



Dietary magnesium-to-iron intake ratios and risk of impaired fasting glucose in Chinese adults: The prospective Jiangsu Nutrition Study (JIN)

Yingting Cao ^a, Shiqi Zhen ^b, Evan Atlantis ^{c, d, e}, Zumin Shi ^{a, b, f, *}

^a Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia

^b Jiangsu Provincial Centre for Disease Control and Prevention, Nanjing, China

^c School of Nursing and Midwifery, Western Sydney University, New South Wales, Australia

^d Capital Markets Cooperative Research Centre, Sydney, New South Wales, Australia

^e School of Medicine, The University of Adelaide, Adelaide, South Australia, Australia

^f Human Nutrition Department, Qatar University, Doha, Qatar

ARTICLE INFO

Article history:

Received 30 July 2017

Received in revised form

30 March 2018

Accepted 17 May 2018

Available online 22 May 2018

Keywords:

Dietary magnesium

Iron intake

Haem-Fe

Type 2 diabetes mellitus

Impaired fasting glucose

Chinese adults

ABSTRACT

Background: Studies have consistently shown that risk of type 2 diabetes (T2D) is positively associated with dietary haem iron intake and inversely associated with dietary magnesium intake in a dose-response way. However, interaction effects of these two clinically important nutrients on T2DM risk in a prospective setting is unknown.

Objective: To determine the five-year risk of developing impaired fasting glucose (IFG) associated with dietary magnesium-to-iron intake ratios (Mg/Fe), including Mg/total Fe, Mg/haem-Fe and Mg/non-haem Fe.

Design: A cohort study of 1056 participants recruited into the Jiangsu Nutrition Study (JIN) from 2002 to 2007, aged at least 20 years and without known diabetes and IFG at baseline were followed up for five years. Dietary magnesium and iron intake at baseline was assessed by 3-day weighed food records. Fasting plasma glucose was measured both at baseline and follow up. Logistic regression models were performed to determine the associations between quartiles (using bottom quartiles as referent categories) of magnesium to iron (including total Fe, haem-Fe and non-haem Fe) ratio and the risk of IFG (>5.6 mmol/L) adjusted for covariates: age, gender, body mass index (BMI), hypertension, serum ferritin, haemoglobin and family history of diabetes.

Results: The mean (SD) intake of total Fe and magnesium was 25.0 (9.2) mg/d and 323 (125) mg/d. The incidence of IFG during 5-year follow up was 11.8%. Inverse associations were found between quartiles (Q) of Mg/haem-Fe and the risk of IFG in the fully adjusted model: odds ratios (OR) were 1.00, 0.59 (95%CI 0.35, 0.98), 0.49 (95%CI 0.28, 0.84), and 0.28 (95% CI 0.14, 0.55) (Q4), respectively. Weaker associations were found for quartiles of Mg/total Fe and no association was found between Mg/non-haem Fe and IFG risk.

Conclusions: Low Mg/haem-Fe ratio is an independent risk factor for developing IFG in Chinese adults. Future research to determine the added predictive value of assessment of low dietary Mg/haem-Fe ratio beyond current T2D risk models in specific populations is justified.

© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

1. Introduction

Type 2 diabetes mellitus (T2DM) is now a major health and economic burden in China. Using the national survey from 2007 to

* Corresponding author. Human Nutrition Department, Qatar University, P.O.Box 2713, Doha, Qatar

E-mail address: zumin.shi@adelaide.edu.au (Z. Shi).

<https://doi.org/10.1016/j.jnim.2018.05.002>

2352-3859/© 2018 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

2008, the prevalence of T2DM and prediabetes was estimated to be 9.7% and 15.6% respectively [1]. Identification of novel risk factors could help strategies to prevent diabetes, resulting in substantial health and economic benefits.

There is a growing body of evidence suggesting several micro-nutrients are associated with T2D risk. For instance, magnesium (Mg) has been shown to play a key role in regulating insulin and glucose metabolism and Mg deficiency is common among people

Abbreviations

T2DM	type 2 diabetes mellitus
Mg	magnesium
Fe	iron
IFG	impaired fasting glucose
JIN	Jiangsu Nutrition Study
BMI	body mass index
Mg/Fe	dietary magnesium-to iron intake
FPG	fasting plasma glucose
Mg/SF	Mg to serum ferritin ratio
SES	socioeconomic status

with T2D [2]. A meta-analysis of prospective studies has confirmed an inverse association between dietary Mg intake and risk of T2DM in a dose-response manner [3].

Conversely, dietary iron (Fe) intake and blood iron status, have been positively associated with T2D in Western and Asian countries [4–6]. Iron overload may promote the development of diabetes via stimulating oxidative stress and inflammation [7,8]. In addition, haem Fe but not non-haem Fe intake has been suggested to be associated with an increased risk of hyperglycaemia previously in another of our previous studies using the same cohort [9]. Similar results have also been found in American men in that only haem-Fe was found to be related to diabetes [10]. A systematic review of prospective studies has evaluated the available evidence for associations between iron intake, body iron stores, and risk of T2DM. The results suggest that higher haem iron intake and increased body iron stores were significantly associated with a greater risk of T2DM, whereas dietary total iron, non-haem iron, or supplemental iron intakes were not significantly associated with T2DM risk [11].

