Manganese from foods and beverages is associated with the reduced risk of type 2 diabetes

Ehab S Eshak [a,b], Isao Muraki [a], Hironori Imano [a], Kazumasa Yamagishi [c], Akiko Tamakoshi [d], Hiroyasu Iso [a,c]

[a]Public Health, Department of Social Medicine, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita Shi, Osaka 565-0871, Japan. (ehab@pbhel.med.osaka-u.ac.jp, muraki@pbhel.med.osaka-u.ac.jp, imano@pbhel.med.osaka-u.ac.jp, iso@pbhel.med.osaka-u.ac.jp)

[b]Department of Public Health and Preventive Medicine, Faculty of Medicine, Minia University, Shalaby land, Minia 61511, Egypt. (eehab@mu.edu.eg)

[c]Department of Public Health Medicine, Faculty of Medicine, and Health Services Research and Development Center, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575 Japan. (yamagishi.kazumas.ge@u.tsukuba.ac.jp)

[d]Department of Public Health, Hokkaido University Graduate School of Medicine, Kita 15 Nishi 7, Kita-ku, Sapporo, 060-8638, Japan. (tamaa@med.hokudai.ac.jp).

Correspondence to Eshak ES, Public Health, Graduate School of Medicine Osaka University 2-2 Yamadaoka, Suita, Osaka, 567-0871 Japan. Tel : +81-6-6879-3763 Fax: +81-6-6879-3919 email:ehab@pbhel.med.osaka-u.ac.jp

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Abstract

Background: Despite the hypoglycemic and antioxidant effects of manganese, no previous studies have investigated the dietary manganese intake/type 2 diabetes associations, except one recent Chinese study.

Methods: We recruited 19,862 Japanese men and women participated in the Japan Collaborative Cohort Study. The participants were those who completed the food frequency questionnaire section at the baseline survey (1988=1990) and the diabetes history at both baseline and 5-year surveys. We calculated the odds ratios (95% CIs) of the 5-year cumulative incidence of self-reported physician diagnosed type 2 diabetes according to quartiles of dietary manganese intake.

Results: Within 5-year period, we confirmed 530 new cases of type 2 diabetes (263 in men and 267 in women) with a 5-year cumulative incidence of 2.7% (3.6% in men and 2.1% in women). Higher manganese intake was inversely associated with the women's but not men's cumulative risk of type 2 diabetes over 5-year period. In a full model adjusted for the participants' characteristics, diabetes risk factors and a wide range of dietary variables, the multivariable odds ratios (95%CIs) of type 2 diabetes across the increasing quartiles of manganese intake (Q1 to Q4) were 1.00, 0.97 (0.65-1.43), 1.04 (0.67-1.61) and 1.10 (0.64-1.92); p-trend=0.66 among men and 1.00, 0.74 (0.51-1.06), 0.62 (0.41-0.94) and 0.53 (0.31-0.88); p-trend=0.01 among women. The association was observed mainly for those with low iron status; premenopausal women and women with low iron intake.

Conclusion: Strong inverse associations between dietary manganese intake with risk of type 2 diabetes were observed in women but not men.

Keywords: epidemiology, diet, manganese, diabetes, follow-up study.

1. Introduction

The multifactorial disease, type 2 diabetes, is becoming a chronic illness with heavy burden at both health and economic aspects [1]. The epidemiology of type 2 diabetes indicates that Japanese men and women are more likely to develop type 2 diabetes than their Western counterparts with the same body size measures; waist circumference and body mass index (BMI) [2].

The role of micronutrient minerals and vitamins in diabetes pathogeneses started to attract the interest of scientists [3,4]. The trace element manganese is a metal that has potential roles in many human body functions including immunity enhancement, cellular and blood glucose homeostasis and scavenging of free radicles [5]. Manganese is essential for the production and expression of oxidoreductases and manganese superoxide dismutase (MnSOD involved in the reduction of oxidative stress [5]. These potentials predict possible beneficial effects of manganese against type 2 diabetes.

