected non-heme iron intake; r=0.995, showed an inverse association between non heme iron and risk of T2DM; 0.80 (0.64, 1.01; P-trend=0.08) (17). Contrary to our findings of no association, a positive association between heme iron intake and risk of T2DM was evident in cross-sectional and prospective studies (15-18, 20) and in systematic reviews and meta-analyses (32-34). The causes for these opposite trends are unknown. The very low dietary intake of heme iron among Japanese might be one suggestion; our study has a mean intake of 0.2 mg/day for heme iron, which was much lower than that for European (1.8 mg/day) (16) and Chinese (1.5 mg/day) (20). The Japanese intake of heme iron is probably not high enough to increase diabetes risk. Another suggestion could be that the previous studies interpreted red meat intake as being solely heme iron (15,16), while the high fish intake in our study contributed largely to the heme iron intake; 45 % of heme iron in this study come from fish intake. Lastly, Luan et al (19), reported a positive association between total iron intake and risk of T2DM in North China, like that found in South China (21), this association disappeared after adjusting for blood lipids. Lipid profile was suggested as a confounder in the Chinese study; unfortunately, we did not have such data for all the subjects of our study.

The significant inverse trend of risk in T2DM across increasing quartiles of zinc intake seen in the current study adds greatly to the scarce literature (22-25). The

scope of many previous studies has been limited to either the reduced zinc status in diabetic patients, caused by urinary loss of zinc due to nephropathy (35), or the moderate decrease in glucose levels and tendency for a reduction in HbA1c with zinc supplementation in healthy (36,37) and T2DM patients (34,38). Only four studies have systematically examined the association between dietary zinc and T2DM, and the results were inconsistent (22-25); inverse associations among women from the Australian Longitudinal Study; hazard ratio (HR) (95%CI) in the highest versus lowest categories of intake was 0.50 (0.32, 0.77; P-trend=0.006) (22) and among women from the Nurse Health Study; HR (95% CI) was 0.92 (0.84, 1.00; P-trend=0.009) (23), but no associations were found in the Multi-Ethnic Study of Atherosclerosis; HR (95% CI) foe extreme quintiles was 1.41 (0.88, 2.27; P-trend=0.33) (24) or among Chinese healthy adults; HR (95% CI) was 0.93 (0.35, 2.46; P-trend=0.98), in whom higher zinc/heme iron ratio was associated with reduced risk of T2DM; HR (95% CI) was 0.21 (0.08, 0.54; P-trend=0.001) (25).

To the best of our knowledge, no epidemiological study has examined the association between dietary copper intake and risk of T2DM, so far. However, high levels of serum copper were detected in T2DM patients (38) and especially in diabetic complications (39); copper overload may be a contributing factor in developing diabetes and/or a result of diabetic complications (5,6-8,12, 38). Moreover, via suppressing the oxidative stress, copper supplementation can prevent Streptozotocin (STZ)-induced type 1 diabetes in mice (40), and through the Fenton reaction, copper facilitates the production of ROS (41); which are associated with development of T2DM (42). In addition, the high correlation between iron and copper; r=0.80 in the current study could be one explanation.

Limitations of our study include; first, some misclassification of outcome and exposure were unavoidable because physician-diagnosed diabetes and the intakes of the elements under study were self-reported. Based on a validation study (28), the FFQ-measured intakes of exposure variables were underestimated by at least a quarter. However, the self-reported diabetes in our study was validated and showed reasonable sensitivity and specificity (29). The actual associations between the studied elements and risk of T2DM could be more robust; because such nondifferential misclassifications were supposed to direct the associations towards the null. Second, only 37% of subjects confirmed their diabetic status at 5-year follow-up. However, there were no much difference in the mean age and BMI between respondents and nonrespondents. Also, there were no significant differences in the proportion of censored subjects, who moved or died, during the follow-up period between quartiles of the exposure variables; P-for difference=0.81, which refute the assumption that excess mortality among diabetic subjects in the highest quartiles of iron and copper intakes led to lower follow-up rate, or the assumption that the lower risk of T2DM in the highest quartile of zinc intake was attributed to patients lost to follow-up. Last, the mutual adjustment for exposure variables might be statistically incorrect, because the high correlations; r (0.70-0.80); however, we liked to examine the associations between each exposure variable with risk of T2DM regardless the effect of other elements, especially that in the model without mutual adjustment, the associations were more or less the same. It is worth mentioning that the correlation of magnesium with iron and copper were also high; the Spearman rank correlation coefficient were 0.84 and 0.64, respectively; however, no interaction by energy-adjusted magnesium intake was evident in the stratified analyses. Strengths of our study include its prospective design, a large sample size that enabled covariates-stratified analyses