However, the interactions between magnesium and iron intake is less studied. In the limited evidence, one of our previous studies using the same cohort found an inverse linear association between magnesium-to-total Fe intake ratio and diabetes, which was independent of known risk factors for diabetes [12]. And such association was only significant when iron intake was higher than the mean iron intake. However, prospective studies assessing iron intake and the risk of diabetes are lacking. In addition, they did not separate haem-Fe and Non-haem Fe when looking at the interactions between dietary magnesium and iron intake.

Chinese population has high intake of vegetables and low intake of animal foods, compared with West populations, whether the different composition of iron intake affects the relation with the risk of diabetes in China is unclear. No study has examined the interaction between magnesium and iron intake including differentiating haem Fe and non-haem Fe in regards to the diabetes risk prospectively.

Therefore, the current study aimed to investigate the interaction between magnesium and iron intake in regards to IFG prospectively in a Chinese population where such interaction has been found in a cross-sectional study design [6]. In addition, the difference of haem Fe and non-haem Fe will be tested. Interactions between risk factors and dietary magnesium to iron intake ratio (Mg/Fe), including Mg/total Fe, Mg/haem-Fe and Mg/Non-haem Fe will also be examined.

2. Materials and methods

2.1. Participants

Data from the Jiangsu Nutrition Study (JIN) cohort with subjects

older than 20 years old were used in the current study. Detailed methodology has been described previously [13]. In brief, in 2002, 2849 adults at least 20 years old living in two cities and six rural areas in Jiangsu Province took part in the Chinese National Nutrition and Health Survey. In 2007, an attempt to re-contact all the original participants was made. Due to the attrition, 1682 were identified for follow-up, 1492 participated in the follow-up interview resulting in a response rate of 52.4%, and 1175 of them had fasting blood samples measures. For the current analysis, we included only those subjects with a fasting plasma glucose <5.6 mmol/l at baseline and without known diabetes ($n = 1056$). The study was conducted aligning with the guidelines in the Declaration of Helsinki, and all procedures were approved by the Jiangsu Provincial Centre for Disease Control and Prevention [14]. Informed consent for participation was obtained from each participant.

2.2. Data collection and measurements

Participants were interviewed at their homes by trained health workers using a pre-coded questionnaire. Interviews took about 2 h to completed and included questions on diet, sociodemographic information, medical history, cigarette smoking, physical activity and other lifestyle factors.

2.3. Dietary measurements

Dietary data including magnesium and iron intake were obtained by food weighing plus consecutive individual 3-day food records (including one weekend) [15]. At the beginning and end of the 3-day survey, investigators weighed all the food stocked in the household. All purchases, home production, and processed snack foods were weighed and recorded each day. Nutrient intake was calculated using the Chinese Food Composition Table [16]. Information about food supplements was not included in this study due to the small number of users.

2.4. Haemoglobin, serum ferritin and fasting plasma glucose measurements

All the participants were asked to take a fasting blood sample in the morning. The samples were analysed for plasma glucose and haemoglobin at the local Centres for Disease Control and Prevention. Haemoglobin was measured by the cyanmethaemoglobin method [17]. Serum ferritin (baseline only) was analysed in a laboratory in the National Centre for Disease Control and Prevention in Beijing using a commercially available RIA kit (Beijing North Institute of Biological Technology, Beijing, China). IFG at follow-up (2007) was defined as fasting plasma glucose >5.6 mmol/l [18].

2.5. Anthropometric measurement and other variables

In both 2002 and 2007 anthropometry was conducted using standard protocols and techniques. Body weight was measured in light indoor clothing without shoes to the nearest 0.1 kg. Height was measured without shoes to the nearest mm using a stadiometer. Body mass index (BMI, kg/m^2) was categorised into four groups underweight ($<18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5\text{--}23.9 \text{ kg}/\text{m}^2$), overweight ($24\text{--}27.9 \text{ kg}/\text{m}^2$) and obese ($\geq 28 \text{ kg}/\text{m}^2$) respectively according to the guideline for Chinese adults [19]. Waist circumference was measured to the nearest mm midway between the inferior margin of the last rib and the crest of the ilium, in the mid-auxillary line in a horizontal plane. Blood pressure was measured twice with a mercury sphygmomanometer on the right upper arm of the subject, who was seated for 5 min before the

measurement. The mean of these two measurements was used in the analyses. Hypertension was defined as a systolic blood pressure above 140 mmHg and/or a diastolic blood pressure above 90 mmHg or the use of antihypertensive drugs.

Cigarette smoking was assessed by asking the frequency of daily cigarette smoking in the past 30 days. Alcohol consumption was asked regarding the frequency (no, 1–2/week, 3–4/week and daily). Education was recoded into either 'Low' (illiteracy, primary school); 'Medium' (junior high school); or 'High' (senior high school or higher), based on six categories of education levels in the questionnaire. Occupation was recoded into 'Manual' or 'Non-manual' based on a question with 12 occupational categories. Sedentary activity was recoded into four categories: <1 h/d, 1–2 h/d, 2–3 h/d, and ≥ 3 h/d based on questions asked on hours spent per day on sedentary activities including watching TV, reading, computer use and video games. Urban/rural area information was also obtained by asking detailed residence. Village and town were defined as rural.