Diet is the main source of manganese; however excess occupational inhalation of manganese can be considered as a source of manganese toxicity [6]. Both manganese deficiency and intoxication can lead to serious metabolic adverse effects [6]. Dietary sources of manganese vary by country; for example, the main sources of manganese were grain products (percent contribution =37%) in the United States [7], bread (percent contribution = 48%) in Canada, [8], rice (45%) in China [9], while green tea (28.3% in men and 33.9% in women) was a major contributor in Japan [8]. The estimated adequate manganese intake for Japanese adults was set at 4.0 and 3.5 mg/day for men and women, respectively [10].

A few previous research articles had investigated the associations between dietary manganese intake and risk of type 2 diabetes and suggested the reduced risk with higher manganese intakes [3,9]; whereas, there were abundant research, with inconsistent conclusions, on the association between levels of manganese concentrations in different biological samples and risk of type 2 diabetes [11-16]; no associations [11,12], inverse associations [13,14], positive association [15] and U-shaped association [16]. However, the supplement of manganese in animal studies reduced the risk of artificially-induced diabetes [17].

Prior to this study, there was no epidemiological research to assess the dietary manganese/type 2 diabetes association in Japanese populations; however, the main source of manganese in Japan, green tea, was inversely associated with the risk of type 2 diabetes [18]. Therefore, we aimed to examine the association between dietary manganese and risk of type 2 diabetes using the data of the Japan Collaborative Cohort (JACC) study. Because there was an evidence of sex differences in the manganese absorption rate, manganese blood levels and biological half-time of manganese, in favor of women than men [19], we hypothesized that dietary manganese intake could be associated with the reduced risk of type 2 diabetes, especially among women.

2. Methods

2.1. Study Population and Their Diet

The JACC Study was a large prospective cohort study sponsored by the Japanese Ministry of Education, Sports and Science. Its baseline data were collected between 1988-1990 from residents of 45 areas across Japan who were aged 40–79 years with the aim of evaluating their cancer risk. The informed consent was received from community leaders or participants

themselves. Details can be found in this cohort profile article [20]. In brief, 61,767 subjects completed a self-administered questionnaire assessing their demographic characteristics, medical history, and lifestyle habits and a 40-items food frequency questionnaire (FFQ) at baseline. A 5-year follow-up survey was conducted among 46,540 participants in 31 areas of the 45 investigated areas at the baseline. A total of 25,846 subjects completed both the baseline FFQ and the 5-year questionnaire and were recruited for the current research. We excluded 3,861 subjects with a past history of diabetes at baseline and 2,123 others with missing data on diabetes history at the 5-year follow-up survey. This left for the analysis 19,862 Japanese (7,316 men and 12,546 women) with valid responses to exposure and outcome variables.

The FFQ assessed the participants consumptions of food and beverages other than plain water over the previous 12 months and had five frequency choices ranged from “almost none” to “almost daily”. The daily manganese intake was calculated by multiplying the middle value of each intake frequency range by the potion sizes determined by a validation study [21] according to the manganese content of 100g of each food item from the Japanese Food Composition Tables, fifth edition. The design of this research was approved by the ethics committees of Hokkaido University and Osaka University.

2.2.Definition of Incident Diabetes

We considered the participants without history of diabetes at baseline who responded “yes” to the 5-year survey’s question: “Have you ever been diagnosed with diabetes by a physician?” as new cases of self-reported physician-ascertained incident diabetes. The baseline participants’ age was 40 years or more; accordingly, we considered all self-reported cases as type 2 diabetes. In a comparison with the laboratory confirmed diabetes and/or medical registry of diabetes treatment, the sensitivity of self-reported diabetes was 75% in 1,837 females and 70% in 1,230 males of our

participants, and the respective values of specificity were 98% in females and 95% in males. Further details of the laboratory diagnosis of diabetes used to validate the collected self-reported incidence can be found in several previous publications [4,18,22].