supported by an adequate statistical power, the use of a validated FFQ, and the consistent endpoint determination.

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Conflict of Interest: none declared

Author contribution

Study conception and design (Ehab S. Eshak, Hiroyasu Iso and Akiko Tamakoshi); data collection (Hiroyasu Iso, Koutatsu Maruyama, Isao Muraki, and Akiko Tamakoshi); statistical analysis (Ehab S. Eshak); drafting the manuscript (Ehab S. Eshak); critical revision of the manuscript (Hiroyasu Iso, Koutatsu Maruyama, Isao Muraki, and Akiko Tamakoshi). All Authors have read and approved the final manuscript.

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Table 1. Participants' baseline characteristics according to quartiles of energy-adjusted iron, copper and zinc intakes.

	Quartiles of energy-adjusted iron intake					Quartiles of energy-adjusted copper intake					Quartiles of energy-adjusted zinc intake				
	1 (Low)	2	3	4 (High)	*P*-trend [a]	1 (Low)	2	3	4 (High)	*P*-trend [a]	1 (Low)	2	3	4 (High)	*P*-trend [a]
Subjects, *n*	4040	4040	4040	4040		4040	4040	4040	4040		4040	4040	4040	4040	
Age, year	52.2 ± 7.6 [b]	52.5 ± 7.5	53.0 ± 7.4	54.2 ± 7.1	<0.001	51.8 ± 7.6	52.6 ± 7.6	53.1 ± 7.6	54.3 ± 7.0	<0.001	52.2 ± 7.6	52.8 ± 7.5	53.0 ± 7.4	53.4 ± 7.2	<0.001
Males, %	53	36	30	28	<0.001	64	33	26	25	<0.001	71	34	23	19	<0.001
Family history of diabetes, %	9.3	10.7	9.2	7.4	0.001	10.3	10.1	9.1	7.2	<0.001	9.0	10.3	9.3	8.4	0.25
History of hypertension, %	14	14	13	13	0.15	14	13	14	13	0.84	16	14	13	11	<0.001
Current smoker, %	32	21	17	15	0.01	40	18	14	13	<0.001	43	19	13	11	<0.001
Body mass index, kg/m^2	22.9 ± 2.9	22.8 ± 2.7	22.8 ± 2.7	22.9 ± 2.8	0.69	22.8 ± 2.7	22.7 ± 2.8	22.8 ± 2.8	23.0 ± 2.9	0.005	22.9 ± 2.8	22.8 ± 2.8	22.8 ± 2.8	22.8 ± 2.8	0.25
Sports >=5 hour/week, %	19	18	19	20	0.13	20	19	20	19	0.20	20	20	19	20	0.36
Walking>=5 hour/week, %	51	50	55	59	<0.001	50	53	53	60	<0.001	51	53	53	59	<0.001
Ethanol intake, g/day	33.6 ± 24.6	26.9 ± 21.9	23.7 ± 20.8	21.3 ± 20.0	<0.001	38.4 ± 23.7	22.1 ± 19.0	17.1 ± 17.1	16.3 ± 17.2	<0.001	41.4 ± 22.4	18.5 ± 15.8	14.1 ± 14.6	12.1 ± 14.1	<0.001
>=1 cup of green tea/day	47	42	37	29	<0.001	55	44	33	23	<0.001	43	43	38	32	<0.001
>=1 cup of coffee /day	54	64	76	88	<0.001	60	66	73	83	<0.001	67	69	71	74	<0.001
Energy intake, Kcal/day	1639 ± 507	1535 ± 455	1554 ± 430	1659 ± 429	0.08	1657 ± 500	1528 ± 456	1536 ± 416	1667 ± 445	0.21	1671 ± 526	1493 ± 453	1531 ± 406	1692 ± 410	0.06
Carbohydrate intake, g/day	256 ± 40	246 ± 31	241 ± 29	252 ± 29	0.06	231 ± 42	248 ± 32	249 ± 28	247 ± 30	<0.001	239 ± 46	256 ± 30	248 ± 25	233 ± 25	0.07
Magnesium intake, mg/day	180 ± 30	219 ± 23	244 ± 24	278 ± 30	<0.001	191 ± 38	221 ± 33	242 ± 31	268 ± 36	<0.001	188 ± 36	219 ± 30	244 ± 30	270 ± 34	<0.001
Iron intake, mg/day	5.1 ± 1.0	6.9 ± 0.4	8.1 ± 0.4	10.1 ± 1.1	<0.001	5.6 ± 1.4	6.9 ± 1.2	8.0 ± 1.1	9.7 ± 1.5	<0.001	5.8 ± 1.6	7.0 ± 1.3	8.0 ± 1.3	9.4 ± 1.7	<0.001
Copper intake, mg/day	1.0 ± 0.12	1.1 ± 0.09	1.2 ± 0.09	1.3 ± 0.14	<0.001	0.97 ± 0.09	1.1 ± 0.03	1.2 ± 0.03	1.4 ± 0.12	<0.001	1.1 ± 0.13	1.1 ± 0.11	1.2 ± 0.11	1.4 ± 0.16	<0.001
Zinc intake, mg/day	6.6 ± 0.71	7.1 ± 0.57	7.5 ± 0.54	8.1 ± 0.71	<0.001	6.5 ± 0.77	7.2 ± 0.56	7.5 ± 0.52	8.0 ± 0.69	<0.001	6.3 ± 0.53	7.1 ± 0.14	7.6 ± 0.13	8.3 ± 0.50	<0.001