2.6. Statistical analysis

Descriptive data are presented as the mean (SD) or as percentage. Chi-square tests were used to compare the differences between categorical variables, and ANOVA was performed to compare differences in continuous variables between groups. The Mg/Fe was recoded into quartiles, and the highest quartile was compared with the lowest quartile (reference group). The association between the quartiles of Mg/Fe at baseline and the risk of IFG at follow up was assessed using multivariable logistic regression models. A set of models were used: model 1 adjusted for age, sex, energy intake; model 2 further adjusted for income, education, region, smoking, alcohol consumption, and sedentary activity; model 3 further adjusted for BMI, hypertension, magnesium intake, total iron intake, highest quartile of serum ferritin and highest quartile of haemoglobin; model 4 further adjusted for family history of diabetes. Interactions between Mg/Fe and separate dietary magnesium and iron intake (including haem-Fe and non-haem Fe, as well demographic, lifestyle and chronic conditions were conducted by adding a multiplicative term as categorical variables and the dichotomised Mg/Fe (<50% vs $\geq 50\%$ of Mg/Fe) in the model. Sensitivity analyses were performed by examining the association between Mg to serum ferritin ratio (Mg/SF) and IFG, and the interactions between Mg/Fe and sex-specific dichotomised serum ferritin (<50% vs $\geq 50\%$) in relation to IFG. We also repeated the main analysis after excluding low serum ferritin (<15 $\mu\text{g/L}$) to explore the potential confounding effect of low serum ferritin. Statistical significance was considered when $P < 0.05$. All statistical analyses were performed with STATA V14 (Stata Corporation, College Station, TX, USA).

3. Results

A total of 1417 households were included with 1308 men and 1541 women at baseline. After 5-year follow up, we identified 125 cases of IFG, among them 23 had diabetes. The mean intake of total Fe and Mg was 25.0 mg/d (non-haem Fe 23.4 mg/d) and 323 mg/d. Most of total Fe intake was from non-haem Fe (91.4%). **Table 1** presents the sample characteristics based on the extreme quartiles of Mg/Fe at baseline. Participants in the lowest quartile of Mg/Fe intake ratio were more likely to have higher social economic status (SES), being smokers, non-manual workers, living in the urban areas and have higher risk of hyperglycaemia, compared with the highest quartile. Similar results are observed in the lowest quartile of the Mg/haem-Fe in terms of SES, smoking, manual occupation, residence and the risk of hyperglycaemia, compared

with the highest quartile. No difference of the risk of IFG was found between the lowest and highest quartile of the Mg/Non-haem Fe.

Dietary magnesium intake alone was not associated with the risk of IFG (**Table 2**). However, separate haem-Fe intake but not total Fe nor non-haem Fe intake was positively associated with the risk of IFG. In the fully adjusted model, comparing with the lowest quartile of haem-Fe intake, the highest quartile was associated with 177% increase of risk of IFG (odds ratio (OR) 2.77, 95% CI (1.42, 5.41), p for trend <0.001).

An inverse association was found across quartiles of both Mg/total Fe intake and Mg/haem-Fe and the risk of IFG (**Table 3**). Comparing with the lowest quartile, the highest quartile of Mg/total Fe intake and Mg/haem-Fe intake ratio had an odds ratio of IFG 0.56 (95% CI 0.32, 0.97) and 0.30 (95% CI 0.16, 0.58) respectively after adjusting for demographic and lifestyle factors. However, after further adjusting for BMI, hypertension, highest quartile of serum ferritin highest quartile of haemoglobin and family history of diabetes, the association was no longer significant between the quartiles of Mg/total Fe and IFG, but remained consistently between the quartiles of Mg/haem-Fe and IFG.

Interactions between subgroups and Mg/haem-Fe are presented in **Fig. 1**. In general, no significant interactions were detected. However, current smoker and drinker seemed to benefit more from a high ratio of Mg/haem-Fe intake against the risk of IFG. There was an interaction between Mg/haem-Fe and sex-specific dichotomised serum ferritin (<50% vs $\geq 50\%$) in relation to incident IFG in women. The inverse association between Mg/haem-Fe and IFG was only found among those with low serum ferritin in women (supplement **Fig 1**). However, no such interaction was found in men. In addition, no association was found when replacing iron intake with serum ferritin, i.e. examining the association between Mg/SF and IFG. When we excluded those with serum ferritin <15 $\mu\text{g/L}$, the inverse association between Mg/haem-Fe and IFG remained (data not shown).

4. Discussion

In this prospective study, we found inverse associations between quartiles of Mg/Fe and the risk of IFG in the Chinese population. In specific, we found a consistent inverse association between quartiles of Mg/haem-Fe and the risk of IFG. No association was found between Mg/non-haem Fe and the risk of IFG. There are generally no interactions between risk factors and Mg/haem-Fe.

The inverse association between quartiles of Mg/total Fe (unadjusted) was found in this prospective study is consistent with the finding in the previous cross-sectional study using the same cohort [12]. This confirms the interaction between magnesium and iron intake when looking at the risk of diabetes prospectively, as suggested by previous evidence that magnesium intake may neutralize the inflammatory effect of iron by increasing utilization of iron and reducing free iron production [20,21]. However, this association was no longer significant when further adjusting for BMI, hypertension, magnesium intake, total iron intake, serum ferritin, haemoglobin and family history of diabetes. This may suggest that in a prospective point of view, the protective effect of Mg/total Fe intake ratio on IFG may not be that strong, which highlights the importance to differentiate the composition of iron intake.

Indeed, when we looked at haem-Fe and non-haem Fe separately, we found a consistent inverse association between Mg/haem-Fe intake (not non-haem-Fe) through all the models. This finding was consistent with our previous cross-sectional study and the prospective Nurse Health Study that found haem-Fe but not non-haem Fe was associated with diabetes [9,22]. In the Health Professionals Follow-up Study cohort, haem-iron derived from red meat but not total iron intake, was positively associated with risk of

Table 1

Characteristics according to extreme quartiles (Q1 lowest and Q4 highest) of magnesium to iron intake ratio baseline in the Jiangsu Nutrition Study (n = 1056).