2.3.Statistical Analyses

Based on the biological justification of sex differences in manganese metabolism [5, 19] the analyses of the manganese/type 2 diabetes were presented for men and women separately. Sex-specific daily manganese intakes were divided into quartiles and the sex-specific age-adjusted trends of participants' characteristics across the increasing quartiles of manganese intake were tested by logistic regression for proportions and linear regression for mean values.

The odds ratios (ORs) with the respective risk limits at 95% confidence (CIs) were estimated by the logistic regression analysis to assess the sex-specific associations between manganese intake, with its lowest quartile serving as a reference, and the cumulative incidence of type 2 diabetes using all the self-reported cases. In upgraded models we adjusted for age and area of residence in the first model, adding to the second model dummy variables representing family history of diabetes [yes and no], past history of hypertension (yes and no), sex-specific quartiles of BMI that was calculated as weight in kg/square of height in meter, smoking status (never, former and current), time spent in sports per week (<3h and ≥3h), time spent in daily walking (<1h and ≥1h), education (junior high school, high school and university or more), occupation (full-time, part-time, self-employed, others, housemaker and unemployed), level of stress (low, normal and high) and sleep hours per day (<6, 6-7, 8-9 and ≥10). In the final model, we adjusted further for sex-specific quartiles of total energy, vitamin C, riboflavin, vitamin K, zinc, iron, copper, calcium and magnesium intakes, and alcohol intake (never, former, current drinker of <23, 23.0 -45.9, 46.0-68.9 and ≥69.0g ethanol/day). The p value for linear trend was calculated

by using a continuous variable of manganese intake assigning the median values in each quartile. According to priori-known physiology of manganese homeostasis [5, 19], we tested the effect modifications by iron intake for both men and women and by menopausal status for women, and computed p-interactions for cross product terms of manganese intake quartiles and dichotomous stratifying variables (> or ≥ value of sex-specific median iron intake and pre- versus post-menopausal status). We also ran a sensitivity analysis by dividing the participants according to their green tea intake [missing or and intakes < 1 cup per day of green tea versus intakes of ≥ 1 cup per day]. SAS 9.4 software (SAS Institute Inc.) was used to conduct the statistics and a two-tailed p-value <0.05 was considered statistically significant.

3. Results

Table 1 shows that men and women in higher intake quartiles of manganese compared with those in the lowest quartile of intake were more likely to walk for one hour or more per day, less likely to have high mental stress and to drink coffee daily and had higher intakes of vitamins, minerals, dietary fiber and total energy. Men in higher quartiles of manganese intake were older and less likely to be unemployed; whereas as women in higher intake categories consumed less alcohol and were less likely to smoke compared with those in the lowest group of manganese intake.

Within 5-year period in the early 1990s, 530 new cases of type 2 diabetes (263 in men and 267 in women) were reported, with a 5-year cumulative incidence of 2.7% (3.6% in men and 2.1% in women). Higher manganese intake was inversely associated with the women's likelihood to develop type 2 diabetes, but similar association was not observed for men. The multivariable ORs (95%CIs) of type 2 diabetes across increasing quartiles of manganese intake (Q1 to Q4) in the fully controlled model were 1.00, 0.74 (0.51, 1.06), 0.62 (0.41, 0.94) and 0.53

(0.31, 0.88); p-trend=0.01 among women and 1.00, 0.97 (0.65, 1.43), 1.04 (0.67, 1.61) and 1.10 (0.64, 1.92); p-trend=0.66 among men (Table 2). P-for sex-interaction was 0.06.

Stratifying our participants by the median iron intake (7.5 mg/d in men and 7.2 mg/d in women) suggested a significant association between manganese intake and risk of type 2 diabetes in women with low iron intake; OR in the highest versus lowest quartiles of manganese intake was 0.25; 95%CI: 0.10, 0.68; p trend=0.01, but not in women with high iron intake; OR was 0.55; 95%CI: 0.26, 1.20; p-trend=0.369; p-interaction by iron intake was 0.067. There was no evidence of interaction with iron intake in men; p-interaction was 0.538 (Supplemental Table I).

