Letter to the Editor

Nonlinear Reduction in Risk for Type 2 Diabetes by Magnesium Intake: An Updated Meta-Analysis of Prospective Cohort Studies*

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Observational studies between magnesium intake and risk of type 2 diabetes yielded inconsistent results. We conducted a system literature search of PubMed database through March 2015 for prospective cohort studies of magnesium intake and type 2 diabetes risk. Study-specific results were pooled in a random-effects model. Subgroup and sensitivity analysis were performed to assess the potential sources of heterogeneity and the robustness of the pooled estimation. Generalized least squares trend estimation was used to investigate the dose-response relationship. A total of 15 papers with 19 analyses were identified with 539,735 participants and 25,252 incident diabetes cases. Magnesium intake was associated with a significant lower risk of type 2 diabetes (RR: 0.77; 95% CI: 0.71-0.82) for the highest compared with lowest category. This association was not significantly modified by the pre-specified study characteristics. In the dose-response analysis, a magnesium intake increment of 100 mg/day was associated with a 16% reduction in type 2 diabetes risk (RR: 0.84; 95% CI: 0.80-0.88). A nonlinear relationship existed between magnesium intake and type 2 diabetes (*P*-nonlinearity=0.003). This meta-analysis further verified a protective effect of magnesium intake on type 2 diabetes in a nonlinear dose-response manner.

The increasing prevalence of type 2 diabetes poses both clinical and public health challenges. As of 2013, 382 million people had diabetes worldwide and type 2 made up about 90% of the cases[1]. In China, diabetes may have reached an epidemic level with one in ten adults having the disease while most patients are unaware of their condition[2]. Finding novel and independent risk factors of diabetes has profound significance in total population prevention.

Diet is considered closely associated the type 2 diabetes development. Magnesium, as an essential cofactor for multiple enzymes involved in glucose metabolism[3-4], received considerable interest for its effect in diabetes prevention in epidemiological studies. Previous two meta-analyses[5-6] reported that higher magnesium intake was associated with a 22% and 15% reduction in the risk of type 2 diabetes respectively. However, they did not test a possible nonlinear association between the exposure and the outcome. Furthermore, three new prospective cohort studies[7-9] were reported after their publications. Therefore, we conducted an updated meta-analysis and assessed whether there was a nonlinear relationship between magnesium intake and type 2 diabetes.

We conducted a systematic literature search of PubMed database from inception to March 2015 using the following search terms: 'magnesium' in combination with 'diabetes'. Studies were included if they met the following criteria: the study design was prospective; the exposure of interest was magnesium intake including dietary or total (dietary and supplemental). Total magnesium was used if both were reported; the outcome of interest was type 2 diabetes incidence; and the adjusted risk estimates with 95% confidence intervals (CI) were reported.

Key information of all included studies was recorded as follows: name of the first author, publication year, and study location; sample size and case number; duration of follow-up; dietary assessment methods; outcome assessment methods; the risk estimate and corresponding 95% CI for the

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highest category of magnesium intake and variables adjusted in the analysis. We used the reported maximally adjusted risk estimates without control for blood glucose and/or insulin levels to avoid overadjustment. Two authors independently conducted the literature search, study selection and data extraction. Any disagreements were resolved by discussion.

Considering that all included studies were cohort studies, the HRs and ORs were directly considered as RRs in this meta-analysis. A DerSimonian and Laird[10] random-effects model, which considers both within-study and between-study variations, was used to calculate the summary risk estimates. We pooled the RRs for the highest *vs* the lowest level from each included study in main analysis. To explore the potential sources of heterogeneity, we conducted several subgroup analyses stratified by geographic region (Asia or Non-Asia), length of follow-up (≥10 or <10 years), the number of case (≥500 or <500), body mass index (BMI) (≥25 or <25 kg/m^2), sex (male or female), adjusted confounders (adjust for cereal fiber or not) and outcome assessment methods (pure self-report or not). We also conducted a sensitivity analysis by omitting one study at each turn and focusing on the studies of dietary magnesium intake to test the robustness of pooled results.