[a] Chi-square test was used for categorical variables; ANOVA was used for continuous variables.
[b] Mean ± SD (all such values).

Table 2. Odds ratios (95% CI) of 5-year incidence of type 2 diabetes according to energy-adjusted intakes for iron, copper and zinc in Japanese men and women

	Quartiles of energy-adjusted iron intake					Quartiles of energy-adjusted copper intake					Quartiles of energy-adjusted zinc intake				
	1 (Low)	2	3	4 (High)	*P*-trend [a]	1 (Low)	2	3	4 (High)	*P*-trend [a]	1 (Low)	2	3	4 (High)	*P*-trend [a]
Subjects, *n*	4040	4040	4040	4040		4040	4040	4040	4040		4040	4040	4040	4040	
Cases, *n*	126	104	84	82		127	109	90	70		138	93	87	78	
Model 1 [b]	1.00 (ref)	1.59 (1.22-2.09)	1.41 (1.17-1.85)	1.38 (1.15-1.80)	0.02	1.00 (ref)	1.69 (1.24-2.30)	1.61 (1.19-2.18)	1.54 (1.15-2.04)	0.03	1.00 (ref)	1.10 (0.90-1.64)	0.94 (0.74-1.25)	0.71 (0.62-1.02)	0.008
Model 2 [c]	1.00 (ref)	1.55 (1.14-2.12)	1.40 (1.08-1.82)	1.39 (1.12-1.87)	0.01	1.00 (ref)	1.52 (1.12-2.08)	1.53 (1.12-2.22)	1.45 (1.11-1.94)	0.01	1.00 (ref)	1.01 (0.81-1.43)	0.85 (0.66-1.21)	0.68 (0.64-1.06)	0.04
Model 3 [d]	1.00 (ref)	1.45 (1.12-1.99)	1.33 (1.05-1.71)	1.33 (1.05-1.75)	0.03	1.00 (ref)	1.56 (1.15-2.31)	1.50 (1.12-2.06)	1.55 (1.13-2.02)	0.002	1.00 (ref)	0.81 (0.69-1.19)	0.80 (0.57-1.07)	0.65 (0.54-0.99)	0.001
Model 4 [e]	1.00 (ref)	1.42 (1.10-1.96)	1.31 (1.03-1.68)	1.32 (1.04-1.70)	0.03	1.00 (ref)	1.52 (1.13-2.36)	1.57 (1.15-2.16)	1.53 (1.12-2.08)	0.003	1.00 (ref)	0.85 (0.66-1.20)	0.82 (0.56-1.10)	0.64 (0.54-1.00)	0.003

