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Dietary magnesium intake and risk of metabolic syndrome: a meta-analysis

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Abstract

Aims—To estimate quantitatively the association between dietary magnesium intake and risk of metabolic syndrome by combining the relevant published articles using meta-analysis.

Methods—We reviewed the relevant literature in PubMed and EMBASE published up until August 2013 and obtained additional information through Google or a hand search of the references in relevant articles. A random-effects or fixed-effects model, as appropriate, was used to pool the effect sizes on metabolic syndrome comparing individuals with the highest dietary magnesium intake with those having the lowest intake. The dose–response relationship was assessed for every 100-mg/day increment in magnesium intake and risk of metabolic syndrome.

Result—Six cross-sectional studies, including a total of 24 473 individuals and 6311 cases of metabolic syndrome, were identified as eligible for the meta-analysis. A weighted inverse association was found between dietary magnesium intake and the risk of metabolic syndrome (odds ratio 0.69, 95% CI 0.59, 0.81) comparing the highest with the lowest group. For every 100-mg/day increment in magnesium intake, the overall risk of having metabolic syndrome was lowered by 17% (odds ratio 0.83, 95% CI 0.77, 0.89).

Conclusion—Findings from the present meta-analysis suggest that dietary magnesium intake is inversely associated with the prevalence of metabolic syndrome. Further studies, in particular well-designed longitudinal cohort studies and randomized placebo-controlled clinical trials, are warranted to provide solid evidence and to establish causal inference.

Introduction

Metabolic syndrome is the name given to a cluster of risk factors for cardiovascular diseases, including coronary heart disease and stroke [1,2]. Reducing the prevalence of metabolic syndrome is of great significance to cardiovascular disease prevention. Proper identification of the risk factors would improve public awareness and inform risk-reducing

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Competing interests

None declared.

Supporting information

Additional Supporting Information may be found in the online version of this article:

prevention programmes for metabolic syndrome and the management of its health consequences. Several risk factors, including vitamin D deficiency [3], an unhealthy diet (e.g. diets high in carbohydrates and high total fat) [4–14], an inactive lifestyle [15], obesity, excess triglycerides, insulin resistance, family history of metabolic syndrome, genetics [16] and aging, have been thought to be determinants of metabolic syndrome.

Magnesium is required for hundreds of physiological processes, including glucose and insulin metabolism [17], but dietary magnesium intake has been inadequate in the general population in both the USA and worldwide [18]. There is evidence to suggest there are potential benefits of dietary magnesium intake in preventing metabolic syndrome and its components [19,20] as well as Type 2 diabetes [21], although the literature is not consistent.

In two double-blind placebo-controlled randomized trials, oral magnesium supplementation at various doses reduced insulin resistance, a central feature of metabolic syndrome [19,22]. Another randomized control trial showed that magnesium supplementation reduced blood pressure and increased HDL cholesterol significantly in the intervention group compared with the placebo group in patients with diabetes, hypertension and hypomagnesaemia at baseline [23]; however, one case–control study has documented a higher prevalence of metabolic syndrome in participants with high serum magnesium levels [24]. In addition, a prospective cohort study has found that there was no significant association between dietary magnesium and the prevalence of metabolic syndrome [14]. Studies directly relating dietary magnesium intake to risk of metabolic syndrome using study designs other than cross-sectional studies are sparse. Only one randomized controlled clinical trial [22], two cohort studies (one in the general population [20] and the other in patients undergoing renal transplant [14]), and three case–control studies [24–26] with either different exposure (dietary magnesium or hypomagnesaemia) or different effect measures (Pearson's correlation coefficients or odds ratios) that directly related magnesium intake to metabolic syndrome were identified, which meant that we did not have enough studies to pool evidence from these study designs. The aim of the present study, therefore, was to aggregate the existing knowledge on the association of dietary magnesium intake and metabolic syndrome in the general population, by conducting a meta-analysis of cross-sectional studies.

