European Journal of Clinical Nutrition (2014) **68**, 510–516

www.nature.com/ejcn

ORIGINAL ARTICLE

Dietary magnesium intake is inversely associated with serum C-reactive protein levels: meta-analysis and systematic review

DT Dibaba, P Xun and K He

BACKGROUND/OBJECTIVES: The aim of this study was to quantitatively summarize the association of dietary magnesium (Mg) intake with serum C-reactive protein (CRP) levels in the general population.
SUBJECTS/METHODS: Observational and experimental studies through February 2013 were reviewed in PubMed and EMBASE. Additional information was retrieved through Google or hand search of related reference lists. The main outcome is either adjusted geometric mean of CRP or odds ratio (OR) of having serum CRP $\geqslant 3$ mg/l. Meta-regression was used to determine the linear association of dietary Mg intake and adjusted geometric means of CRP levels. A fixed-effects model was used to pool ORs of interest, comparing those in the lowest with those in the highest group of dietary Mg intake.
RESULTS: A data set derived from seven cross-sectional studies including 32 918 participants was quantitatively assessed. A weighted inverse association between Mg intake and serum CRP levels was observed (β-coefficient: -0.0028; 95% confidence interval (CI), -0.0043 to -0.0013; $P_{trend} = 0.001$) from four cross-sectional studies. The pooled OR (95% CI) of having CRP $\geqslant 3$ mg/l was 1.49 (1.18–1.89) on comparing the lowest to the highest group of Mg intake from three studies with the data available. Qualitative assessment among five intervention studies also showed a potential beneficial effect of Mg intake on serum CRP levels.
CONCLUSIONS: This meta-analysis and systematic review indicates that dietary Mg intake is significantly and inversely associated with serum CRP levels. The potential beneficial effect of Mg intake on chronic diseases may be, at least in part, explained by inhibiting inflammation.

European Journal of Clinical Nutrition (2014) **68,** 510–516; doi:10.1038/ejcn.2014.7; published online 12 February 2014

Keywords: magnesium; inflammation; C-reactive protein; meta-analysis; systematic review

INTRODUCTION

Magnesium (Mg), an essential mineral, is found abundantly in whole grains, green leafy vegetables, legumes and nuts, and it is required by hundreds of body physiologies involving over 350 enzymes.[1] However, according to the National Health and Nutrition Examination Survey (NHANES), 1999–2000, about 60% of US population consumed inadequate dietary Mg. Dietary Mg intake has been related to several health outcomes including those related to metabolic and inflammatory processes such as hypertension, metabolic syndrome,[2–4] type 2 diabetes,[5] cardiovascular diseases,[1,6–8] osteoporosis and some cancers (for example, colon, breast).[9] One suggested mechanism for the beneficial effect of Mg intake is that Mg may reduce the levels of C-reactive protein (CRP)—a well-documented indicator of a low-grade or chronic inflammation.

Laboratory studies have linked Mg deficiency to acute inflammatory response mediated by calcium, *N*-methyl-D-aspartic acid or *N*-methyl-D-aspartate, interleukin-6 (IL-6) and tumor necrosis factor-alpha.[9] So far, findings from epidemiological studies on the association of Mg and CRP levels are not consistent. Several cross-sectional studies reported an inverse association between serum Mg concentrations and CRP levels in children,[10] women[4] and obese patients.[11] Also, in a study of samples from NHANES 1999–2002, a national representative population in the United States, people with total daily Mg intake below the recommended daily allowance (RDA) were 40% more likely to have elevated CRP levels.[12] In addition, a cross-sectional study also found an inverse association between dietary Mg intake and serum CRP levels.[13] However, another recent cross-sectional study found no association between dietary Mg intake and CRP levels.[14] Therefore, we summarized the literature quantitatively to estimate the overall association of Mg and CRP levels by conducting a meta-analysis as well as systematic review.

MATERIALS AND METHODS

Data source and study selection

We searched the databases including PubMed, EMBASE and Google up to February 2013, along with the references obtained from the identified studies and reviews using the terms 'magnesium', 'Mg', 'dietary micronutrient' combined with 'C-reactive protein', 'high sensitivity C-reactive protein', 'CRP', 'hs-CRP' and 'biomarkers of inflammation'.

Observational studies, reporting either mean or odds ratio (OR), are included in the quantitative meta-analysis. Other studies that included one cohort study, two cross-sectional studies reporting outcomes (correlation coefficient (*r*) or ORs) on continuous scale and five intervention studies that reported correlation coefficients, geometric mean, or median level of CRP or changes in CRP levels between baseline and the end of study are included for a systematic review.