	Mg/Total Fe			Mg/Haem Fe			Mg/Non-haem Fe		
	Q1 (n = 264)	Q4 (n = 264)	p-value	Q1 (n = 264)	Q4 (n = 264)	p-value	Q1 (n = 264)	Q4 (n = 264)	p-value
Median magnesium to iron intake ratio	10.6	15.7		67.6	- ^a		11.9	17.4	
Age, mean (SD)	48.5 ± 13.8	49.3 ± 13.4	0.83	47.5 ± 13.0	50.8 ± 13.2	0.010	50.1 ± 13.4	48.5 ± 13.4	0.20
BMI mean (SD)	23.4 ± 3.1	23.3 ± 3.4	0.79	23.3 ± 3.1	23.8 ± 3.4	0.057	23.3 ± 3.3	23.2 ± 3.2	0.73
Nutrients intake (mean ± SD)									
Carbohydrate (g/d)	302.1 ± 96.0	341.0 ± 94.2	<0.001	271.9 ± 78.6	383.3 ± 109.0	<0.001	328.1 ± 105.6	308.3 ± 82.8	0.009
Protein (g/d)	73.5 ± 22.2	75.1 ± 22.2	0.002	76.4 ± 19.3	67.6 ± 23.5	<0.001	70.8 ± 24.5	76.8 ± 21.1	<0.001
Fat (g/d)	86.1 ± 35.7	79.2 ± 35.5	0.14	88.4 ± 33.8	67.5 ± 38.6	<0.001	82.3 ± 39.1	84.8 ± 36.3	0.39
Energy (Kcal/d)	2317.0 ± 644.4	2415.5 ± 661.5	0.20	2249.5 ± 573.6	2422.9 ± 76.1	0.006	2345.4 ± 673.5	2355.5 ± 630.6	0.99
Magnesium (mg/d)	282.6 ± 83.8	380.2 ± 148.2	<0.001	276.0 ± 77.4	395.7 ± 168.3	<0.001	306.1 ± 111.2	348.4 ± 144.4	<0.001
Total Fe (mg/d)	29.0 ± 9.6	23.2 ± 7.9	<0.001	24.2 ± 8.1	28.4 ± 11.1	<0.001	29.3 ± 10.2	22.5 ± 7.6	<0.001
Haem Fe (mg/d)	4.3 ± 5.3	1.5 ± 1.6	<0.001	5.8 ± 4.8	0.3 ± 0.3	<0.001	1.8 ± 2.2	3.3 ± 3.9	<0.001
Non-haem Fe (mg/d)	24.7 ± 9.4	21.8 ± 7.9	<0.001	18.4 ± 5.7	28.2 ± 11.0	<0.001	27.5 ± 10.1	19.2 ± 7.0	<0.001
SES (%)			0.014			<0.001			0.018
Low	20.2	31.2		12.6	58.2		33.1	20.3	
Medium	34.6	34.6		28.6	28.5		32.7	33.3	
High	45.2	34.2		58.8	13.3		34.2	46.4	
Smoker (%)	34.5	26.1	0.038	34.1	25.0	0.040	30.3	28.4	0.57
Alcohol drinker (%)	28.4	27.3	0.29	30.3	22.7	0.093	23.9	26.5	0.71
Physical activity (%)			0.11			<0.001			0.36
<1 h	13.3	17.0		10.2	27.7		15.9	13.3	
1–2 h	25.0	35.2		25.4	39.8		31.8	28.8	
2–3 h/day	47.0	36.7		48.1	27.3		40.5	42.4	
>=3 h/day	14.8	11.0		16.3	5.3		11.7	15.5	
Manual occupation (%)	41.7	58.0	0.002	38.6	69.3	<0.001	45.8	51.1	0.14
Residence (%)			<0.001			<0.001			0.004
Urban	22.0	10.2		20.1	7.6		18.9	11.4	
Rural	78.0	89.8		79.9	92.4		81.1	88.6	
IFG (%)	15.9	9.5	0.068	18.9	6.1	<0.001	12.9	12.5	0.86
Family history of diabetes (%)	3.2	2.9	0.22	3.0	1.1	0.29	3	3	0.55
Serum ferritin (µg/L) (mean ± SD)	101.7 (76.6)	89.8 (76.3)	0.21	101.1 (80.2)	82.2 (77.6)	0.010	90.6 (73.0)	93.5 (75.6)	0.88
Haemoglobin (g/L) (mean ± SD)	131.7 (18.0)	132.7 (17.8)	0.66	130.6 (17.2)	136.0 (16.2)	0.001	131.9 (17.6)	130.7 (17.5)	0.17

BMI, body mass index.

SES, social economic status.

IFG, impaired fasting glucose.

^a No intake of haem-Fe (e.g. vegetarians).**Table 2**

Odds ratio of impaired fasting glucose of intake of magnesium, total Fe intake, haem Fe and Non-haem Fe in the Jiangsu Nutrition Study (n = 1056).