[a] Median value of iron, copper and zinc intakes in each quartile were used to test for a linear trend across quintiles. There were no interactions with sex; P for interaction >0.1.
[b] Model 1 Odds ratio (95% confidence intervals) estimated by using Logistic regression model adjusted for age and sex.
[c] Model 2 Odds ratio (95% confidence intervals) estimated by using Logistic regression model adjusted for age and sex and for non-dietary factors including: family history of diabetes, past history of hypertension, smoking status, body mass index, hours of walking and hours of exercise.
[d] Model 3 Odds ratio (95% confidence intervals) estimated by using Logistic regression model adjusted for age, sex, non-dietary factors including: family history of diabetes, past history of hypertension, smoking status, body mass index, hours of walking and hours of exercise and dietary factors including: alcohol intake, coffee intake, green tea intake, quartiles of total energy intake and quartiles of energy-adjusted intakes for magnesium and carbohydrate.
[e] Model 4 Odds ratio (95% confidence intervals) estimated by using Logistic regression model adjusted for age, sex, family history of diabetes, past history of hypertension, smoking status, body mass index, hours of walking and hours of exercise, alcohol intake, coffee intake, green tea intake, quartiles of total energy intake and quartiles of energy-adjusted intakes for magnesium and carbohydrate and adjusted further for quartiles of energy-adjusted iron, copper and zinc mutually.

Table 3. Odds ratios (95% CI) of 5-year incidence of type 2 diabetes according to energy-adjusted intakes for iron, copper and zinc stratified by age, sex, family history of diabetes, smoking status, body mass index, alcohol intake and magnesium intake.