Methods

Data sources and study selection

We searched the PubMed, EMBASE and Google Scholar databases for articles published up to August 2013 using the terms 'magnesium', 'Mg', 'dietary magnesium intake' and 'dietary micronutrient', combined with 'metabolic syndrome', 'MetS', 'insulin resistance syndrome', 'syndrome X', 'Reaven's syndrome' and 'metabolic cardiovascular syndrome'. Additional information was found through a hand search of the references of relevant articles. We followed the PRISMA guidelines for this process; the PRISMA checklist is shown in Table S1.

Studies were included in the meta-analysis if they were published in English before August 2013 and met all the following criteria: 1) a cross-sectional design; 2) dietary magnesium

intake was the exposure of interest; 3) metabolic syndrome was the outcome of interest ; 4) data were available on odds ratios or relative risk with 95% CIs, or the relevant data could be derived from the reported results; and 5) the study was conducted among the general population.

Data extraction

Data were carefully extracted from the original study independently by two authors (D.D. and P.X.). Discrepancies were resolved through group discussion. The collected data included the first author's name, year of publication, number of participants, age, percentage of male participants, exposure assessment and category, outcome definition, adjusted covariates, adjusted odds of having metabolic syndrome and 95% CIs for the corresponding categories.

We re-computed the odds ratio with 95% CI, taking the lowest magnesium intake category as the reference for one study [27] that reported the odds ratio using the highest magnesium intake group as the reference. We also extracted the odds ratios (and 95% CIs) of metabolic syndrome for every 100-mg/day increment in dietary magnesium intake. If a study did not provide the linear association of magnesium intake with risk of metabolic syndrome, we estimated it using the method described by Greenland and Longnecker [28], or calculated it under a linear assumption if appropriate.

Data synthesis and analyses

The included studies were cross-sectional studies that reported odds ratios and relative risk as measures of effect size. We extracted the odds ratios and 95% CIs of having metabolic syndrome across categories of dietary magnesium intake, with the highest or the lowest group as the reference, or for a dose-response relationship. In all included studies, data from fully adjusted models were used.

Odds ratios and 95% CIs were transformed to their natural logarithms for computing the corresponding standard errors and inverse variance. A random-effects or fixed-effects model, as appropriate, was used to assess the pooled association between dietary magnesium intake and the prevalence of metabolic syndrome by comparing participants in the highest with those in the lowest magnesium intake group. We also pooled the odds ratios (95% CIs) for linear trend (per 100-mg/day increment in magnesium intake). Cochran's chi-squared test was used to examine heterogeneity among the included studies and I^2 was computed to determine the degree of inconsistency across studies. Publication bias was assessed using Egger's asymmetry test. All analyses were conducted using STATA statistical software (version 13, STATA Corp., College Station, TX, USA). All statistical tests were two sided and a P value ≤ 0.05 was considered to indicate statistical significance.

Results

Literature search

The study selection process for the meta-analysis is shown in Fig. 1. A total of 78 articles were identified by searching the databases. Of those, 66 articles were excluded because they

either did not report results on the association of dietary magnesium intake and metabolic syndrome or they were not original studies. Of the remaining 12 studies, we further excluded one cross-sectional study because it reported the risk of metabolic syndrome on Z-score [29]. Two cohort studies were excluded because the samples were too low to be combined [14,20]. Three case-control studies were identified, but one of these reported only correlation coefficients [24] and another one only presented the association between hypomagnesaemia and metabolic syndrome [26], which meant that the three case-control studies could not be pooled. A final total of six identified eligible cross-sectional studies were included in the present meta-analysis.

Study characteristics

The information extracted from the six included cross-sectional studies is shown in Table 1 [27–34]. The six studies included a total of 24 473 participants with 6311 prevalent cases of metabolic syndrome. Four out of six studies, including 19 744 participants with 4989 cases of metabolic syndrome, compared the risk of metabolic syndrome between the highest and the lowest magnesium intake groups, and reported linear association (per 100-mg/day increment in magnesium intake)[27,30] or such information could be derived from two of the studies [31,32]. One study that included 4519 participants and 1166 cases reported only the linear association [33]. Another study reported the results of linear association across quartiles of magnesium intake but in magnesium/day/kg, hence relevant information could not be derived from it for analysing the dose-response relationship and it was therefore excluded from the dose-response meta-analysis [34].

