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ARTICLE

Dietary manganese and type 2 diabetes mellitus: two prospective cohort studies in China

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Abstract

Aims/hypothesis The association between dietary Mn and type 2 diabetes is unclear. We aimed to elucidate whether dietary Mn is associated with type 2 diabetes, to investigate whether this association is independent of dietary total antioxidant capacity (TAC) and to explore the underlying mechanisms in their association.

Methods Two prospective cohorts of 3350 and 7133 Chinese adults (20–74 years old) were enrolled including, respectively, 244 and 578 individuals newly diagnosed with type 2 diabetes, with mean values of 4.2 and 5.3 years of follow-up. Cox's proportional-hazards regression and linear regression were performed to investigate the association between dietary Mn and type 2 diabetes (diagnosed by OGTT) or HbA_{1c} and to analyse the joint association between dietary Mn and TAC. Restricted cubic spline (RCS) regression was applied to the non-linear association between dietary Mn and incidence of type 2 diabetes. Mediation analysis was applied to explore potential mediators in their association in a subgroup of 500 participants.

Results Dietary Mn intakes were 4.58 ± 1.04 and 4.61 ± 1.08 (mean ± SD) mg/day in the two cohorts. Dietary Mn was inversely associated with type 2 diabetes incidence and HbA_{1c} concentration in both cohorts ($p_{trend} < 0.01$ and <0.01 for type 2 diabetes, and $p_{trend} < 0.01$ and =0.02 for HbA_{1c}, respectively, in each cohort) independent of TAC, adjusted for age, sex, BMI, tobacco use, alcohol consumption, physical activity, diabetes inheritance, total energy, carbohydrate, total fatty acids, fibre, calcium, Mg, hypertension, hyperlipidaemia, and impaired glucose tolerance or FBG (all at baseline). Their inverse association was stronger in the presence of diets with high, compared with low, TAC. In RCS, intakes of >6.01 and 6.10–6.97 mg/day were associated with a significantly lower type 2 diabetes incidence in the two respective cohorts. Mediation analysis showed that high plasma Mn and low oxidative stress (increased Mn superoxide dismutase and decreased 8-hydroxydeoxyguanosine) contributed to the association between dietary Mn and both type 2 diabetes and HbA_{1c}.

Conclusions/interpretation Dietary Mn was inversely associated with type 2 diabetes independently of TAC. In addition, this association was stronger in a high- rather than low-TAC diet. Plasma Mn and oxidative stress were mediators in the association between dietary Mn and type 2 diabetes. Future studies on absolute Mn intake should be conducted to study the potential non-linearity and optimal levels of dietary Mn and type 2 diabetes.

Keywords Antioxidant capacity · Diet · Manganese · Type 2 diabetes

Shanshan Du and Xiaoyan Wu contributed equally to this article.

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Abbreviations

8-OHdG	8-Hydroxydeoxyguanosine
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
FFQ	Food frequency questionnaire
F-insulin	Fasting insulin
HDNNCDS	Harbin Cohort Study on Diet, Nutrition and Chronic Non-communicable Diseases
HDL-c	HDL-cholesterol
HPHS	Harbin People's Health Study
LDL-c	LDL-cholesterol

Research in context

What is already known about this subject?

- The association between dietary Mn and type 2 diabetes has been reported in animal models but not in human studies
- Plasma Mn and Mn superoxide dismutase have been suggested as biomarkers of dietary Mn and are associated with type 2 diabetes

What is the key question?

- In humans, is dietary Mn associated with type 2 diabetes, is this association modified by dietary total antioxidant capacity, and what are the potential mechanisms involved in the association between dietary Mn and type 2 diabetes?

What are the new findings?

- Dietary Mn intake was inversely associated with type 2 diabetes incidence and the association was stronger in diets with high, compared with low, total antioxidant capacity
- Plasma Mn and oxidative stress were mediators in the association between dietary Mn and type 2 diabetes

How might this impact on clinical practice in the foreseeable future?

- The study could provide evidence for the beneficial effect of dietary Mn on prevention of type 2 diabetes and help develop guidelines on dietary Mn

MnSOD	Mn superoxide dismutase
PBG	Postprandial blood glucose
P-insulin	Postprandial insulin
RCS	Restricted cubic spline
SBP	Systolic blood pressure
SEM	Structural equation modelling
SOD	Superoxide dismutase
TAC	Total antioxidant capacity

Introduction

In China, the prevalence of diabetes has reached 10.9%, contributing to the largest number of individuals with diabetes around the world [1]. Diet and nutrients are established risk factors for type 2 diabetes and offer potentially modifiable prevention and treatment strategies [2].

Mn is one of the essential micronutrients for humans [3] and dietary consumption is a principal source of Mn in the body [3]. Animal studies have found an association between dietary Mn and glucose metabolism: low dietary Mn can impair insulin secretion and glucose metabolism [4], while Mn supplementation modifies the enzyme profiles of carbohydrate metabolism [5] and improves high-fat-diet-induced beta cell injury and insulin resistance in animal models of diabetes [6]. However, acute oral Mn supplementation does not consistently affect glucose tolerance in non-diabetic or type 2 diabetic individuals [7], and few studies have reported the possible effect of dietary Mn in type 2 diabetes. The association between dietary Mn and type 2 diabetes in human studies is unclear, especially in longitudinal cohort studies.