	Quartiles of intake				P for trend	N
	Q1	Q2	Q3	Q4		
Magnesium intake						
Model1	1.00	0.72 (0.43, 1.20)	0.46 (0.25, 0.86)*	0.69 (0.34, 1.40)	0.123	1056
Model2	1.00	0.73 (0.43, 1.24)	0.51 (0.27, 0.96)*	0.87 (0.41, 1.83)	0.330	1048
Model3	1.00	0.80 (0.47, 1.37)	0.51 (0.27, 0.98)*	0.96 (0.44, 2.08)	0.397	1035
Model4	1.00	0.82 (0.48, 1.40)	0.52 (0.27, 1.00)	0.97 (0.45, 2.13)	0.438	1035
Total Fe intake						
Model1	1.00	0.94 (0.54, 1.65)	1.03 (0.56, 1.90)	1.23 (0.63, 2.39)	0.513	1056
Model2	1.00	0.94 (0.54, 1.66)	1.04 (0.56, 1.92)	1.39 (0.70, 2.77)	0.340	1048
Model3	1.00	0.89 (0.50, 1.58)	1.00 (0.53, 1.88)	1.31 (0.65, 2.65)	0.423	1035
Model4	1.00	0.87 (0.49, 1.56)	0.99 (0.53, 1.86)	1.30 (0.64, 2.62)	0.438	1035
Haem-Fe intake						
Model1	1.00	1.40 (0.75, 2.63)	2.03 (1.11, 3.69)*	3.06 (1.71, 5.48)**	<0.000	1056
Model2	1.00	1.22 (0.63, 2.36)	1.66 (0.86, 3.18)	2.51 (1.33, 4.74)**	0.001	1048
Model3	1.00	1.38 (0.70, 2.73)	1.90 (0.96, 3.77)	2.83 (1.45, 5.53)**	0.001	1035
Model4	1.00	1.35 (0.68, 2.67)	1.87 (0.94, 3.71)	2.77 (1.42, 5.41)**	0.001	1035
Non-haem Fe intake						
Model1	1.00	0.89 (0.52, 1.51)	0.66 (0.37, 1.20)	0.63 (0.31, 1.26)	0.128	1056
Model2	1.00	0.93 (0.54, 1.59)	0.72 (0.39, 1.31)	0.79 (0.38, 1.63)	0.375	1048
Model3	1.00	0.91 (0.52, 1.58)	0.68 (0.37, 1.27)	0.74 (0.35, 1.56)	0.291	1035
Model4	1.00	0.89 (0.51, 1.55)	0.67 (0.36, 1.25)	0.73 (0.35, 1.54)	0.272	1035

Model 1 adjusted for age, sex and energy intake.

Model 2 further adjusted for social economics status, smoking and alcohol consumption.

Model 3 further adjusted for BMI, hypertension, highest quartile of serum ferritin and highest quartile of haemoglobin.

Model 4 further adjusted for family history of diabetes.

P for trend was performed using nutrients intake as continuous variables in different models.

Table 3
Odds ratio of impaired fasting glucose of intake of magnesium: total Fe, magnesium: haem Fe and magnesium: non-haem Fe in the Jiangsu Nutrition Study (n = 1056).

	Quartiles of magnesium to iron intake ratio				P for trend	N
	Q1	Q2	Q3	Q4		
Mg/Total Fe						
Model1	1.00	0.64 (0.39, 1.06)	0.60 (0.36, 0.99)*	0.51 (0.29, 0.87)*	0.016	1056
Model2	1.00	0.69 (0.41, 1.15)	0.62 (0.37, 1.04)	0.56 (0.32, 0.97)*	0.042	1048
Model3	1.00	0.86 (0.51, 1.45)	0.61 (0.35, 1.07)	0.66 (0.38, 1.15)	0.074	1035
Model4	1.00	0.89 (0.52, 1.51)	0.62 (0.35, 1.08)	0.66 (0.38, 1.15)	0.070	1035
Mg/Haem-Fe	1.00					
Model1	1.00	0.63 (0.39, 1.02)	0.44 (0.26, 0.75)**	0.26 (0.14, 0.48)**	<0.001	1056
Model2	1.00	0.60 (0.37, 0.98)*	0.47 (0.28, 0.81)**	0.30 (0.16, 0.58)**	<0.001	1048
Model3	1.00	0.60 (0.36, 0.99)*	0.49 (0.28, 0.85)*	0.27 (0.14, 0.55)**	<0.001	1035
Model4	1.00	0.59 (0.35, 0.98)*	0.49 (0.28, 0.84)*	0.28 (0.14, 0.55)**	<0.001	1035
Mg/Non-haem Fe	1.00					
Model1	1.00	0.87 (0.51, 1.48)	0.86 (0.51, 1.47)	0.99 (0.59, 1.67)	0.972	1056
Model2	1.00	0.89 (0.52, 1.53)	0.89 (0.51, 1.53)	0.95 (0.56, 1.61)	0.849	1048
Model3	1.00	0.97 (0.55, 1.70)	0.96 (0.55, 1.69)	1.02 (0.59, 1.76)	0.968	1035
Model4	1.00	0.94 (0.54, 1.65)	0.94 (0.54, 1.65)	1.01 (0.59, 1.74)	0.953	1035

Model 1 adjusted for age, sex and energy intake.

Model 2 further adjusted for social economics status, smoking and alcohol consumption.

Model 3 further adjusted for BMI, hypertension, highest quartile of serum ferritin and highest quartile of haemoglobin.

Model 4 further adjusted for family history of diabetes.