In five of the six studies included in the meta-analysis, both men and women were included, while in one study only women were included. The age of the participants in these studies was 18 years. Two studies used a semi-quantitative food frequency questionnaire, three studies used 24-h diet recalls and one used 3-day food records. One study used interview and the US Department of Agriculture Food and Nutrition Database to code food for magnesium intake, and another study used interview and the Taiwan Nutritional Database and E-Kitchen nutritional analysis software (Nutritional Chamberlain Line, Professional Edition, version 2001/ 2003, E-Kitchen Inc, Taichung, Taiwan) to analyse magnesium intake. In the original studies, participants were categorized into tertiles, quartiles or quintiles based on the distributions of dietary magnesium intake.

In the six cross-sectional studies included in the meta-analysis, the average (median or mean) dietary magnesium intake ranged from 117 to 423 mg/day. In all six studies, metabolic syndrome was defined using the National Cholesterol Education Program/Adult Treatment Panel III criteria. Metabolic syndrome was diagnosed if a participant met the diagnostic criteria for at least three of the five components of metabolic syndrome [35]. In almost all studies, age, gender, physical activity, total energy intake, carbohydrate intake, smoking status, alcohol intake and dietary fibre intake were adjusted for in the final model as potential confounders, because those variables are associated with both magnesium intake and risk of metabolic syndrome. Some of the studies adjusted for additional covariates including race/ethnicity, education and family history of diabetes.

Magnesium intake and risk of metabolic syndrome: highest vs lowest

As shown in Fig. 2, for the five cross-sectional studies [31,32,34] that reported risk of having metabolic syndrome according to magnesium intake categories, the pooled estimate from the meta-analysis indicated an inverse association between dietary magnesium intake and the prevalence of metabolic syndrome. The odds ratio (95% CI) was 0.69 (0.59, 0.81) comparing the highest with the lowest groups of dietary magnesium intake. There was no significant heterogeneity among the studies ($I^2=43.5\%$; $P=0.13$) and there was no evidence of publication bias (Egger's test; $P=0.38$).

Magnesium intake and risk of metabolic syndrome: dose–response relationship analysis

Five studies [27,30–33], comprising 24 263 participants, reported the odds ratios (95% CI) of having metabolic syndrome for every 100-mg/day increment in dietary magnesium intake or such information could be derived from the published data. The pooled odds ratio (95% CI) was 0.83 (0.77, 0.89). No significant heterogeneity among the studies was found ($I^2=0.0\%$, $P=0.45$). No evidence indicated publication bias (Egger's test; $P=0.65$).

Discussion

The cumulative evidence from the present meta-analysis indicates that dietary magnesium intake and the prevalence of metabolic syndrome are inversely associated. Metabolic syndrome is less prevalent in participants with a higher level of dietary magnesium intake. Results from this study support the hypothesis that a low level of dietary magnesium intake is a risk factor for metabolic syndrome.

The inverse association found in the present study is supported by the findings from a randomized controlled trial [22], a prospective cohort study [20] and a case–control study [26]. One cross-sectional study [29], which was not eligible for the present meta-analysis, also reported an inverse association between dietary magnesium and risk of metabolic syndrome on Z-score. The present findings are not consistent, however, with results from another case–control study [24], which reported metabolic syndrome was more prevalent in participants with high dietary magnesium intake, and a prospective cohort study, which found no significant difference in the risk of having prevalent metabolic syndrome between the highest and the lowest dietary magnesium intake groups [14].