Plasma Mn and Mn superoxide dismutase (MnSOD) have been recommended as potential biomarkers for Mn nutritional status in the human body [3], and both of them have been associated with type 2 diabetes. Low serum Mn has been associated with a high risk of type 2 diabetes [8]. However, higher levels of Mn in serum [9] and urine [10, 11] have also been reported in individuals with diabetes, and similar whole-blood Mn levels between diabetic and non-diabetic individuals have been observed [12]. MnSOD plays a major role in the downregulation of oxidative stress [13], a pathogenic factor of type 2 diabetes [14]. Whether serum Mn and oxidative stress contribute to the association between dietary Mn and type 2 diabetes has not been reported. No data in humans have been reported to explain the possible mechanism of their association. It is important to clarify these connections to understand the effect of dietary Mn on type 2 diabetes. In epidemiological research, mediation analysis has been paid much attention recently when assessing whether and how the effect of an exposure on an outcome could be explained by an intermediate variable [15]. It can be employed to explore the mediators in the association between dietary Mn and type 2 diabetes.

Dietary Mn has been reported to increase MnSOD and participate in antioxidant defences in the human body [6]. However, many antioxidants in the diet were also proposed to affect plasma antioxidant capacity and oxidative stress [16] and were inversely associated with type 2 diabetes [17]. Whether dietary antioxidants affect the association between dietary Mn and type 2 diabetes is ambiguous. Dietary total

antioxidant capacity (TAC), which is the capacity of total food antioxidants to scavenge free radicals [18], is a potential marker of diet quality [19]. Thus, TAC was used in our current study to investigate whether the association between dietary Mn and type 2 diabetes was independent of TAC.

In this research, two prospective cohort studies in China were used. We intended to investigate whether dietary Mn was associated with type 2 diabetes and whether their association was independent of TAC, carbohydrate, fatty acids, fibre, calcium and Mg. The non-linear association between dietary Mn and type 2 diabetes was also examined. Mediation analysis was used to explore the mediators in their association.

Methods

Study population

Two prospective study cohorts were recruited in Harbin, the capital and largest city of Heilongjiang province in north China, to investigate the impacts of diet and nutrition on chronic non-communicable diseases. They were the Harbin People's Health Study (HPHS) [20, 21] and the Harbin Cohort Study on Diet, Nutrition and Chronic Non-communicable Diseases (HDNNCDS) (registered at http://www.chictr.org.cn/showproj.aspx?proj=6833 as ChiCTR-ECH-12002721) [22]. Participants in the HPHS and the HDNNCDS were recruited in 2008 and 2010, and the first follow-up surveys were conducted in 2012 and 2015–2016, with an average of 4.2 and 5.3 years follow-up, respectively. The follow-up rates were 92.1% and 91.6% in the HPHS and the HDNNCDS, respectively. At baseline, all participants were aged 20 to 74 years old, without type 1 diabetes and malignancies, and had lived in Harbin for more than 2 years. In the present study, we further excluded the following individuals: those with type 2 diabetes (self-reported or diagnosed based on OGTT) at baseline ($n = 571$ and 1189); those taking glucose-lowering medication ($n = 42$ and 111); those with dietary restriction for diseases or weight loss ($n = 167$ and 394); those with extremely high or low total energy intake (<3347 kJ or >18,828 kJ); as well as those with more than ten blank items in the dietary questionnaire ($n = 28$ and 86). Finally, 3350 and 7133 participants were included in the HPHS and the HDNNCDS, respectively.

The two studies were approved by the ethics committee of Harbin Medical University and were conducted in accordance with the Declaration of Helsinki. All participants signed informed consent.

Data collection and calculation

Each participant completed a questionnaire, including demographic data (name, age, sex, education level, home address and phone number), lifestyles (smoking, alcohol consumption and physical activity), current and family disease histories, and dietary habits [20, 21, 23]. Dietary habits were recorded through a food frequency questionnaire (FFQ). Before dietary surveys, two random subgroups of residents (from the HPHS and the HDNNCDS, respectively) were recruited and were asked to complete two FFQs (FFQ1 and FFQ2) and a 3-day dietary record to validate the reliability of the FFQs. There was satisfactory consistency for intake of nutrients and foods [20, 23]. The energy-adjusted correlation coefficients for nutrients and foods in the HPHS were 0.53–0.77 and 0.55–0.76 between the two FFQs, and were 0.48–0.69 and 0.45–0.66 between FFQ2 and dietary records; and in the HDNNCDS were 0.52–0.78 and 0.61–0.70 between the two FFQs, and were 0.52–0.71 and 0.61–0.69 between FFQ2 and dietary records. For dietary Mn and TAC, the energy-adjusted correlation coefficients between the two FFQs and FFQ2 and dietary records were 0.63 and 0.60, and 0.57 and 0.58 in the HPHS; and 0.68 and 0.66, and 0.62 and 0.61 in the HDNNCDS. More detailed information can be found in electronic supplementary material (ESM) Methods.

The FFQ covered 103 food items assigned to 14 food groups: rice, wheaten foods, potato and its products, beans, vegetables, fruits, livestock, poultry, dairy, eggs, fish, snacks, beverage and ice cream. The frequency and amount of each food item were recorded to calculate food and nutrient intakes. In accordance with the nutrient contents in the Chinese Food Composition table [24], dietary nutrient intakes were calculated by summing the amounts from each food item. Dietary TAC was calculated according to the content of redox-active compounds [25].