Because the range of magnesium intake and the cutoffs for the categories varied among studies, we also estimated a RR with 95% CI of type 2 diabetes for a 100 mg/day increase in magnesium intake in a dose-response meta-analysis. The methods proposed by Greenland and Longnecker [11] and Orsini et al.[12] were applied, requiring the number of cases and total participants or person-years as well as the effect size with their variance estimates for at least three quantitative exposure categories. In addition, we modeled magnesium intake using restricted cubic splines with three knots at percentiles 10%, 50%, and 90% of the distribution[13]. The *P* value for nonlinear relationship was calculated by testing the null hypothesis that second spline regression coefficient is equal to zero.

Statistical heterogeneity among studies was evaluated by Q and I^2 statistic[14-15]. A *P* value below 0.1 or an I^2 above 50% represents substantial heterogeneity. Potential publication bias was assessed by Begg's test (rank correlation method)[16] and Egger's test (linear regression method)[17] . All analyses were performed using STATA version 12.0 (StataCorp LP, College Station, Texas). $P<0.05$ was considered statistically significant except where otherwise specified.

The detailed steps of our literature search are shown in Figure 1. We initially identified 1578 articles from the database search and excluded 1558 ones after evaluations of titles and abstracts. Twenty articles appeared relevant to this meta-analysis and were selected for full-text review. Five articles were excluded because they only reported serum magnesium and type 2 diabetes. Finally, we identified 15 papers[7-9,18-29] with 19 analyses of magnesium intake and risk of type 2 diabetes. Each of four studies[19,20,23,25] consisted of two separate estimates.

The characteristics of the included prospective cohort studies are presented in Table 1. These studies were published between 1999 and 2014, with a follow-up duration ranging from 4 to 20 years.

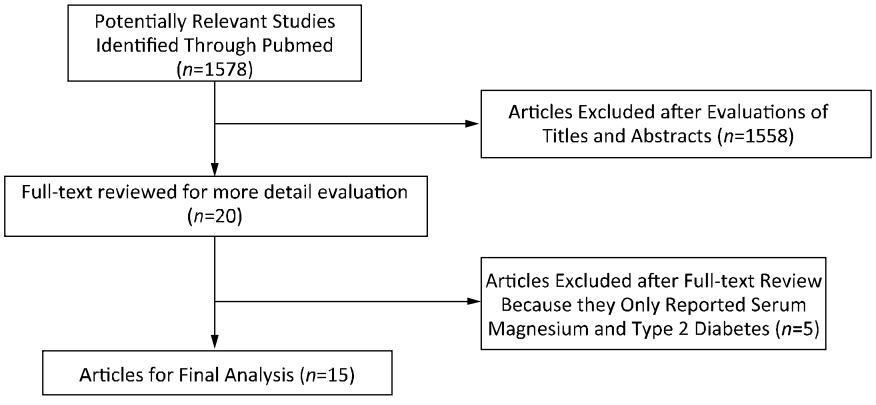

Figure 1. A flow chart of selection for prospective cohort studies between magnesium intake and risk of type 2 diabetes incidence.

Table 1. Characteristics of Included Prospective Cohort Studies of Magnesium and Type 2 Diabetes