Although the p-interaction with menopausal status was not of a level of statistical significance; p=0.812, the magnitude of observed inverse association between dietary manganese and risk of type 2 diabetes seen in women varied by the menopausal status: in premenopausal women; OR in the highest versus lowest quartiles of manganese intake was 0.26; 95%CI: 0.08, 0.83; p trend=0.032, while OR in postmenopausal women was 0.63; 95%CI: 0.34, 1.16; p trend=0.108 (Supplemental Table II).

The main dietary sources of manganese in our sample were green tea (84% in men and 86% in women), rice (10% in men and 6% in women) and oolong tea (2% in men and 4% in women). Because green tea contains large amounts of polyphenols that might be responsible for the reduced risk of type 2 diabetes such as catechins, for which we do not have data to adjust for, we stratified men and women in our cohort by their reported green tea intake. There was no difference in the associations between dietary manganese intake and risk of type 2 diabetes in men and women whose dietary manganese intake was not attributed mainly to green tea

(missing, never, or intakes <1 cup per day of green tea) and those who reported valid response to green tea intake of one cup or more per day (Supplemental Table III).

4. Discussion

The analyses of the dietary intakes and 5-year cumulative incidence of type 2 diabetes data in a cohort of 19,862 Japanese men and women revealed an inverse association between manganese intake and risk of type 2 diabetes among women but not men, independent of known diabetes risk factors or other dietary intakes.

The observed associations between dietary manganese intake and risk of type 2 diabetes is plausible considering the previous evidence from experimental animal studies and observational human studies on mechanisms by which manganese can affect the pathogenesis of diabetes [5]. Animal studies pointed to impaired insulin synthesis and secretion from the pancreas, accelerated insulin degradation and glucagon release in manganese-deficient animal models [23] and protective effects of manganese supplementation against risk of artificially induced diabetes in mice [17]. Manganese, by being involved in carbohydrate, lipid and amino acids metabolism, together with its role in elimination of reactive oxygen species [5] also has the potency to reduce the risk of type 2 diabetes. Since the early 1960s, Rubenstein et al [24], reported that oral and intravenous administration of manganese to a male diabetic patient aged 18 years, lowered hyperglycemia and speeded up cellular glucose uptake. Later on, some epidemiological studies pointed to low manganese levels in various biological samples of diabetic patients compared with non-diabetic controls [13,14]. However, some others found no difference [11,12], and one study reported higher plasma manganese in diabetic Chinese [15].

while another Chinese study had the conclusion of a U-shaped association; diabetics had either higher or lower levels of plasma manganese than controls [16].

A dietary pattern with high manganese intake was associated with the lower risk of type 2 diabetes in 71,270 women participated in a French cohort prospective study; women in the third and fourth quartiles of that dietary pattern in comparison to women in lowest quartile had HRs (95% CIs) of 0.78 (0.68, 0.89) and 0.82 (0.72, 0.94), respectively [3]. Recently, a prospective study has shown that dietary manganese was inversely associated with type 2 diabetes incidence and HbA1c concentrations in two Chinese cohorts; 3,350 subjects from the Harbin People's Health Study (HPHS) followed-up for 4.2 years, and 7,133 subjects from the Harbin Cohort Study on Diet, Nutrition and Chronic Noncommunicable Diseases (HDNNCDS) followed-up for 5,2 years. The multivariable HRs (95%CIs) for incident type 2 diabetes in the highest (≥4.91 mg/d in HPHS and 4.98 mg/d in HDNNCDS) against lowest (<4.22 mg/d in HPHS and <4.27 in HDNNCDS) tertiles of dietary manganese intake were 0.52 (0.33, 0.82; p-trend= <0.01) in HPHS and 0.61 (0.43, 0.88; p-trend= <0.01) in HDNNCDS [9]; however, sex-specific results were not reported in these studies.