P for trend was performed using nutrients intake as continuous variables in different models.

type 2 diabetes [23]. This may suggest that haem-Fe was associated with other unknown factors in red meat, however, adjusting red meat did not change the association between magnesium: haem-Fe intake ratio (data not shown), suggesting that the effect of haem-Fe on hyperglycaemia is independent of red meat intake. One systematic review and meta-analysis on the haem iron, red meat and the risk of type 2 diabetes found that processed red meat is associated with increased risk, with a small increased risk may possibly from high intakes of red meat [24]. The possible mechanism may be involved with glycation and lipoxidation endproducts, and the protein modifications present in processed red meat may influence insulin output by pancreatic islet cells. However, we do not have processed red meat information, so that the effect of processed meat cannot be checked in this study. These results are also consistent with the general protective effect of plant sourced foods versus animal sourced foods in terms of development diabetes.

In addition, dietary Mg intake alone was not associated with the risk of IFG found in this study, which is consistent with the previous cross-sectional study using the same cohort [12] and another cross-sectional study in China [25]. However, other prospective studies have reported an inverse association between dietary Mg and the diabetes risk (e.g. The Coronary Artery Risk Development in Young Adults (CARDIA) Study and the Health Professionals' Follow-up Study (HPFS) [26,27]. The inconsistent results may be explained by following possibilities: 1) both CARDIA and HPFS investigated the American population, where magnesium-enriched foods are more likely to be consumed by people from middle-up SES, and the benefit of reduced risk of T2DM may also be attributed to a general high quality and healthy life. China has the opposite situation that people from lower SES are more likely to consume magnesium enriched foods as they are relatively cheaper in China, but the benefit of reduced risk of T2MD may be overshadowed by poor life habits and quality; 2) both CARDIA and HPFS used food questionnaires using self-reported dietary intake to estimate magnesium intake, where our study used 3-day weighing plus food records. The difference in nutrients assessment may be contribute to the inconsistent results; 3) both CARDIA and HPFS have a long following up period (≥ 12 years), whereas we only had 5-year follow-up. It is possible that 5-year follows is not long enough to detect any difference in dietary Mg intake against the risk of T2DM. However, when looked at the ratio between Mg/haem-Fe, a consistent

inverse association was present. This suggests an interaction between dietary Mg and haem-Fe against the risk of T2DM that dietary Mg protects against the increased T2DM conferred by haem-Fe intake.

Subgroup analyses did not find significant interactions between demographic factors, lifestyle factors and obesity and Mg/haem-Fe intake, in relation to the risk of IFG. However, it seems that current smoking may benefit more from a high ratio of magnesium to haem-Fe intake to prevent developing hyperglycaemia. Active smoking has been associated with the risk of diabetes in previous prospective studies [28–30]. One of the mechanisms may be that smoking generally increases insulin resistance by altering the distribution of body fat or by exerting a direct toxic on pancreatic tissue [28,29]. Increased magnesium intake has been demonstrated to prevent hyperlipidaemia and insulin resistance [31], which could be an explanation of the potential interaction.

Although we focused on dietary iron intake as a predictor in the present study, serum ferritin as well as iron intake has been associated with increased risk of diabetes [6]. When we substituted serum ferritin with dietary iron intake, i.e. examining the association between the Mg/SF in relation to the risk of IFG, no significant associations were found. This may suggest that dietary iron intake, to an extent, particularly considering the interaction with dietary magnesium, in relation to the risk of IFG, is a reasonable measure. However, when we further examined interactions between Mg/haem-Fe and the level of ferritin (<50% vs $\geq 50\%$), a potential interaction that participants with lower level of ferritin (<50%) seem to have lower risk of IFG comparing with their counterparts. This is consistent with the previous findings that serum ferritin levels are also positively associated the risk of diabetes [6,32].

The prevalence of diabetes in China is higher in urban area than the rural area [33,34]. Our study suggests that increasing dietary intake of magnesium relative to haem-Fe may be an effective strategy for preventing diabetes, especially in urban areas where the consumption of animal foods is typically higher versus rural areas. Plant-based foods have been previously shown to be associated with lower risk of diabetes risk [35]. Despite the low consumption of haem-Fe found in this cohort, our sensitivity analysis did not change the overall findings after excluding those with low serum ferritin. This may suggest that high dietary intake of Mg may be protective against developing diabetes and is independent of