Author, Year and Location	Sample Size; Case Number	Duration (years)	Dietary Assessment Method	Outcome Assessment	Magnesium Intake (highest *vs.* lowest)	Adjusted RR (95% CI)	Adjusted Covariates
W. H. Linda Kao, 1999, USA[20]	White: 9506; 739 Black: 2622; 367	6	Validated FFQ	Glucose levels, use of diabetic medication or self-report	>0.17 mg/4.2 kJ daily *vs.* ≤0.12 mg/4.2 kJ daily	White: 1.08 (0.78-1.49) black: 0.98 (0.57-1.72)	Age, BMI, sex, education, family history, WHR, sports index, diuretic use, intakes of alcohol, calcium, and potassium
Katie A Meyer, 2000, USA[24]	35,988; 1141	6	Validated FFQ	Self-reported	360 mg/day *vs.* 220 mg/day	0.67 (0.55-0.82)	Age, BMI, education, smoking, WHR, physical activity, intakes of total energy, alcohol, whole grains, and cereal fiber
Allison M.Hodge 2004, Australia[18]	31,641; 365	4	FFQ	Confirmed self-report	A 500 mg/day increment	0.73 (0.51-1.04)*	Age, BMI, sex, education, country of birth, family history, WHR, weight change, physical activity, and intakes of total energy and alcohol
RUY LOPEZ-R IDAURA, 2004, USA[23]	Men: 42,872; 1333 Women: 85,060; 4084	Men:11 Women:17	Validated FFQ	Confirmed self-reported	Men:457 mg/day *vs.* 270 mg/day Women: 373 mg/day *vs.* 222 mg/day	Men: 0.72 (0.58-0.89) Women: 0.73 (0.65-0.82)	Age, family history, hypertension, hypercholesterolemia, smoking, BMI, physical activity, intakes of total energy, alcohol, glycemic load, polyunsaturated fats, trans fatty acid, processed meat and cereal fiber
YI QING SONG, 2004, USA[27]	38,025; 918	6	Validated FFQ	Confirmed self-reported	433 mg/day *vs.* 255 mg/day	0.89 (0.71-1.10)	Age, BMI, family history, smoking, physical activity, and intakes of total energy and alcohol
ROB M. VAN DAM, 2006, USA[28]	41,186; 1964	8	Validated FFQ	Confirmed self-reported	244 mg/day *vs.* 115 mg/day	0.65 (0.54-0.78)	Age, BMI, education, family history, smoking, physical activity, and intakes of total energy, alcohol, coffee, sugar-sweetened drinks, red meat, processed meat, and calcium
Matthias B. Schulze, 2007, Germany[26]	25,067; 844	7	Validated FFQ	ICD 10th	377 mg/day *vs.* 268 mg/day	0.99 (0.78-1.26)	Age, BMI, sex, education, sports activity, cycling, occupational activity, smoking, WC, and intakes of total energy, alcohol, carbohydrate, PUFA-to-SFA ratio, MUFA-to-SFA ratio, and cereal fiber
Raquel Villegas, 2009, China[29]	64,191; 2270	6.9	Validated FFQ	Confirmed self-reported	318.1 mg/day *vs.* 213.8 mg/day	0.80 (0.68-0.93)	Age, BMI, WHR, smoking, physical activity, income, education, occupation, hypertension, and intakes of total energy and alcohol
Beth N. Hopping, 2010, USA[19]	Men: 36,256; 4555 Women: 39,256; 4032	14	FFQ	Glucose levels, use of diabetic medication,or self-report	Men: ≥185.4 mg/4184 kJ daily *vs.* <129.3 mg/ 4184 kJ daily Women: ≥200.2 mg/ 4184 kJ daily *vs.* <139.3 mg/4184 kJ daily	Men: 0.77 (0.70-0.85) Women: 0.84 (0.76-0.93)	BMI, physical activity, education, ethnicity, and total energy intake