Anthropometric measurement and biochemical assessment

Anthropometric measurements, including height, weight, waist circumference and blood pressure, were all measured by professional examiners. BMI was calculated as weight (kg) divided by the square of height (m). Fasting (more than 10 h) and postprandial (2 h after an OGTT) blood samples were collected. Fasting blood glucose (FBG), 2 h postprandial blood glucose (PBG), triacylglycerol, total cholesterol, HDL-cholesterol (HDL-c) and LDL-cholesterol (LDL-c) were determined by an automatic analyser (Hitachi 7100, Tokyo, Japan). Fasting and postprandial insulin (F-insulin and P-insulin respectively) were measured by a chemiluminescence immune analyser (Elecsys 2010, Roche Diagnostics, Indianapolis, IN, USA). Insulin resistance index (HOMA-IR) and β cell function (HOMA-β) were calculated using the following equations: HOMA-IR = (FBG × F-insulin)/(22.5 × 7.175), and HOMA-β = (20 × F-insulin/7.175)/(FBG − 3.5) (FBG in mmol/l, F-insulin in pmol/l) [26]. HbA_{1c} was determined by high-performance liquid chromatography (VARIANT II, Bio-Rad, Hercules, CA, USA).

Five hundred participants without type 2 diabetes at baseline from the HDNNCDS were randomly selected to further explore the possible mediation effects of plasma Mn and oxidative stress in the association between dietary Mn intake and type 2 diabetes. Plasma Mn was measured by flame-atomic absorption spectrophotometry (Unicam-929 spectrophotometer, Unicam, Cambridge, UK) [27]. Total plasma superoxide dismutase (SOD) and MnSOD were determined using the SOD activity kit employing tetrazolium salt to detect superoxide generated by xanthine oxidase and hypoxanthine (Cayman Chemical, Ann Arbor, MI, USA). One unit of SOD was defined as the amount of enzyme needed to exhibit 50% dismutation of the superoxide radical [28]. The intra-assay and inter-assay variances were 4.6% and 5.1%, respectively. Plasma 8-hydroxydeoxyguanosine (8-OHdG) was determined by enzyme-linked immunosorbent assay [29].

Definition of diseases

Type 2 diabetes was defined as FBG ≥7.0 mmol/l and/or PBG ≥11.1 mmol/l and/or self-reported medication for diabetes. Impaired glucose tolerance was defined as PBG 7.8–11.1 mmol/l (based on OGTT) and without self-reported medication for diabetes, and impaired FBG was defined as FBG 6.1–6.9 mmol/l and without self-reported medication for diabetes. Obesity was defined as BMI ≥28 kg/m^2. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg, and/or diastolic blood pressure (DBP) ≥90 mmHg, and/or self-reported medication for hypertension. Hyperlipidaemia was defined as triacylglycerols ≥2.26 mmol/l and/or total cholesterol ≥6.22 mmol/l and/or HDL-c <1.04 mmol/l and/or LDL-c ≥4.14 mmol/l and/or self-reported medication for hyperlipidaemia.

Statistics

Dietary Mn was adjusted for total energy in the residual model for the positive association between dietary nutrients and total energy [30]. Continuous and frequency variables were expressed as mean ± SD and percentage, and their variations between type 2 diabetic and non-type 2 diabetic individuals were examined by the unpaired *t* test and the χ^2 test, respectively. Cox's proportional-hazards regression was employed to explore the association between tertiles of dietary Mn intake and type 2 diabetes incidence, and data were expressed as RR (95% CI). Linear regression was used to explore the association between dietary Mn and HbA_{1c} concentration. We tested statistical interactions between Mn and TAC using continuous cross-product terms by the likelihood ratio test in models to examine their joint associations. If the interaction term was significant, we depicted the joint associations by stratifying all participants into two categories of sex (male and female) or TAC (high and low) and repeating the analyses above. Restricted cubic spline (RCS) regression [31] was performed to find the non-linear association between dietary Mn and type 2 diabetes. The reference value was 4.5 mg/day dietary Mn, which is classed as an adequate dietary intake [32], and knots were placed at the 5th, 25th, 50th, 75th and 95th percentiles of dietary Mn. All analyses were conducted in the HPHS and the HDNNCDS separately.

Mediation analyses were performed to examine any mediating effects of BMI, waist circumference, blood pressure, insulin, HOMA-IR, HOMA-β and blood lipids in the association between dietary Mn and type 2 diabetes incidence or HbA_{1c} concentration in the HPHS and the HDNNCDS. Structural equation modelling (SEM) [33] was conducted among participants with plasma Mn, MnSOD and 8-OHdG values to investigate whether plasma Mn and oxidative stress were mediators in the association between dietary Mn and type 2 diabetes or HbA_{1c} concentration. Dietary Mn and type 2 diabetes/HbA_{1c} were set as independent and dependent variables, respectively. Serum Mn, MnSOD and 8-OHdG were set as mediator variables. Plasma MnSOD and 8-OHdG were $\log_{10}$-transformed because of their skewed distributions and all variables were standardised.

All missing covariate values (<4% for dietary covariates; <1% for other covariates) were replaced by the population median, or exclusion of the missing data had no appreciable effect.

SPSS 22.0 (Beijing Stats Data Mining, Beijing, China) and the packages *Hmisc* (for RCS) and *lavaan* (for mediation analysis and SEM) in R version 3.0.3 (http://www.r-project.org/) were used in statistical analysis. All *p* values were two-tailed and $p < 0.05$ was considered statistically significant.

Results

Baseline characteristics of all participants

The average dietary Mn intakes in the HPHS and the HDNNCDS were 4.58 ± 1.04 and 4.61 ± 1.08 (mean ± SD) mg/day, respectively. Table 1 lists the main food groups that contributed to ≥1% dietary Mn intake. In the HPHS, rice contributed the most (43.52%), followed by vegetables (20.19%), wheat (19.21%), fruit (6.24%) and beans (5.85%). In the HDNNCDS, the main food sources of Mn were rice (45.38%), wheat (18.82%), vegetables (18.61%), beans (6.19%) and fruit (5.78%). Participants with different dietary Mn intakes had significantly different dietary food group intakes (Table 1).