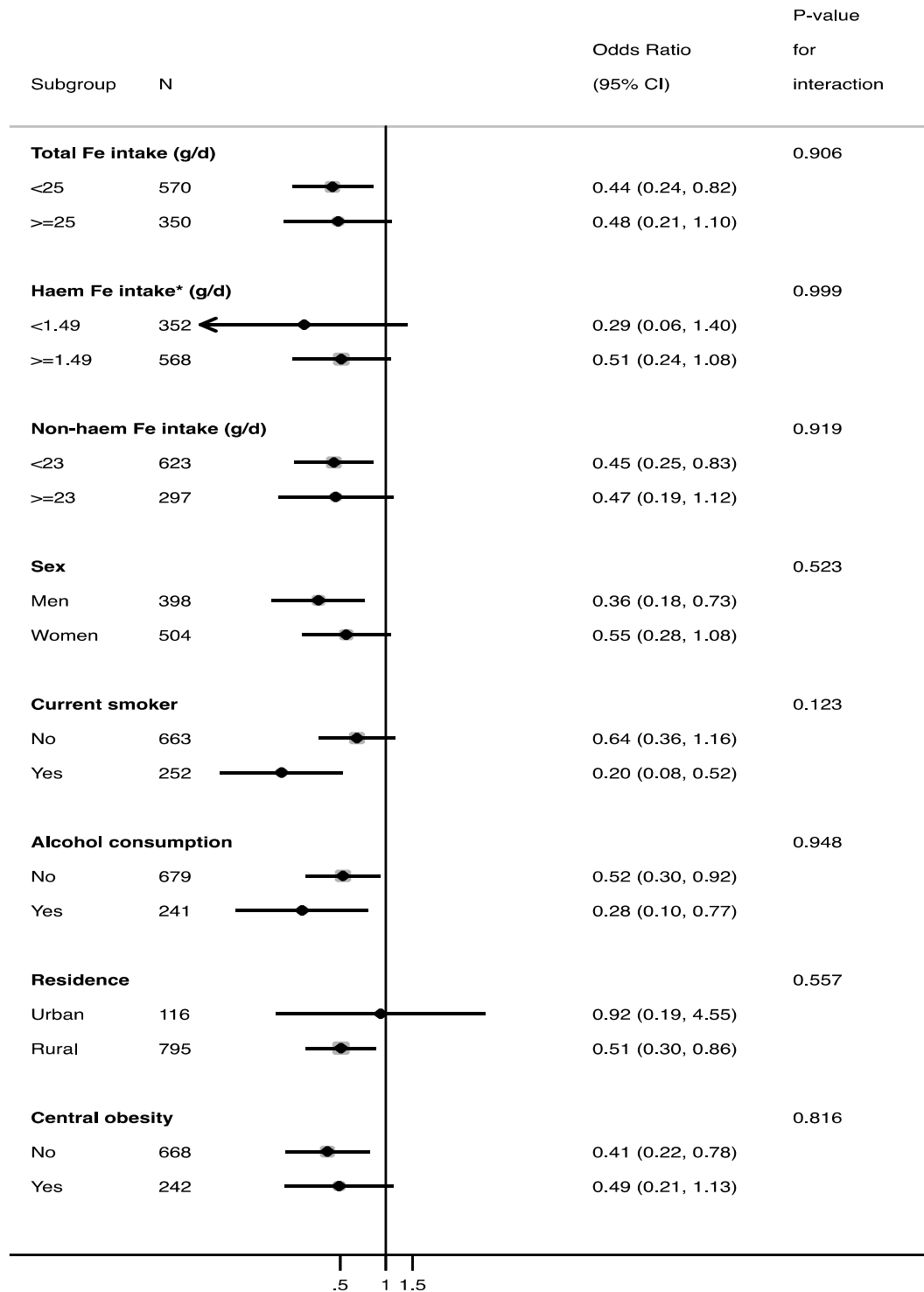


Fig. 1. Subgroup analyses of the associations between the ratio of magnesium: haem Fe (above vs below 50%) and IFG at follow up. The cut-off of total Fe intake, haem Fe intake and non-haem Fe intake were according to the mean value. Model 2 as shown in Table was adjusted *the cut-off for haem Fe intake was the median value.

serum ferritin status. Strategies that increase vegetable intake among urban dwelling populations may be effective for diabetes prevention.

There are several limitations of this study. First, we had a high rate of lost to follow-up due to migration and city construction. However, loss to follow-up may not influence the findings since the exposure variables were measured at baseline. Due to the small

number of incident cases of diabetes, we were not able to use diabetes as the outcome measure. No data on inflammation related markers make it impossible to check the interactions between inflammation and the exposure in relation to IFG, as magnesium has been suggested to be inversely associated with systemic inflammation and insulin resistance [36]. Although fasting glucose is easier to collect than an oral glucose tolerant test in Chinese

population, impaired glucose tolerance and the association with Mg/Fe may also need to be explored in the future. In addition, 3-day food records may not be a good indicator of long-term habitual dietary intake, further studies using other measurements such as food frequency questionnaire are needed [37]. The strength of the study is that we used fasting plasma glucose level as the marker of IFG, which is not usually measured in large cohort studies. Furthermore, nutrient intake was assessed by a weighed food record. The prospective study design raises the possibility of a causal relation between exposure of for future longitudinal studies to further confirm such associations.

In conclusion, this prospective study in a Chinese cohort confirms the association between the ratio of magnesium and iron intake that found previously in cross-sectional analysis of the JIN baseline data. Furthermore, it highlights the consistent independent benefits of a high Mg/haem-Fe but not with Mg/non-haem-Fe associated with reduce risk of IFG. Future research to confirm the added predictive value of dietary Mg/haem-Fe to current T2D risk models in specific populations is justified.

Acknowledgements

The authors are grateful to the participating regional Centres for Disease Control and Prevention in Jiangsu Province, including the Nanjing, Xuzhou, Jiangyin, Taicang, Suining, Jurong, Sihong and Haimen centres, for the support in data collection. Y.C carried out the data analyses and wrote the manuscript; S.Z conducted the dietary intake calculation; E.A and Z.S contributed to the writing of the manuscript, critically reviewed the manuscript and approved the final version.

This research did not receive any specific grant from funding in the public, commercial, or not-for-profit sectors.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jnim.2018.05.002>.