In our study, the observed sex difference, with lower risk of type 2 diabetes in women with high manganese intake than that observed in men, could be attributed biologically to higher absorption, bioavailability and retention of manganese in women than in men [19, 25], which were attributed partially to the sex differences in iron status. Higher manganese absorption rate, higher manganese blood concentrations and longer half-time of manganese were reported in case of iron deficiency and low ferritin levels [19, 26] frequently seen in women. In our study, a significant interaction with dietary iron intake was observed and dietary manganese was inversely associated with risk of type 2 diabetes in women with low iron intake, but not in those

with higher iron intake. Moreover, one report suggested female sex hormones might also mediate the sex difference in manganese status; however, a scientific evidence was lacking [19]. Stratifying our studied women by menopausal status showed the robust association between manganese intake and risk of type 2 diabetes in premenopausal women more than in postmenopausal women; here, we also point to the low ferritin levels and higher prevalence of iron deficiency anemia in premenopausal than postmenopausal women [27].

Our study is the first to investigate the association between dietary manganese intake and risk of type 2 diabetes among Japanese population. The findings could add to the biological justifications and explanations of why green tea consumption was associated with the reduced risk of diabetes in Japan [18]; manganese content could have played a hidden role as the major source of manganese in our cohort was green tea, 85% contribution. The study strengths include its prospective design, large sample size, sex-specific analyses and controlling for a wide range of hypothesized confounding factors. On the other hand, limitations of the current investigation include the lack of manganese data from water, supplements and occupational exposure. However, it has been shown that water contribution to manganese intake is minimal; concentrations of manganese in drinking water = 1 to 100 mcg/L [5], and manganese supplement was not popular in Japan during the early 1990s. Second, we ascertained our outcome by self-reported data; however, the self-reported incidence of diabetes in our study had good specificity and sensitivity to laboratory data and medical therapy registries for both sexes [4,18,28]. Third, the 5-year follow-up survey was conducted in 31 out of 45 baseline study areas, and some of the respondents to the 5-year survey had missing data on incident diabetes; therefore, we have lost a considerable proportion (58%) of the JACC study participants. However, we tested if there were any sort of selection bias due to these loses and fond no significant differences between included

and excluded subjects as regard to diabetes risk factors, sociodemographic characteristics or dietary intakes [4,22,28]. Fourth, we used the 5-year cumulative incidence of diabetes because the precise date of diabetes diagnosis cannot be determined. With such short follow-up duration, revers causation cannot be totally excluded. Last, manganese bioavailability was shown to be affected by other nutrients; consuming iron, copper, calcium dietary fiber, polyphenols and phytate together with manganese could impair manganese bioavailability; while zinc enhances it [5,19]. We adjusted for most of these variables however, residual confounding by polyphenols, phytate or other nutrients could still persist.

In conclusion, this is the first Japanese prospective study to show an inverse association between dietary manganese intake and risk of type 2 diabetes. The association was observed mainly for women, especially those with low iron status, independent of other dietary intakes or known diabetes risk factors.

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Author contribution

Eshak ES, Iso H and Tamakoshi A designed the research, Muraki I, Hironori H, Yamagishi K participated in data collection, Eshak ES conducted the statistical analyses and drafted the manuscript, Muraki I, Hironori H, Yamagishi K, Iso H and Tamakoshi A provided critical review of the content. All authors have approved this research article after careful reading.

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Table 1. Sex-specific participants' characteristics (mean ± standard deviation, proportion)[a] according to quartiles of dietary manganese intake.