The demographic characteristics of all participants at baseline are summarised in Table 2. During follow-up, 244 and 578 individuals developed type 2 diabetes in the HPHS and the HDNNCDS, respectively. They had lower dietary Mn intakes and were older compared with the non-diabetic participants. Individuals with diabetes tended to have higher BMI, waist circumference, SBP, DBP, FBG, PBG, F-insulin, P-

Table 1 Dietary sources of Mn and dietary characteristics of participants in different Mn intake groups

	Contribution to dietary Mn intakes (%)	Dietary Mn intake tertiles			*p* value
		T1	T2	T3	
HPHS					
Food groups					
Rice (g/day)	43.52	151.32 ± 103.53	187.52 ± 110	273.55 ± 157.93	<0.01
Wheat (g/day)	19.21	122.91 ± 94.42	130.53 ± 87.85	146.92 ± 120.31	<0.01
Potato (g/day)	1.53	69.07 ± 78.27	49.38 ± 45.71	49.28 ± 49.20	<0.01
Beans (g/day)	5.85	46.12 ± 47.81	42.73 ± 42.28	52.27 ± 55.25	<0.01
Vegetable (g/day)	20.19	167.76 ± 108.97	241.66 ± 115.96	461.83 ± 293.21	<0.01
Fruit (g/day)	6.24	136.93 ± 135.07	154.52 ± 145.37	190.30 ± 210.38	<0.01
Livestock (g/day)	1.04	100.50 ± 83.33	56.29 ± 53.30	43.16 ± 41.77	<0.01
Energy and macronutrients					
Energy (kJ/day)		9258.07 ± 3253.46	8491.55 ± 2453.99	10,154.93 ± 2866.27	<0.01
Carbohydrate (g/day)		311.26 ± 129.11	319.86 ± 106.51	414.25 ± 135.71	<0.01
Carbohydrate (%)		54.23 ± 8.00	60.79 ± 5.54	65.36 ± 5.63	<0.01
Lipid (g/day)		81.94 ± 26.39	63.33 ± 16.52	62.54 ± 15.57	<0.01
Lipid (%)		33.64 ± 6.76	27.90 ± 4.66	23.07 ± 4.38	<0.01
Protein (g/day)		69.94 ± 35.15	59.37 ± 21.48	72.91 ± 26.77	<0.01
Protein (%)		12.13 ± 2.91	11.31 ± 1.87	11.57 ± 2.31	<0.01
HDNNCDS					
Food groups					
Rice (g/day)	45.38	162.34 ± 109.86	203.45 ± 129.76	286.15 ± 167.22	<0.01
Wheat (g/day)	18.82	125.21 ± 98.01	133.37 ± 101.19	141.45 ± 119.03	<0.01
Potato (g/day)	1.63	79.20 ± 88.90	52.21 ± 52.16	50.66 ± 53.36	<0.01
Beans (g/day)	6.19	47.72 ± 51.13	43.06 ± 44.52	61.82 ± 75.17	<0.01
Vegetable (g/day)	18.61	167.35 ± 113.96	220.02 ± 127.80	433.66 ± 284.27	<0.01
Fruit (g/day)	5.78	141.11 ± 133.87	144.25 ± 138.24	169.91 ± 170.55	<0.01
Livestock (g/day)	1.09	108.85 ± 93.80	57.29 ± 53.14	46.94 ± 50.29	<0.01
Energy and macronutrients					
Energy (kJ/day)		9896.48 ± 3237.54	8814.58 ± 2775.60	10,240.25 ± 2911.37	<0.01
Carbohydrate (g/day)		333.23 ± 131.24	332.9 ± 121.64	415.43 ± 136.69	<0.01
Carbohydrate (%)		54.40 ± 8.43	60.81 ± 6.11	65.06 ± 5.98	<0.01
Lipid (g/day)		86.82 ± 27.64	65.18 ± 17.74	63.87 ± 16.85	<0.01
Lipid (%)		33.34 ± 7.22	27.98 ± 5.28	23.40 ± 4.76	<0.01
Protein (g/day)		75.61 ± 35.95	61.05 ± 23.56	72.97 ± 24.26	<0.01
Protein (%)		12.25 ± 3.03	11.21 ± 1.89	11.54 ± 1.99	<0.01

Continuous variables were expressed as the mean ± SD

insulin, HOMA-IR, HbA_{1c}, total cholesterol, triacylglycerols, LDL-c and prevalence of obesity, hypertension and hyperlipidaemia, but lower HOMA-β, compared with non-diabetic individuals. The dietary intakes of participants with and without type 2 diabetes are shown in ESM Table 1.

Association between dietary Mn and type 2 diabetes

All participants were divided into three groups by tertiles of dietary Mn, the first (T1), second (T2) and third (T3) intake groups, and their risk for type 2 diabetes was compared by Cox's proportional-hazards regression (Table 3). In the HPHS, the RRs (95% CI) of T2 (4.22–4.91 mg/day) and T3 (≥4.91 mg/day) were 1.16 (0.81, 1.67) and 0.52 (0.33, 0.82), compared with T1 (<4.22 mg/day), adjusted for age, sex, BMI, smoking, alcohol consumption, physical activity, diabetes inheritance, total energy, carbohydrate, total fatty acids, fibre, calcium, TAC, Mg, hypertension, hyperlipidaemia and impaired glucose tolerance or FBG (all at baseline), and the p_{trend} was <0.01. In the HDNNCDS, the RRs (95% CI) of T2 and T3 (4.27–4.98 and ≥4.98 mg/day) were 0.99 (0.75, 1.31) and 0.61 (0.43, 0.88), compared with T1 (<4.27 mg/day) after