	Energy-adjusted iron intake					Energy-adjusted copper intake					Energy-adjusted zinc intake				
	Q1 (Low)	Q2	Q3	Q4(High)	P- trend[a]	Q1 (Low)	Q2	Q3	Q4 (High)	P- trend[a]	Q1 (Low)	Q2	Q3	Q4(High)	P- trend[a]
Age															
40-54 year															
Cases/Subjects, *n*	60/2344	43/2288	32/2175	35/1909		71/3161	57/2948	42/2607	42/2607		59/2258	34/2189	38/2157	39/2112	
OR (95% CI)[b]	1.00 (ref)	1.21 (0.77-1.86)	1.03 (0.63-1.61)	0.80 (0.50-1.31)	0.23	1.00 (ref)	1.37 (0.95-2.23)	1.50 (0.99-2.41)	1.49 (0.99-2.16)	0.04	1.00 (ref)	1.01 (0.65-1.22)	0.74 (0.45-1.00)	0.69 (0.46-0.94)	0.005
55-65 year															
Cases/ Subjects, *n*	66/1696	61/1752	52/1865	47/2131		69/1618	62/1790	53/1916	42/2120		79/1782	59/1851	49/1883	39/1928	
OR (95% CI)[b]	1.00 (ref)	1.55 (1.05-2.30)	1.51 (1.01-2.21)	1.56 (1.05-1.86)	0.02	1.00 (ref)	1.62 (1.09-2.44)	1.44 (1.04-2.14)	1.41 (0.98-2.25)	0.04	1.00 (ref)	1.19 (0.80-1.68)	1.08 (0.75-1.88)	1.06 (0.72-1.63)	0.53
P- interaction					0.0003					0.88					0.03
Sex															
Male															
Cases/ Subjects, *n*	80/2160	45/1454	44/1219	31/1122		98/2570	46/1326	36/1057	20/1002		107/2852	39/1393	30/932	24/778	
OR (95% CI)[b]	1.00 (ref)	1.44 (0.95-2.23)	1.36 (0.91-2.11)	1.37 (0.97-2.34)	0.14	1.00 (ref)	2.06 (1.25-3.29)	1.85 (1.09-3.11)	1.70 (1.12-3.00)	0.02	1.00 (ref)	0.87 (0.48-1.23)	0.79 (0.51-1.23)	0.63 (0.49-1.04)	0.07
Female															
Cases/ Subjects, *n*	46//1880	59/2586	40/2821	51/2918		29/1470	63/2714	54/2983	50/3038		31/1188	54/2647	57/3108	54/3262	
OR (95% CI)[b]	1.00 (ref)	1.38 (0.92-2.10)	1.41 (0.95-2.06)	1.25 (0.92-2.32)	0.41	1.00 (ref)	1.23 (0.89-1.99)	1.36 (1.04-2.33)	1.25 (0.90-1.66)	0.62	1.00 (ref)	0.91 (0.69-1.27)	0.89 (0.60-1.23)	0.72 (0.59-1.10)	0.10
P- interaction					0.77					0.03					0.13
Family history of diabetes															
Yes															
Cases/ Subjects , *n*	16/333	15/383	11/331	13/264		16/365	15/361	12/327	12/258		15/319	15/366	17/321	8/305	
OR (95% CI)[b]	1.00 (ref)	1.40 (0.89-2.91)	1.49 (0.91-2.93)	1.48 (0.98-2.71)	0.05	1.00 (ref)	1.49 (0.88-2.90)	1.38 (0.89-2.36)	1.46 (0.94-2.27)	0.03	1.00 (ref)	1.09 (0.50-3.25)	1.25 (0.61-3.63)	0.94 (0.44-2.13)	0.62
No															
Cases/ Subjects, *n*	110/3707	89/3657	73/3709	69/3776		111/3765	94/3679	78/3713	58/3782		123/3721	78/3674	70/3719	70/3735	
OR (95% CI)[b]	1.00 (ref)	1.38 (0.99-1.96)	1.21 (0.90-1.88)	1.13 (0.91-1.72)	0.12	1.00 (ref)	1.60 (0.91-2.40)	1.70 (1.10-2.60)	1.67 (1.00-2.13)	0.04	1.00 (ref)	1.03 (0.80-1.50)	0.99 (0.66-1.30)	0.88 (0.45-1.18)	0.18
P- interaction					0.04					0.88					0.51
Smoking status															
Current smoker															
Cases/ Subjects, *n*	47/1297	23/845	28/699	18/625		60/1607	28/742	17/583	11/534		66/1737	20/786	17/506	13/437	
OR (95% CI)[b]	1.00 (ref)	1.40 (0.90-2.43)	1.26 (0.84-1.90)	1.50 (0.96-2.77)	0.04	1.00 (ref)	1.87 (0.96-3.58)	2.01 (0.98-4.11)	1.51 (0.95-3.27)	0.06	1.00 (ref)	0.92 (0.63-1.49)	0.83 (0.47-1.25)	0.65 (0.30-1.11)	0.08
Non-current smoker															
Cases/ Subjects, *n*	79//2743	81/3195	56/3341	64/3415		67/2433	81/3298	73/3457	59/3506		72/2303	73/3254	70/3534	65/3603	
OR (95% CI)[b]	1.00 (ref)	1.48 (0.95-2.08)	1.64 (1.07-1.97)	1.29 (0.88-2.39)	0.71	1.00 (ref)	1.46 (1.03-1.95)	1.36 (1.01-1.87)	1.33 (0.90-1.80)	0.02	1.00 (ref)	1.03 (0.85-1.29)	0.90 (0.78-1.16)	0.80 (0.53-1.07)	0.07
P- interaction					0.05					0.81					0.20
Body mass index															
<25 kg/m^2															
Cases/ Subjects, *n*	66/3226	64/3311	53/3290	49/3220		72/3267	66/3330	52/3286	42/3164		83/3257	47/3255	52/3282	50/3253	
OR (95% CI)[b]	1.00 (ref)	1.16 (0.80-1.73)	1.24 (0.85-1.82)	1.16 (0.83-1.77)	0.48	1.00 (ref)	1.32 (0.93-1.98)	1.46 (0.98-2.16)	1.42 (0.99-2.14)	0.03	1.00 (ref)	0.87 (0.57-1.20)	0.89 (0.58-1.15)	0.88 (0.48-1.13)	0.12
≥ 25 kg/m^2															
Cases/ Subjects, *n*	60/814	40/729	31/750	33/820		55/773	43/710	38/754	28/876		55/783	46/785	35/785	28/787	
OR (95% CI)[b]	1.00 (ref)	1.62 (1.17-2.46)	1.64 (1.13-2.19)	1.53 (1.16-2.41)	0.01	1.00 (ref)	1.90 (1.10-3.45)	1.56 (1.06-3.21)	1.54 (1.05-2.84)	0.005	1.00 (ref)	1.04 (0.67-1.25)	0.85 (0.62-1.14)	0.82 (0.58-1.03)	0.07
P- interaction					0.03					0.78					0.36