A possible explanation for the inconsistent results is that metabolic syndrome has multiple dietary and non-dietary risk factors, including high fructose diets, high carbohydrate diets [15,36], high saturated fat intake [37] or a high percentage of total dietary fat intake [38], and physical inactivity [36]. Although the primary studies adjusted for some potential confounding variables, the covariates varied across studies; thus, residual confounding or confounding from unknown or unmeasured factors cannot be completely excluded. Also, the inconsistent results may be explained by the different sample sizes of the original studies. For example, Huang *et al.* [34] reported a nonsignificant inverse association, which may reflect the fact that the sample size in that study was relatively small. In addition, the variability in the characteristics of the study population might partially explain the inconsistent findings of the original studies, although the test for heterogeneity was not

significant. For example, the study by Huang *et al.* [34] was conducted among elderly patients with Type 2 diabetes who were likely to have higher prevalence of metabolic syndrome. Nevertheless, in the sensitivity analysis, excluding one study each time did not substantially change the overall association, the pooled odds ratios (95% CIs) varied from 0.61 (0.45,0.82) by excluding the study by Song *et al.* [30] to 0.72 (0.61, 0.86) by excluding the study by McKeown *et al.* [32].

One of the strengths of the present study is that the included studies were found to have insignificant heterogeneity, showing that the evidence of a pooled association between dietary magnesium and metabolic syndrome is robust. In addition, the relatively large sample size obtained from the various study populations included in the meta-analysis strengthens the evidence generated from it. The present meta-analysis is based on cross-sectional studies, and therefore does not warrant a causal inference, but the data included in it were the first of their kind and highlight a need for future studies to establish the causal link and to further understand the dose–response relationship between dietary magnesium intake and risk of metabolic syndrome. The study also shares the strength of the original studies in that potential confounding variables were adjusted for, and in that the present study used the fully adjusted model of the original studies.

The main limitation of the present study is that the meta-analysis is only based on cross-sectional studies. As dietary intake that relied on participant recall was used in the assessment of dietary magnesium intake during the original data collection, recall bias in the original studies, although not high, could not be excluded. Another limitation is that dietary measurement errors may have occurred, although errors are likely to be non-differential and might somewhat attenuate the observed association.

Dietary magnesium acts through several mechanisms to prevent the cluster of health disorders that arises as a consequence of metabolic syndrome. There are a number of suggested mechanisms. The first is magnesium effects on glucose metabolism. Intracellular magnesium is reported to be functionally related to glucose metabolism by promoting the autophosphorylation of the β -subunit of insulin receptor by tyrosine-kinase switching on the receptor, which is important for insulin sensitivity and Type 2 diabetes [39]. Intracellular magnesium can also promote the translocation of glucose transporter protein (GLUT4) to the cell membrane for glucose uptake in the cell. Extracellular magnesium is also reported to increase the affinity of insulin binding to its receptor [40]. Animal studies support this explanation and have shown that magnesium deficiency has a deleterious effect on glucose metabolism as a result of impairment of both insulin secretion and action, thus predisposing to Type 2 diabetes [40–42]. Deficiency of intracellular and extracellular magnesium therefore impairs intracellular signalling and may induce insulin resistance. A second possible mechanism is magnesium effects on fat metabolism. Magnesium is a known cofactor of lipoprotein lipase, which promotes chylomicron clearance: both lipolysis and hepatic uptake of lipids. One study has reported that magnesium supplementation reduced and delayed postprandial increase in serum and chylomicron triacylglycerol [43,44]. Reduced activity of lipoprotein lipase attributable to magnesium deficiency causes hyperlipidaemia, which predisposes to diabetes and cardiovascular disease [45,46]. A third mechanism is magnesium effects on inflammatory mediators and proatherogenic changes.