Table 2 Baseline demographic and biochemical characteristics of participants with/without diagnosed type 2 diabetes during follow-up

	HPHS		HDNNCDS	
	Participants without T2D	Participants with T2D	Participants without T2D	Participants with T2D
Participants (*n*)	3106	244	6555	578
Dietary Mn intakes (mg/day)	4.60 ± 1.05	4.41 ± 1.02*	4.61 ± 1.07	4.48 ± 1.07*
Age (years)	49.51 ± 10.09	51.08 ± 10.94*	49.76 ± 9.19	52.53 ± 9.16*
Male (%)	31.78	35.53	32.82	47.81*
Education (%)				
Middle school and below	34.08	47.06*	28.15	35.40*
Senior middle school	35.26	26.47	34.68	33.21
College and above	30.65	26.47	37.16	31.39
Smoker (%)				
Current	14.21	10.53	15.54	20.51*
Ever	2.39	2.63	2.76	3.66
Never	83.40	86.84	81.70	75.82
Alcohol consumption (%)	30.59	28.38	34.09	37.64*
Physical activity (%)				
Light	82.54	89.55*	81.31	80.90*
Moderate	16.43	10.45	17.28	16.10
Vigorous	1.03	0.00	1.42	3.00
BMI (kg/m^2)	24.71 ± 3.30	26.58 ± 4.08*	24.69 ± 3.44	26.01 ± 3.47*
Waist circumference (cm)	83.43 ± 9.76	88.27 ± 11.15*	84.64 ± 10.04	89.69 ± 9.59*
SBP (mmHg)	129.19 ± 19.80	137.46 ± 24.08*	133.69 ± 18.05	141.98 ± 19.01*
DBP (mmHg)	78.79 ± 11.03	81.15 ± 9.32*	81.13 ± 8.97	85.16 ± 10.49*
FBG (mmol/l)	5.15 ± 0.67	5.52 ± 0.76*	5.03 ± 0.69	6.09 ± 1.25*
PBG (mmol/l)	6.00 ± 1.53	7.10 ± 2.30*	5.79 ± 1.76	9.58 ± 3.43*
F-insulin (pmol/l)	59.01 ± 60.59	77.35 ± 44.96*	56.63 ± 33.73	68.21 ± 37.26*
P-insulin (pmol/l)	258.25 ± 240.82	370.37 ± 323.31*	285.25 ± 208.94	350.77 ± 256.80*
HOMA-IR	1.74 ± 1.96	2.41 ± 1.27*	1.61 ± 1.05	2.35 ± 1.40*
HOMA-β	151.65 ± 106.36	137.41 ± 76.41*	167.40 ± 113.27	125.55 ± 107.05*
HbA_{1c} (mmol/mol)	38.86 ± 5.46	47.94 ± 10.60*	36.14 ± 4.86	43.79 ± 11.48*
HbA_{1c} (%)	5.71 ± 0.50	6.54 ± 0.97*	5.46 ± 0.44	6.26 ± 1.05*
Total cholesterol (mmol/l)	4.87 ± 0.93	5.02 ± 0.74*	5.13 ± 1.01	5.45 ± 1.28*
Triacylglycerol (mmol/l)	1.68 ± 1.31	2.11 ± 1.66*	1.63 ± 1.49	2.83 ± 3.89*
HDL-c (mmol/l)	1.29 ± 0.34	1.29 ± 0.39	1.29 ± 0.33	1.18 ± 0.30*
LDL-c (mmol/l)	3.91 ± 1.06	4.15 ± 0.86*	3.00 ± 0.86	3.12 ± 0.88*
Obesity (%)	15.84	28.95*	15.93	25.27*
Hypertension (%)	33.73	50.00*	33.80	55.47*
Hyperlipidaemia (%)	40.71	47.37*	47.94	69.37*
Dietary energy intake (kJ/day)	9290.66 ± 2930.65	9336.82 ± 3067.05	9622.38 ± 3019.69	10,057.99 ± 3348.31*

Continuous and frequency variables were expressed as the mean ± SD and percentage. * $p < 0.05$ when compared with individuals without type 2 diabetes
T2DM, type 2 diabetes

adjustment for all the above potential confounders as in the HPHS ($p_{trend} < 0.01$).

No significant joint associations were found between dietary Mn and sex in the HPHS or the HDNNCDS ($p_{interaction}$ = 0.92 and 0.22, respectively). The joint associations of dietary Mn intake and TAC was significant, and $p_{interaction}$ was <0.01 and 0.01 in the HPHS and the HDNNCDS, respectively. The two cohorts consistently showed that dietary Mn intake was inversely associated with type 2 diabetes incidence in diets with low and high TAC, and the inverse association was stronger in diets with high compared with low TAC (Fig. 1). Detailed information is shown in ESM Table 2.

In multivariable linear regressions (Table 3), we analysed the association between dietary Mn intake and HbA_{1c},

Table 3 Association between dietary Mn and type 2 diabetes incidence/HbA_{1c} in HPHS and HDNNCDS