References

- [1] Yang W, et al. Prevalence of diabetes among men and women in China. *N. Engl. J. Med.* 2010;362(12):1090–101.
- [2] Barbagallo M, Dominguez LJ. Magnesium and type 2 diabetes. *World J. Diabetes* 2015;6(10):1152–7.
- [3] Dong JY, et al. Magnesium intake and risk of type 2 diabetes: meta-analysis of prospective cohort studies. *Diabetes Care* 2011;34(9):2116–22.
- [4] Jiang R, et al. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *Jama* 2004;291(6):711–7.
- [5] Lee D-H, Folsom A, Jacobs D. Dietary iron intake and type 2 diabetes incidence in postmenopausal women: the Iowa Women's Health Study. *Diabetologia* 2004;47(2):185–94.
- [6] Shi Z, et al. Association between serum ferritin, hemoglobin, iron intake, and diabetes in adults in Jiangsu, China. *Diabetes Care* 2006;29(8):1878–83.
- [7] Fernández-Real JM, López-Bermejo A, Ricart W. Cross-talk between iron metabolism and diabetes. *Diabetes* 2002;51(8):2348–54.
- [8] Swaminathan S, et al. The role of iron in diabetes and its complications. *Diabetes Care* 2007;30(7):1926–33.
- [9] Shi Z, et al. Iron intake and body iron stores, anaemia and risk of hyperglycaemia among Chinese adults: the prospective Jiangsu Nutrition Study (JIN). *Publ. Health Nutr.* 2010;13(09):1319–27.
- [10] Jiang R, et al. Dietary iron intake and blood donations in relation to risk of type 2 diabetes in men: a prospective cohort study. *Am. J. Clin. Nutr.* 2004;79(1):70–5.
- [11] Bao W, et al. Dietary iron intake, body iron stores, and the risk of type 2 diabetes: a systematic review and meta-analysis. *BMC Med.* 2012;10:119.
- [12] Shi ZM, et al. Association between magnesium : iron intake ratio and diabetes in Chinese adults in Jiangsu Province. *Diabet. Med.* 2008;25(10):1164–70.
- [13] Shi Z, et al. Monosodium glutamate is not associated with obesity or a greater prevalence of weight gain over 5 years: findings from the Jiangsu Nutrition Study of Chinese adults. *Br. J. Nutr.* 2010;104(3):457–63.
- [14] Li Y, et al. Exposure to the Chinese famine in early life and the risk of hyperglycemia and type 2 diabetes in adulthood. *Diabetes* 2010;59(10):2400–6.
- [15] Shi Z, et al. Dietary fat and sleep duration in Chinese men and women. *Int. J. Obes.* 2008;32(12):1835–40 (London).
- [16] Yang Y, H.M.P.X. China Food Composition Table. Peking: China Institute of Nutrition and Food Safety, China CDC; 2002.
- [17] Dallman PR. Diagnosis of anemia and iron deficiency: analytic and biological variations of laboratory tests. *Am. J. Clin. Nutr.* 1984;39(6):937–41.
- [18] Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2006;29(Suppl 1):S43–8.
- [19] Chen C, Lu FC, P.R.C. Department of Disease Control Ministry of Health. The guidelines for prevention and control of overweight and obesity in Chinese adults. *Biomed. Environ. Sci.* 2004;17(Suppl):1–36.
- [20] Piomelli S, Jansen V, Dancis J. The hemolytic anemia of magnesium deficiency in adult rats. *Blood* 1973;41(3):451–9.
- [21] Cinar V, et al. Effects of magnesium supplementation on blood parameters of athletes at rest and after exercise. *Biol. Trace Elem. Res.* 2007;115(3):205–12.
- [22] Rajpathak S, et al. Iron intake and the risk of type 2 diabetes in women: a prospective cohort study. *Diabetes Care* 2006;29(6):1370–6.
- [23] Jiang R, et al. Body iron stores in relation to risk of type 2 diabetes in apparently healthy women. *Jama* 2004;291(6):711–7.
- [24] White DL, Collinson A. Red meat, dietary heme iron, and risk of type 2 diabetes: the involvement of advanced lipoxidation endproducts. *Adv Nutr* 2013;4(4):403–11.
- [25] Zhang J, et al. Association between toenail magnesium and type 2 diabetes in Chinese adults. *Nutrients* 2017;9(8).
- [26] Lopez-Ridaura R, et al. Magnesium intake and risk of type 2 diabetes in men and women. *Diabetes Care* 2004;27(1):134–40.
- [27] He K, et al. Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006;113(13):1675–82.
- [28] Rimm EB, et al. Cigarette smoking and the risk of diabetes in women. *Am. J. Publ. Health* 1993;83(2):211–4.
- [29] Rimm EB, et al. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. *Br. Med. J.* 1995;310(6979):555–9.
- [30] Will JC, et al. Cigarette smoking and diabetes mellitus: evidence of a positive association from a large prospective cohort study. *Int. J. Epidemiol.* 2001;30(3):540–6.
- [31] Olatunji LA, Soladoye AO. Increased magnesium intake prevents hyperlipidemia and insulin resistance and reduces lipid peroxidation in fructose-fed rats. *Pathophysiology* 2007;14(1):11–5.
- [32] Zhan Y, Tang Z, Yu J. Serum ferritin, diabetes, diabetes control, and insulin resistance. *Acta Diabetol.* 2014;51(6):991–8.
- [33] Dong Y, et al. Prevalence of Type 2 diabetes in urban and rural Chinese populations in Qingdao, China. *Diabet. Med.* 2005;22(10):1427–33.
- [34] Bragg F, et al. Association between diabetes and cause-specific mortality in rural and urban areas of China. *Jama* 2017;317(3):280–9.
- [35] Satija A, et al. Plant-based dietary patterns and incidence of type 2 diabetes in US men and women: results from three prospective cohort studies. *PLoS Med.* 2016;(6):13. p. e1002039.
- [36] Kim DJ, et al. Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. *Diabetes Care* 2010;33(12):2604–10.
- [37] Thompson FE, Byers T. Dietary assessment resource manual. *J. Nutr.* 1994;124(11 Suppl). p. 2245s–2317s.