Studies have documented that magnesium prevents chronic low-grade inflammation, a well-established intermediate pathogenic state for metabolic syndrome and its consequences (cardiac disease, hypertension and Type 2 diabetes), by preventing the activation of inflammatory mediators and proatherogenic changes [18]. A fourth mechanism is magnesium effects as a cofactor in adenosine triphosphate (ATP)-transfer reactions and regulating enzymes of glycolysis. Several studies have documented magnesium as an important cofactor in all ATP-transfer reactions and as a regulator of the rate-limiting enzymes of glycolysis. A fifth possible mechanism is magnesium effects on smooth muscle activity through regulation of Ca^{2+} -ion transport. This also modulates the activity of many membrane and intracellular ion transport pump mechanisms, which maintain critical intracellular levels of cytosolic free calcium and sodium. The role of calcium in the contraction and relaxation of smooth muscles depends on intracellular magnesium steady activity. Magnesium ions actively promote muscle relaxation, offset calcium-related excitation–contraction coupling, and decrease cellular responsiveness to depolarizing stimuli by stimulating Ca^{2+} -dependent K^{+} channels, which serve to offset the potential depolarizing influence of cellular calcium accumulation; therefore, calcium-induced contraction of vascular smooth muscles is sensitive to changes in magnesium concentration [47–49]. This mechanism may explain the hypertension in metabolic syndrome observed in populations with magnesium deficiency. Further studies are warranted to better understand the mechanisms, for example, if calcium levels modify the association between magnesium and metabolic syndrome.

In conclusion, the findings from the present meta-analysis provide evidence that dietary magnesium intake is inversely associated with the prevalence of metabolic syndrome. Further studies, especially well-designed longitudinal cohort studies and randomized placebo-controlled trials, are warranted to provide stronger evidence and establish causal inference.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What's new?

- This is a meta-analysis of original studies on the association of dietary magnesium intake and risk of metabolic syndrome.
- The results of the meta-analysis could inform programmes focusing on the prevention of metabolic syndrome and its complications, including cardiovascular diseases.

FIGURE 1.

Study selection process. Mg, magnesium; MetS, metabolic syndrome; OR, odds ratio.

FIGURE 2.

Multivariable adjusted odds ratios (95% CI) of having prevalent metabolic syndrome in participants with the highest level of dietary magnesium intake compared with those with the lowest. The overall estimate is from fixed-effects models. The dots indicate the adjusted odds ratios. The size of the shaded square is proportional to the weight of each study. Horizontal lines represent 95% CIs. The diamond markers indicate the pooled odds ratios. OR, odds ratio.

FIGURE 3.

Multivariable adjusted odds ratios (95% CI) of having metabolic syndrome for every 100-mg/day dietary magnesium intake increment. The overall estimate is from a fixed-effects model. Dots indicate the adjusted odds ratios. The size of the shaded square is proportional to the weight of each study. Horizontal lines represent 95% CIs. Diamond markers indicate the pooled odds ratios. OR, odds ratio.