	Men					Women				
	Q1	**Q2**	**Q3**	**Q4**	**P-trend[b]**	**Q1**	**Q2**	**Q3**	**Q4**	**P-trend[b]**
Number of subjects, n	1829	1829	1829	1829		3136	3137	3137	3136	
Manganese intake, mg/d	2.7 ± 0.7	4.6 ± 0.5	6.4 ± 0.6	9.7 ± 1.8	<0.001	2.5 ± 0.5	4.1 ± 0.5	5.9 ± 0.5	8.6 ± 1.6	<0.001
Age, y	55.9 ± 10.1	55.4 ± 9.9	56.3 ± 9.4	56.7 ± 8.6	0.002	55.7 ± 9.8	55.8 ± 9.6	55.8 ± 9.5	55.9 ± 8.8	0.45
History of hypertension, %	21.6	20.4	20.8	20.9	0.46	20.3	21.3	20.0	19.8	0.44
Current smoker, %	50.6	50.3	53.4	51.4	0.36	4.3	4.0	3.5	3.9	0.06
Sports>=5 hour/wk, %	7.3	7.4	7.9	8.3	0.40	4.2	3.9	2.3	2.9	0.28
Walking>=1hour/d, %	43.4	50.7	53.6	59.8	<0.001	46.1	53.6	53.6	57.1	<0.001
Higher education, %	18.3	18.0	19.3	15.7	0.10	9.1	9.7	11.3	9.7	0.11
High mental stress, %	25.3	25.7	21.2	19.8	0.001	21.0 ± 8	21.4	20.2	18.4	<0.001
BMI, kg/m²	22.7 ± 2.7	22.5 ± 2.7	22.6 ± 2.5	22.6 ± 2.7	0.45	22.8 ± 3.1	22.7 ± 2.9	22.7 ± 2.9	22.9 ± 2.9	0.13
Unemployed, %	19.0	16.7	14.7	13.9	<0.001	50.1	49.2	48.7	51.4	0.61
Sleep duration, h/d	7.4 ± 1.1	7.4 ± 1.0	7.4 ± 1.1	7.5 ± 1.0	0.14	7.0 ± 1.0	7.1 ± 1.0	7.0 ± 1.0	7.1 ± 1.0	0.04
Ethanol intake, g/d	33.8 ± 22.5	33.8 ± 21.1	33.5 ± 21.9	33.3 ± 21.8	0.85	10.7 ± 14.1	9.1 ± 10.9	8.6 ± 10.7	9.2 ± 12.7	0.04
>=1 cup of green tea/d, %	23.4	71.6	97.5	99.6	<0.001	10.4	70.8	96.5	99.2	<0.001
>=1 cup of black tea/d, %	1.0	2.1	2.7	1.5	0.12	1.4	2.5	3.1	2.0	<0.001
>=1 cup of oolong tea/d, %	2.7	5.4	4.1	5.1	<0.001	2.6	9.4	9.3	10.2	<0.001
>=1 cup of coffee/d, %	46.2	48.9	43.8	29.1	<0.001	42.1	49.7	43.8	32.4	<0.001