		Participants/*N*	Model 1	Model 2	Model 3
Type 2 diabetes RR (95% CI)					
HPHS					
Dietary Mn intake (mg/day)	<4.22	84/1118	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	4.22–4.91	107/1118	1.34 (0.98, 1.83)	1.14 (0.79, 1.63)	1.16 (0.81, 1.67)
	≥4.91	53/1114	0.60 (0.41, 0.88)	0.51 (0.32, 0.81)	0.52 (0.33, 0.82)
	p_{trend}		<0.01	<0.01	<0.01
HDNNCDS					
Dietary Mn intake (mg/day)	<4.27	194/2387	1.00 (ref.)	1.00 (ref.)	1.00 (ref.)
	4.27–4.98	224/2393	1.03 (0.83, 1.28)	1.07 (0.83, 1.36)	0.99 (0.75, 1.31)
	≥4.98	160/2353	0.73 (0.58, 0.93)	0.69 (0.51, 0.95)	0.61 (0.43, 0.88)
	p_{trend}		0.01	0.02	<0.01
HbA_{1c} β (*p* value)					
HPHS		244/3350	−0.048 (0.01)	−0.170 (<0.01)	−0.190 (<0.01)
HDNNCDS		578/7133	−0.063 (<0.01)	−0.080 (<0.01)	−0.060 (0.02)

Data are presented as RR (95% CI) or β (*p* value)

Model 1 was adjusted for age, sex, BMI, tobacco use, alcohol consumption, physical activity, diabetes inheritance

Model 2 was further adjusted for total energy, carbohydrate, total fatty acids, fibre, calcium, TAC and Mg

Model 3 was adjusted for all variables in Model 2 as well as baseline diseases (hypertension, hyperlipidaemia and impaired glucose tolerance or FBG) for the type 2 diabetes analysis and baseline HbA_{1c} concentration for the HbA_{1c} analysis

adjusted for all the above potential confounders. In the HPHS and the HDNNCDS, the standardised regression coefficients (β) of dietary Mn to HbA_{1c} were −0.190 (p_{trend} <0.01) and −0.060 (p_{trend} =0.02), respectively. The two cohorts showed a statistically significant inverse association between dietary Mn and HbA_{1c}.

In RCS (Fig. 2), the RRs for type 2 diabetes were decreased with an increase in dietary Mn, and intakes of >6.01 mg/day had a significant RR lower than 1.00 in the HPHS; and the RR was decreased when dietary Mn intake was <6.64 mg/day and increased when intake was >6.64 mg/day. Significantly decreased RR (<1.00) was observed when intake ranged from 6.10 to 6.97 mg/day in the HDNNCDS.

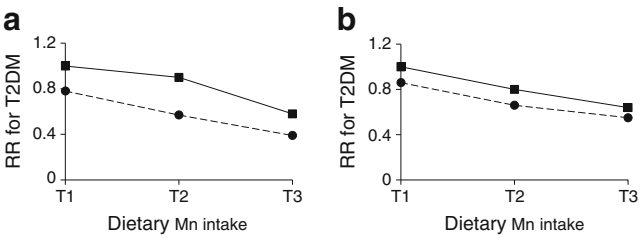

Fig. 1 Joint associations of dietary Mn and TAC on type 2 diabetes incidence. Tertile-specific RRs were given for T1, T2 and T3 of dietary Mn intake, in contexts of low- and high-TAC diet in the HPHS (**a**) and the HDNNCDS (**b**). Square, low-TAC diet; circle, high-TAC diet; $p_{interaction}$ < 0.01 in both the HPHS and the HDNNCDS. The models were adjusted for age, sex, BMI, tobacco use, alcohol consumption, physical activity, diabetes inheritance, total energy, carbohydrate, total fatty acids, fibre, calcium, TAC, Mg and diseases (hypertension, hyperlipidaemia and impaired glucose tolerance or FBG) (all at baseline). T2DM, type 2 diabetes

Mediators in the association between dietary Mn and type 2 diabetes

Mediation effects of anthropometric and biochemical indicators Mediation analyses were employed to examine the mediation effects of anthropometric and biochemical indicators, including BMI, waist circumference, SBP, DBP, F-insulin, P-inulin, HOMA-IR, HOMA-β, total cholesterol, triacylglycerol, HDL-c and LDL-c, in the association between dietary Mn and type 2 diabetes or HbA_{1c} concentration at follow-up (ESM Table 3). In the HPHS, F-insulin, P-insulin, HOMA-IR, total cholesterol and LDL-c were all significant mediators in the association between dietary Mn and type 2 diabetes. In the HDNNCDS, the mediation effects of all the above indicators were non-significant. For HbA_{1c}, the mediation effects of F-insulin, P-insulin, HOMA-IR, HOMA-β, total cholesterol and LDL-c were significant in the HPHS, but not in the HDNNCDS.

Mediation effects of plasma Mn and oxidative stress We investigated the roles of plasma Mn and MnSOD in the association between dietary Mn and type 2 diabetes in 500 randomly selected participants, and 41 diabetic individuals were diagnosed during follow-up. The dietary Mn, plasma Mn, MnSOD, 8-OHdG, demographic and biochemical indicators of the population are summarised in ESM Table 4. In linear regression (ESM Table 5), dietary Mn was significantly positively associated with plasma Mn and MnSOD with the standardised β values of 0.53 and 0.31, respectively, adjusted for age, sex, BMI, smoking, alcohol consumption, physical