Table 1

Characteristics of the cross-sectional studies included in the meta-analysis

Source	No. of participants/cases	Age	Proportion of male participants, %	Assessment of exposure	Exposure category	Variables adjusted for	Assessment of outcome	Measure of association
Huang <i>et al.</i> , 2012, Taiwan [34]	210/156	65 years	46.7	Dietary magnesium intake was derived from 24-h dietary intake recall using the Taiwan Nutritional Database and E-Kitchen nutritional analyses software	Quartiles, mg/day/kg: <2.3; 2.3–3.2; 3.3–4.4; 4.5.	Gender, age, physical activity, total energy intake, carbohydrate intake (%energy), protein intake (%energy), total fat intake (%energy), smoking status and alcohol intake.	Diagnosis of metabolic syndrome was made using either NCEP-ATPIII or IDF criteria.	Odds ratios (95% CIs) across quintiles: 1.00 (reference); 2.10(0.73, 6.06); 1.68(0.60, 4.70); 0.49(0.17, 1.43). <i>P</i> for linear trend=0.153.
Beydoun MA <i>et al.</i> , 2008, USA [33]	4519/1166	18 years	Exact figure unavailable	One 24-h dietary intake recall for each of the 1999–2000 and 2001–2002 periods, and two for 2003–2004 were obtained from NHANES	Continuous, per 100 mg/day magnesium intake.	Gender, ethnicity, dietary groups, e.g. calcium, phosphorus, dairy products, fats,	NCEP-ATP III criteria.	Odds ratio (95% CI) per 100 mg/day increment in magnesium intake: 0.83 (0.72, 0.96).
McKeown <i>et al.</i> , 2008, USA [32]	535/213	60 years	33.0	3-day food records were obtained from participants. Foods were coded for magnesium using US Department of Agriculture Food and Nutrient Database for Dietary Studies (Version 1.0).	Quartiles, median, mg/day: 188.4; 240.0; 297.5; 384.0.	Age, gender, race, education, marital status, smoking status, alcohol intake, exercise, BMI, total energy intake, percentage of energy from saturated fatty acid intake, lipid-lowering medication use and blood pressure medication use.	NCEP/ATP III criteria except for replacing abdominal adiposity with: BMI 31kg/m ² for male and 27kg/m ² for female participants.	Odds ratios (95% CIs) across quintiles: 1.00 (reference); 0.74(0.45, 1.24); 0.55(0.32, 0.97); 0.36(0.19, 0.69). <i>P</i> for linear trend=0.002
Ford <i>et al.</i> , 2007, USA [31]	7669/1982	20 years	50.5	A single 24-h dietary intake recall recorded by NHANES III Dietary Data Collection from 1988 to 1994 was used.	Quintiles, mg/day: Male: 221; 222–292; 293–376; 377–465; 466. Female: 164; 165–213; 214–263; 264–336; 337.	Gender, race or ethnicity, education, smoking, concentration of C-reactive protein, alcohol use, physical activity, family history of early coronary heart disease, use of vitamin or supplement, history of diabetes (except model for hyperglycemia), percent calories from fat, percent calories from carbohydrate, fibre intake, and total energy intake.	NCEP/ATP III criteria.	Odds ratios (95% CIs) across quintiles: 1.00 (reference); 0.84 (0.58, 1.23); 0.76 (0.54, 1.07); 0.62 (0.40, 0.98); 0.56 (0.34, 0.92). <i>P</i> for linear trend = 0.029

Source	No. of participants/cases	Age	Proportion of male participants, %	Assessment of exposure	Exposure category	Variables adjusted for	Assessment of outcome	Measure of association
Bo <i>et al.</i> , 2006, Italy [27]	1653/381	45–64	47.2	Semi-quantitative food frequency questionnaire assessed average frequency of and portion intake of 148 foods consumed during 12 months before examination	Tertiles, mg/day: Male: <269.1; 269.1–337.4; >337.4, Female: <278.1; 278.1–338.6; >338.6.	Age, gender, BMI, smoking status, alcohol intake, level of physical activity, dietary intake of total calories, total % of fat and dietary intake of fibre.	NCEP/ATP III criteria.	Computed odds ratio* (95% CI) for tertile 3 as compared with tertile 1: 0.97 (0.59, 1.61). <i>P</i> for trend = 0.07
Song <i>et al.</i> , 2005, USA [30]	9,887 / 2,413	45	0	Semi-quantitative food frequency questionnaire was used to assess the amount of magnesium intake by asking participants how often on average they had of a commonly used portion size during previous year	Quintiles, mg/day: <277; 277–309; 309–341; 341–383; >383.	Age, smoking, total calories, alcohol, multivitamin use, parental history of myocardial infarction before age 60 years, total fat intake, cholesterol, folate and glycaemic load.	NCEP/ATP III criteria.	Odds ratios (95% CIs) across quintiles: 1.00 (reference); 0.91 (0.78, 1.06); 0.84 (0.72, 0.99); 0.81 (0.68, 0.96); 0.73 (0.60, 0.88). <i>P</i> for linear trend = 0.0008

IDF, International Diabetes Federation; NCEP/ATP, National Cholesterol Education Program/Adult Treatment Panel; NHANES, National Health and Nutrition Examination Survey; SFA: saturated fatty acid.

* In Bo *et al.* (2006), the reference was changed to the lowest magnesium intake group and odds ratio was re-calculated for the highest magnesium intake group.