Number of rice bowls/d	2.8 ± 1.2	3.8 ± 1.6	4.0 ± 1.6	4.6 ± 1.6	<0.001	2.5 ± 0.9	3.0 ± 1.3	3.1 ± 1.2	3.4 ± 1.2	0.04
Zinc intake mg/d	6.2 ± 1.6	7.5 ± 2.1	7.9 ± 2.0	9.0 ± 2.1	<0.001	6.1 ± 1.5	6.9 ± 1.8	7.2 ± 1.7	7.8 ± 1.8	<0.001
Magnesium intake mg/d	187 ± 53	225 ± 61	240 ± 61	277 ± 63	<0.001	94 ± 53	218.± 57	231 ± 54	261 ± 57	<0.001
Calcium intake, mg/d	437 ± 161	492 ± 173	517 ± 177	577 ± 177	<0.001	461 ± 165	502 ± 169	525 ± 170	572 ± 170	<0.001
Copper intake, mg/d	0.94 ± 0.26	1.19 ± 0.34	1.28 ± 0.33	1.53 ± 0.35	<0.001	0.92 ± 0.24	1.07 ± 0.30	1.15 ± 0.26	1.31 ± 0.29	<0.001
Iron intake, mg/d	5.8 ± 2.0	7.1 ± 2.2	8.0 ± 2.2	10.0 ± 2.4	<0.001	5.9 ± 1.9	6.8 ± 2.1	7.6 ± 2.0	9.3 ± 2.2	<0.001
Riboflavin intake mg/d	0.9 ± 0.3	1.1 ± 0.4	1.3 ± 0.4	1.7 ± 0.4	<0.001	0.9 ± 0.3	1.1 ± 0.4	1.3 ± 0.4	1.6 ± 0.4	<0.001
Vitamin C intake mg/d	80 ± 33	105± 36	126 ± 38	165 ± 43	<0.001	95 ± 35	116 ± 36	137 ± 37	171 ± 41	<0.001
Vitamin K intake µg/d	156 ± 69	179 ± 73	189 ± 75	214 ± 77	<0.001	171 ± 68	185 ± 71	195 ± 69	216 ± 72	<0.001
Total dietary fiber intake, g/d	8.4 ± 3.0	10.1 ± 3.5	10.6 ± 3.5	12.2 ± 3.6	<0.001	9.3 ± 3.0	10.2 ± 3.3	10.6 ± 3.1	11.9 ± 3.3	<0.001
Total Energy intake, Kcal/d	1452 ± 369	1767 ± 486	1849 ± 473	2073 ± 493	<0.001	1255 ± 285	1436 ± 380	1494 ± 348	1615 ± 364	<0.001

[a]Continuous variables were expressed as men ± SD and categorical variables as percentages.

[b]P-trend were calculated by age-adjusted linear regression for continuous variables and age-adjusted logistic regression for categorical variables.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) of type 2 diabetes according to quartiles and one standard deviation increment of dietary manganese intake

	Quartiles of dietary manganese intake					One SD increment in dietary manganese
	Q1(low)	Q2	Q3	Q4	*P*-trend [a]	
Men, n	1829	1829	1829	1829		
Cases, n	66	65	70	62		
Age- and area-adjusted OR (95%CI)	1.00	0.98 (0.68, 1.40)	1.05 (0.73, 1.50)	0.99 (0.68, 1.45)	0.966	0.98 (0.86, 1.12)
Multivariable OR (95%CI) [b]	1.00	1.00 (0.70, 1.44)	1.06 (0.74, 1.52)	0.99 (0.68, 1.46)	0.989	0.98 (0.85, 1.12)
Multivariable OR (95%CI) [c]	1.00	0.97 (0.65, 1.43)	1.04 (0.67, 1.61)	1.10 (0.64, 1.92)	0.664	1.00 (0.80, 1.23)
Women, n	3136	3137	3137	3136		
Cases, n	82	70	62	53		
Age- and area-adjusted OR (95%CI)	1.00	0.80 (0.57, 1.11)	0.73 (0.52, 1.04)	0.66 (0.47, 0.96)	0.026	0.87 (0.76, 1.01)
Multivariable OR (95%CI) [b]	1.00	0.77 (0.55, 1.08)	0.69 (0.49, 0.98)	0.61 (0.42, 0.89)	0.009	0.86 (0.74, 0.99)
Multivariable OR (95%CI) [c]	1.00	0.74 (0.51, 1.06)	0.62 (0.41, 0.94)	0.53 (0.31, 0.88)	0.014	0.85 (0.69, 0.98)

[a] Median values of manganese intakes in each quartile were used to test the linear trend across quartiles.

[b] Adjusted further for family history of diabetes, past history of hypertension, quintiles of body mass index, weekly sports hours, daily time spent in walking, daily hours of sleep, cigarettes smoking, educations, occupation, and mental stress.

[c] Adjusted further for ethanol intake, and quartiles of total calorie, total dietary fiber, vitamin C, riboflavin, vitamin K, calcium, magnesium zinc, copper and iron intakes.