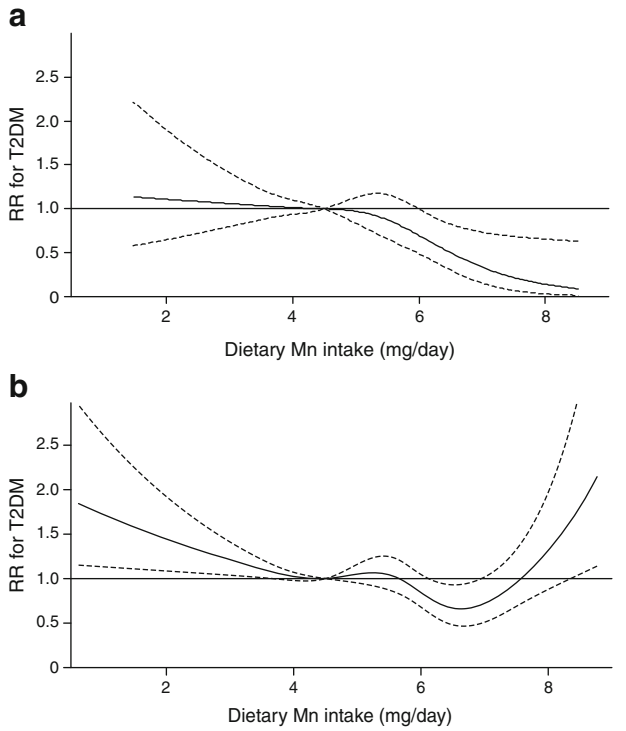

Fig. 2 Association between dietary Mn intake and type 2 diabetes incidence in RCS in the HPHS (**a**) and the HDNNCDS (**b**). Solid line, RR; dotted lines, 95% CI; RR, risk ratio for type 2 diabetes incidence. T2DM, type 2 diabetes

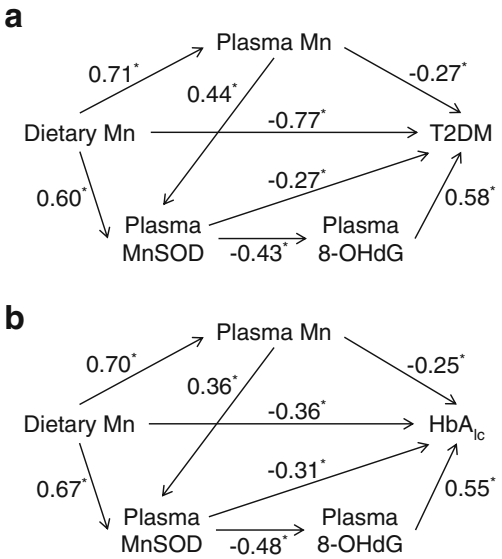

Fig. 3 SEM models for the association between dietary Mn and type 2 diabetes incidence (**a**) and HbA_{1c} concentration (**b**). Indicators not connected by arrows were not significantly associated with each other. The direction of the arrow shows the direction of the association between the two indicators, and the numbers near the arrows are the pathway coefficients between the two indicators. $^{*}p < 0.05$. T2DM, type 2 diabetes

activity, diabetes inheritance, dietary total energy, carbohydrate, total fatty acids, fibre, calcium, TAC and Mg (Model 2). The standardised β values were 0.55 and 0.30, still significant, even after we further adjusted for hypertension, hyperlipidaemia, and impaired glucose tolerance or FBG (Model 3). An inverse association was also observed between dietary Mn and 8-OHdG after adjusting for the above potential confounders with the standardised β of −0.29 (Model 3).

In SEM (Fig. 3), there were significant direct and indirect effects of dietary Mn on type 2 diabetes. The indirect effects were mediated by plasma Mn, MnSOD and 8-OHdG, and they were plasma Mn → type 2 diabetes, plasma MnSOD → type 2 diabetes, plasma Mn → MnSOD → 8-OHdG → type 2 diabetes. For HbA_{1c}, the direct and indirect effects of dietary Mn were significant. The indirect effects of dietary Mn on HbA_{1c} were plasma Mn → HbA_{1c}, MnSOD → HbA_{1c}, plasma Mn → MnSOD → 8-OHdG → HbA_{1c}.

Discussion

To our knowledge, this is the first population-based study to investigate the association between dietary Mn and type 2 diabetes and to explore the underlying mechanisms of the association. In two prospective cohorts of Chinese adults, dietary Mn was inversely associated with type 2 diabetes independently of TAC and their association was more pronounced in the context of a higher-TAC diet. Increased plasma Mn and decreased oxidative stress partly mediated their association.

In this study, two prospective cohorts were used. In the HPHS, an inverse association was found between dietary Mn and type 2 diabetes (diagnosed by fasting glucose and OGTT). Surprisingly, the same result was observed in the HDNNCDS. The two cohorts consistently indicated the significant inverse association between dietary Mn and type 2 diabetes. Furthermore, their association was more pronounced in participants with higher-TAC diets. In human bodies, the enzymatic and non-enzymatic antioxidants co-existed and jointly contributed to antioxidative defence. Mn participates in MnSOD, an important enzymatic antioxidant [18]. The components of TAC, mainly including flavonoids, phenolic acids, carotenoids and polyphenols, participate in non-enzymatic antioxidant defence [34] and have also been reported to modify systemic inflammation [35]. These may help explain the potential joint association of Mn and TAC in type 2 diabetes. However, more studies are needed to give a clear description of the joint association between Mn and TAC and a potential mechanism.

In the two cohorts, the average dietary Mn intakes were both approximately 4.6 mg/day, similar to those in Asian countries [36, 37]. The RCS, which characterises a dose–response association between a continuous exposure and an outcome [38], showed that Mn intakes of >6.01 and 6.10–6.97 mg/day, much higher than adequate intake (4.5 mg/day), were associated with low type 2 diabetes incidence in

the HPHS and the HDNNCDS, respectively. Based on these results, we suggest increasing dietary Mn intake. Previous studies may provide some supporting evidence for the benefits of increasing dietary Mn intake. In mice susceptible to fat-induced diabetes, Mn supplementation improved the activity of MnSOD in liver mitochondria, insulin secretion and glucose homeostasis, and decreased lipid peroxidation [6]. In addition, a U-shaped spline was observed in the HDNNCDS, but not in the HPHS. The sample size and heterogeneity between the two cohorts may be important reasons. Previous studies have shown possible U-shaped association between plasma Mn and type 2 diabetes: both low and high levels of plasma Mn have been associated with higher odds of type 2 diabetes in a case–control study [8]; and serum Mn in the 4th quartile (Q4) (the highest compared with the lowest serum level, OR 1.15) has higher odds than Q3 (OR 0.76) in a cross-sectional study [39]. All these findings show that extreme Mn levels may be associated with high type 2 diabetes risk. However, the optimal dietary Mn intake is hard to determine for scarce data. Future studies with more data on absolute Mn intake are needed to study the potential non-linearity between dietary Mn, type 2 diabetes and optimal intake levels.