Alcohol intake [c]															
< median, g/day															
Cases/ Subjects, *n*	65/2520	74/3064	57/3291	65/3438		42/1797	82/3242	72/3587	65/3687		40/1459	72/3327	79/3715	70/3812	
OR (95% CI)[b]	1.00 (ref)	1.30 (0.91-1.88)	1.40 (0.99-1.85)	1.29 (0.92-1.63)	0.10	1.00 (ref)	1.44 (0.96-1.91)	1.51 (1.14-2.10)	1.31 (0.91-1.62)	0.07	1.00 (ref)	1.01 (0.69-1.16)	0.89 (0.64-1.14)	0.70 (0.52-1.08)	0.08
≥median, g/day															
Cases/ Subjects, *n*	61/1520	30/976	27/749	17/602		85/2243	27/798	18/453	5/353		98/2581	21/713	8/325	8/228	
OR (95% CI)[b]	1.00 (ref)	1.60 (1.16-2.66)	1.15 (0.90-2.16)	1.41 (0.97-2.54)	0.08	1.00 (ref)	1.88 (1.06-5.44)	2.51 (1.07-5.88)	2.83 (1.05-6.91)	0.05	1.00 (ref)	1.08 (0.50-1.41)	0.83 (0.56-1.17)	0.76 (0.50-1.12)	0.11
P- interaction					0.91					0.36					0.69
Magnesium intake [d]															
< median, mg/day															
Cases/ Subjects, *n*	75/2911	68/2846	30/1120	25/1203		96/2477	71/2552	32/1456	29/1595		100/2607	63/2647	32/1322	28/1504	
OR (95% CI)[b]	1.00 (ref)	1.46 (0.97-1.71)	1.58 (1.09-1.92)	1.41 (0.94-1.64)	0.06	1.00 (ref)	1.58 (1.06-2.01)	1.59 (1.14-2.00)	1.55 (1.06-1.99)	0.01	1.00 (ref)	0.84 (0.59-1.06)	0.91 (0.60-1.16)	0.80 (0.51-1.06)	0.10
≥median, mg/day															
Cases/ Subjects, *n*	51/1129	36/1194	54/2920	57/2837		31/1563	38/1488	58/2584	41/2445		38/1433	30/1393	55/2718	50/2536	
OR (95% CI)[b]	1.00 (ref)	1.48 (1.00-1.98)	1.44 (0.90-2.03)	1.46 (0.96-1.86)	0.06	1.00 (ref)	1.61 (1.09-2.13)	1.62 (1.10-2.62)	1.49 (1.03-2.11)	0.03	1.00 (ref)	1.01 (0.55-1.51)	0.87 (0.58-1.16)	0.79 (0.53-1.09)	0.13
P- interaction					0.87					0.69					0.78

[a] Median value of iron, copper and zinc intakes in each quartile were used to test for a linear trend across quintiles.

[b] Except for the factor of stratification, Odds ratio (95% confidence intervals) estimated by using Logistic regression model adjusted for age, sex, family history of diabetes, past history of hypertension, smoking status, body mass index, hours of walking and hours of exercise, alcohol intake, coffee intake, green tea intake, total energy intake and energy-adjusted intakes for magnesium and carbohydrate, and mutually for energy-adjusted iron, copper and zinc intakes.

[c] Median alcohol intake was 23g/day.

[d] Median energy-adjusted magnesium intake was 230.7 mg/day.