Continued

Author, Year and Location	Sample Size; Case Number	Duration (years)	Dietary Assessment Method	Outcome Assessment	Magnesium Intake (highest *vs.* lowest)	Adjusted RR (95% CI)	Adjusted Covariates
DAE JUNG KIM, 2010, USA[21]	4497; 330	20	Validated history diet questionnaire	Glucose levels or use of diabetic medication	201.5 mg/1000 Kcal *vs.* 99.9 mg/1000 Kcal	0.53 (0.32-0.86)	Age, BMI, sex, ethnicity, study center, education, smoking, physical activity, family history, systolic blood pressure, and intakes of total energy, alcohol, saturated fat, and crude fiber
Kyoko Kirii, 2010, Japan[22]	17,592; 459	5	Validated dietary questionnaire	Confirmed self-report	303 mg/day *vs.* 158 mg/day	0.64 (0.44-0.94)	Age, BMI, family history, smoking, hours of walking and sports participation, and intakes of total energy, alcohol, green tea, and coffee
A Nanri, 2010, Japan[25]	Men: 25,872; 634 Women: 33,919; 480	5	Validated FFQ	Confirmed self-report	Men: 348 mg/day *vs.* 213 mg/day Women: 333 mg/day *vs.* 213 mg/day	Men: 0.86 (0.63-1.16) Women 0.92 (0.66-1.28)	Age, BMI, study area, smoking, family history, leisure time physical activity, hypertension, and intakes of total energy, alcohol, coffee, and calcium
A. Hata, Japan,2013[8]	1999; 417	15.6	Validated FFQ	a self-administered questionnaire	214.7 mg/day *vs.* 132.9 mg/day	0.63 (0.44-0.90)	Age, sex, family history of diabetes, BMI, HDL cholesterol, triglycerides, hypertension, smoking habits, alcohol intake and regular exercise, and intakes of total energy, carbohydrate, crude fiber, saturated fatty acid, polyunsaturated fatty acid and vitamin C.
Lu-Chen Weng, 2012, Taiwan[9]	1604; 141	4.6	Validated FFQ	Glucose levels or self-reported diabetic drug use	405.9 mg/day *vs.* 212.4 mg/day	0.38 (0.21-0.7)	Age, sex, age sex interaction, caloric intake per day, residential area, family history of diabetes, BMI, central obesity, education, smoking habit, drinking habit, frequency of activity, hypertension, hypercholesterolemia, hypertriglyceridemia and low HDL-cholesterol.
Adela Hruby, USA,2014[7]	2582; 179	6.9	Validated FFQ	Glucose levels or self-reported diabetic drug use	395 mg/day *vs.* 235 mg/day	0.49 (0.27-0.88)	age, sex, energy intake, parental history of diabetes, BMI, physical activity score, smoking status, alcohol intake, hypertension and dietary fiber

Note. FFQ=food frequency questionnaire; ICD=International classification disease; BMI=Body mass index; WHR=Waist-hip Ratio; PUFA=polyunsaturated fatty acid; SFA= saturated fatty acid; MUFA= monounsaturated fatty acid. *RR corresponds approximately to the difference between the 87.5th and 12.5th percentiles of magnesium intake.

They totally involved 539,735 participants and 25,252 incident cases. The exposure and outcome assessments were mainly based on food frequency questionnaire and validated self-reported of physician diagnosis, respectively. Among the 15 papers, eight were conducted in the United States, three in Japan, two in China, one in Australia and one in Germany. All studies defined type 2 diabetes as the outcome with one exception[21] that did not further distinguish diabetes subtypes. While it also confirmed that the great majority of cases were type 2 diabetes.

The results from the random-effects model combining the RRs for the association between magnesium intake and type 2 diabetes risk are shown in Figure 2. The summary RR for the highest compared with lowest intake was 0.77 (95% CI: 0.71-0.82), suggesting that higher magnesium intake was associated with a significant lower risk of type 2 diabetes. We observed moderate heterogeneity (P=0.014, I^2=46.6%) and no evidence of publication bias (P for Begg test =0.18, P for Egger test=0.36).

Table 2 represents the results of subgroup analyses according to some pre-specified factors. A significant inverse association between magnesium intake and type 2 diabetes was observed in all but one subgroup consisting of participants with BMI <25 kg/m^2, and the association was not significantly modified by these characteristics (P for interaction ≥0.207). The sensitivity analyses that omitted one study at a time and calculated the combined RR for the remaining studies yielded consistent results. The combined RRs were all statistically significant and similar with one another, with a narrow range from 0.76 (95% CI: 0.72-0.80) to 0.78 (95% CI: 0.75-0.82). When we restricted to the studies of dietary magnesium intake, the summary RR for the highest compared with lowest intake was 0.77 (95% CI: 0.72-0.83).