To further explore the potential mechanisms in the association between dietary Mn and type 2 diabetes, mediation analysis was performed. Mn is an essential mineral nutrient and the plasma Mn level reflects Mn nutritional status in the human body [3]. Mn supplementation can increase plasma Mn [40]. Meanwhile, low plasma Mn was associated with increased risk for type 2 diabetes [39], and individuals with type 2 diabetes have had lower plasma Mn level than healthy non-diabetic control individuals [41]. Consequently, we speculated that plasma Mn played a role in the association between dietary Mn and type 2 diabetes. However, no study has been undertaken. To verify this speculation, we performed mediation analysis. Our data showed that high dietary Mn contributed to high plasma Mn, which then contributed to low type 2 diabetes incidence. These findings revealed the mediating role of plasma Mn in their association.

MnSOD is a typical Mn-dependent metalloenzyme and acts as a primary antioxidant in the mitochondrial matrix [42]. Animal studies reported increased activity of MnSOD in pancreatic beta cells after Mn supplementation [6], and MnSOD can scavenge reactive oxygen species and decrease oxidative stress [42], which could inactivate a series of stress pathways contributing to the onset and progression of diabetes, such as NF-κB, c-Jun N-terminal kinase (JNK)/stress-activated protein kinase (SAPK), and p38 mitogen-activated protein kinase (MAPK) [43]. Thus, we hypothesised that decreased oxidative stress was a mediator in the association between dietary Mn and type 2 diabetes. In this study, we specifically measured serum oxidative stress (indicated by MnSOD and 8-OHdG) and mediation analysis showed that dietary Mn increased serum MnSOD and decreased 8-OHdG, in turn decreasing type 2 diabetes risk. This indicated that oxidative stress mechanistically mediated their association.

Some studies have reported that dietary Mn was associated with abdominal obesity, blood pressure and blood lipid [44, 45]. Whether they were also mediators in the association between dietary Mn and type 2 diabetes was unclear. In this study, we also examined the mediation effects of BMI, waist circumference, blood pressure, insulin, HOMA-IR, HOMA-β and blood lipid in their association. However, no mediation effects were observed. Thus, we could not conclude whether these indicators were mediators in their association.

In summary, the mediation analysis, with plasma Mn and oxidative stress included in the regression model of dietary Mn and type 2 diabetes, revealed that dietary Mn was inversely associated with type 2 diabetes, and that plasma Mn and oxidative stress partly mediated their association. However, these are not the sole explanations for the association between dietary Mn and type 2 diabetes. Other mechanisms not included in the current study may exist. For example, previous studies have reported that dietary Mn may activate enzymes involved in glucose metabolism [46], influence insulin signalling pathways [4] and downregulate reactive oxygen species independently of MnSOD [47]. More studies are warranted to understand the mechanisms underlying their association.

HbA_{1c} is a measure of total glycaemic exposure with less day-to-day perturbation than fasting glucose or OGTT, and is an alternative screening tool for diabetes [48]. It is noteworthy that significant inverse associations between dietary Mn and HbA_{1c}, and significant mediation effects of plasma Mn and oxidative stress were observed, which added credence to the findings in type 2 diabetes.

In the current study, cereals, vegetables, beans and fruit were the main food sources of dietary Mn, which were consistent with previous studies. It has been suggested that cereals, vegetables and beans are the major food groups contributing to dietary Mn in Korean children [49], and more than 42% of dietary Mn was reported from rice in south China [44]. Although refined grains were positively associated with type 2 diabetes, the potential protective effect of food groups rich in Mn has been documented [50]. Therefore, more food groups rich in Mn, including whole grains, vegetables and fruits, should be recommended.

One strength of our study is the diagnosis of type 2 diabetes with fasting blood glucose, OGTT and HbA_{1c} in both prospective cohorts. In addition, we measured plasma Mn and oxidative stress and examined the underlying mechanism of the association between dietary Mn and type 2 diabetes. There were some limitations. The study participants were all Chinese, which made the study less generalisable to the world population. Our results were also limited by the possibility of residual or unaccounted-for confounders, although we adjusted for many potential demographic, lifestyle, diet and disease-history confounders. Additionally, dietary intakes were

recorded by FFQ, which could not accurately estimate absolute nutrient intakes.

In conclusion, our findings from two prospective cohorts provide the first strong evidence supporting the inverse association between dietary Mn and type 2 diabetes, which was independent of TAC, and which was more pronounced in the presence of a high-TAC diet. Plasma Mn and oxidative stress partially mediated their association. Our findings highlight the importance of dietary Mn intake in type 2 diabetes. Future studies on absolute Mn intake should be conducted to study their non-linear association and optimal dietary intakes.

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Data availability The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement CS and LN contributed to the conception and design of the study. XW, SD, WD, LL, JQ and YN contributed to acquisition of data. SD, XW and TH contributed to data analysis. YN, LN and CS contributed to funding acquisition. SD, XW and TH wrote the original draft. All authors reviewed and edited the draft, and approved the final manuscript. CS and LN are responsible for the integrity of the work as a whole.

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