On average, the combined RR of type 2 diabetes was 0.84 (0.80-0.88) for a 100 mg/day increase in magnesium intake with obvious heterogeneity among studies (P<0.001, I^2=62.6%). We also observed a significant nonlinear dose-response relationship between magnesium intake and type 2 diabetes risk (P-nonlinearity=0.003). The dose-response relationship between magnesium intake and type 2 diabetes risk is presented in Figure 3. Compared with an intake of 115 mg/d (mean intake in the lowest category) of magnesium, the RRs (95% CIs) of type 2 diabetes for intakes of 160mg, 200 mg, 260 mg, 300 mg, 350 mg and 410 mg/d were 0.89 (0.86-0.91), 0.8 (0.75-0.84), 0.68 (0.62-0.75), 0.63 (0.57-0.7), 0.6 (0.55-0.66), and 0.58 (0.53-0.63) respectively.

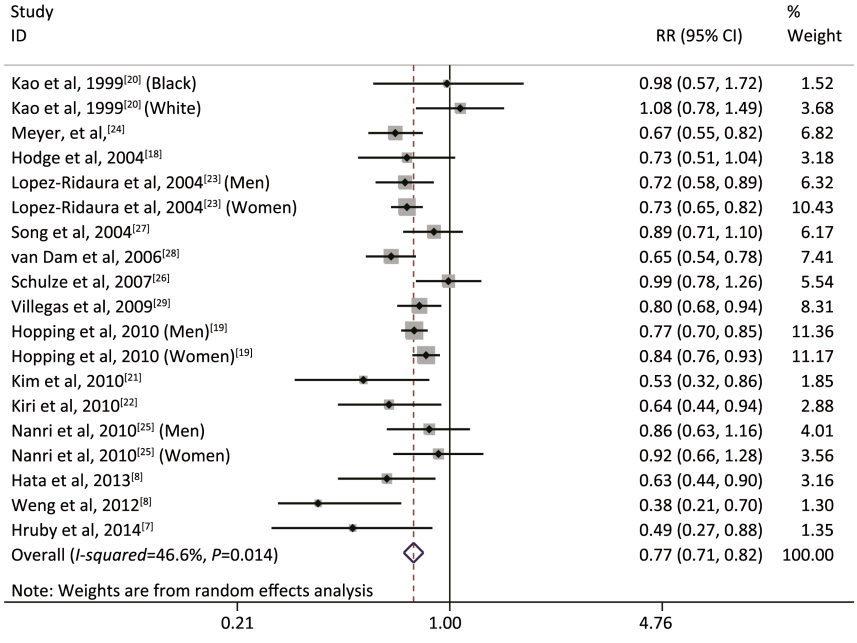

Figure 2. A forest plot of magnesium intake (highest vs lowest) and type 2 diabetes risk.

Table 2. Subgroup Analysis of Magnesium Intake and Diabetes Risk according to Included Studies Characteristics

Group	No of Estimates	RR (95% CI)	*P* for Eterogeneity	I^2 (%)	*P* for Interaction
Total	19	0.77 (0.71-0.82)	0.014	46.6	
Geographic region					
Asia	6	0.74 (0.62-0.88)	0.018	50.9	0.681
Non-Asia	13	0.77 (0.71-0.84)	0.101	45.7	
No of case					
≥500	10	0.79 (0.73-0.85)	0.022	53.6	0.207
<500	9	0.70 (0.59-0.82)	0.106	39.3	
Follow up years					
≥10	6	0.76 (0.70-0.82)	0.19	32.8	0.581
<10	13	0.78 (0.69-0.88)	0.01	54.2	
Gender					
Male	6	0.77 (0.71-0.83)	0.879	0	0.803
Female	10	0.75 (0.68-0.83)	0.041	48.6	
Adjusting for cereal fiber					
Yes	7	0.72 (0.63-0.81)	0.091	45.1	0.593
No	12	0.79 (0.73-0.87)	0.054	43.4	
BMI (kg/m^2)					
≥25	7	0.73 (0.65-0.83)	0.303	12.1	0.304
<25	4	0.88 (0.51-1.52)	0.02	69.3	
Pure self-report in outcome assessment					
Yes	11	0.74 (0.69-0.79)	0.397	4.9	0.481
No	8	0.8 (0.69-0.92)	0.007	63.9	

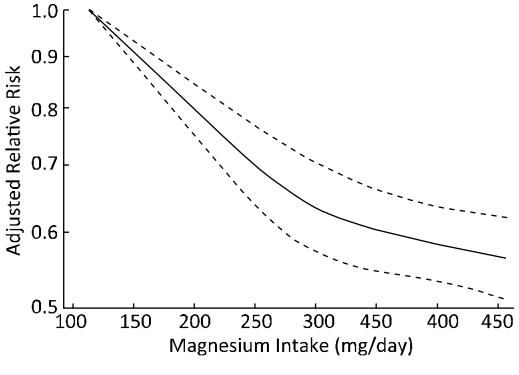

Figure 3. Relationship between magnesium intake and risk of type 2 diabetes incidence in a restricted cubic spline model. The lowest value of 115 mg/day of magnesium intake was used for the estimation of all relative risks. Solid line represents relative risk and long dashed lines represent 95% confidence intervals.

Previous meta-analyses[5-6] did not evaluate a potential non-linearity between magnesium intake and type 2 diabetes. Therefore whether diabetes risk would decrease in a constant rate with magnesium intake increasing needs further research. Our study found a nonlinear relationship between magnesium intake and type 2 diabetes. The fitting curve showed that the risk of type 2 diabetes decreased with higher magnesium intake when intake was below 260 mg/day while this trend slowed down after 300 mg/day. As a matter of fact, 300 mg/day is an approximate and recommended intake level for women in the USA and men have a higher suggested value. This indicated that 300 mg/day of magnesium intake is a basic level for its effect against type 2 diabetes. To those who aim to reduce type 2 diabetes risk by increasing magnesium intake, awareness of their current level is necessary. Magnesium intake against type 2 diabetes may be more effective in baseline lower situations.

It was believed that the protective effect of magnesium on diabetes was mediated through glucose homeostasis via glucose metabolism, insulin sensitivity and insulin action[30]. Magnesium deficiency was thought to damage the proliferation and mass of β-cells, thus affecting insulin production[31]. Mg supplementation was also shown to prevent fructose-induced insulin insensitivity[3]. Although our meta-analysis only included observational studies, some other population-based intervention trials[32-35] also approved that magnesium supplementation improved insulin sensitivity, reduced insulin resistance and plasma fasting glucose levels in both non-diabetes subjects and diabetes patients.

Moderate heterogeneity emerged in primary analysis while no interactions were observed among the predefined factors. This heterogeneity maybe derived from the difference of unreported characteristics among the included studies. In subgroup analysis, magnesium intake was not associated with a lower risk of type 2 diabetes in BMI<25 subjects. It is considered that overweight individuals are prone to insulin resistance and more susceptible to magnesium intake effects on improving insulin sensitivity[27]. However, a recent study reported a significant protective effect of magnesium on BMI<25 persons other than overweight individuals[8]. It was also included in our meta-analysis but did not alter the pooled estimation direction because of a small weight. Whether the magnesium-diabetes association is modified by BMI needs further researches.

Our study had some important strengths. All included original studies in this meta-analysis used a prospective design, which eliminated the possibility of reverse causation and minimized selection bias. In addition, the large number of cases involved enhanced the statistical power of the current study. Furthermore, the dose-response analysis gave us a more direct exhibition of the relationship between magnesium intake and type 2 diabetes. Potential limitations of this study should also be considered. First, as a meta-analysis of observational studies, the chance for residual confounding effect can not be fully eliminated, especially unadjusted dietary factors correlated with both magnesium intake and diabetes. Another limitation is the misclassification of the exposure and the outcome because they were mainly based on self-administered questionnaires and self-reports. Moreover, all included studies did not evaluate the effect of magnesium intake change during follow-up period on outcome incidence.

In conclusion, the present meta-analysis of prospective cohort studies further verified a protective effect of magnesium intake on type 2 diabetes in a nonlinear dose-response manner. Increasing magnesium intake especially in those with low basic level would make a beneficial contribution to control type 2 diabetes risk in general population.

AUTHORS CONTRIBUTIONS

XU Tian designed the study, collected and analyzed the data, wrote the manuscript; CHEN Guo Chong analyzed the data; ZHAI Lin collected the data; KE Kai Fu designed the study.

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