Data extraction

Data were carefully extracted from the original studies independently by two authors (DD and PX), and any disagreements were resolved by consensus. The data that we collected included the first author's name, year of publication, study name, number of participants, age, percent of

Department of Epidemiology and Biostatistics, School of Public Health, Indiana University, Bloomington, IN, USA. Correspondence: Dr K He, Department of Epidemiology and Biostatistics, School of Public Health, Indiana University, 1025 E. Seventh Street, SPH C032, Bloomington, IN 47405, USA.
E-mail: kahe@indiana.edu
Received 5 June 2013; revised 11 September 2013; accepted 13 September 2013; published online 12 February 2014

male participants, exposure assessment and category, outcome assessment, adjusted covariates and adjusted average levels of CRP or ORs of having serum CRP $\geqslant$3 mg/l with 95% confidence intervals (CIs) for corresponding categories and/or continuous exposure.

Data synthesis and analysis

The included studies were categorized into two groups: cross-sectional studies with adjusted geometric mean as the outcome and cross-sectional studies with OR as the outcome. We extracted adjusted geometric means of CRP levels with 95% CIs as well as median Mg levels for each quintile of Mg intake in cross-sectional studies.[4,13–15] In all the studies, data from fully adjusted models were used.

Data transformed to their natural logarithms (ln) were used to compute the corresponding standard errors and inverse variance. A random-effects meta-regression[16] was used to assess the overall linear relation between Mg intake and geometric mean levels of CRP with inverse variance as weights for each study. We also extracted ORs with 95% CIs in three cross-sectional studies.[10,17,18] Natural logarithms-transformed ORs and 95% CIs were used to compute the corresponding standard errors. Fixed-effects models were used to combine ORs of having CRP $\geqslant$3 mg/l by comparing participants in the lowest with those in the highest group of Mg intake because there was no significant heterogeneity found among studies. Cochran's chi-square test was used to examine heterogeneity among included studies and I^2 was computed to determine the degree of inconsistency across studies.[19,20] Publication bias was assessed by Egger's test[21] and Begg's test.[22] All analyses were conducted using STATA statistical software (version 12.1, Stata Corp., College Station, TX, USA). All statistical tests were two-sided and *P*-value $\leqslant$0.05 was considered statistically significant.

RESULTS

Initially, 60 articles were identified, but 53 articles were excluded because they did not meet the prespecified inclusion criteria. So, seven cross-sectional analyses were included in the meta-analysis. The study selection process for the meta-analysis is presented in Figure 1. Two more cross-sectional studies and one cohort study were also identified and included in the systematic review because the results could not be pooled with other studies (Table 1). In addition, five intervention studies were identified for systematic review (Table 2).

The final data set for this meta-analysis is comprised of 32 918 participants from seven cross-sectional studies. Six studies were conducted in the USA and one study in Italy (Table 1). Five studies included both men and women, and two studies consisted women only. Five studies used semiquantitative food frequency questionnaires to collect dietary data, whereas other two studies used secondary dietary data from NHANES (1999–2000 and 1999–2002). In the original studies, dietary Mg intake was either categorized into three/four groups on the basis of RDA levels[10,18] or divided into tertiles or quintiles.[4,13–15,17] Serum CRP was measured by using high sensitivity assay techniques (Table 1).

In the three cross-sectional studies[10,17,18] that calculated ORs as the effect sizes, the median Mg intake ranged from 205 to 397.9 mg/day. In the four cross-sectional studies that calculated geometric means as the outcomes, median dietary Mg intake ranged from 225 to 422 mg/day. In almost all studies, age, body mass index (BMI), smoking, physical activity, alcohol intake and dietary calorie intake were considered as potential confounders.

As shown in Figure 2, for the four cross-sectional studies that measured geometric mean CRP, the pooled estimate indicated that Mg intake (mg/day) was inversely associated with serum CRP levels (mg/l), with the meta-regression model:

$$\ln(\text{CRP}) = 1.3286 - 0.0028 \times \text{Mg}$$

$$\text{Adjusted } R^2 = 45.75\%, P = 0.001$$

Statistically significant heterogeneity was found among these studies ($I^2 = 94.5\%$).

The combined association between adjusted OR of having serum CRP $\geqslant$3 mg/l with each unit (mg/day) increment in Mg intake is presented in Figure 3. A statistically significant inverse association was observed (pooled OR: 1.49; 95% CI: 1.18–1.89). Non-significant heterogeneity among the studies was found ($I^2 = 38.8\%$, $P = 0.195$). In addition, no evidence of publication bias existed (Egger's test: $P = 0.308$; Begg's test: $P = 0.602$).

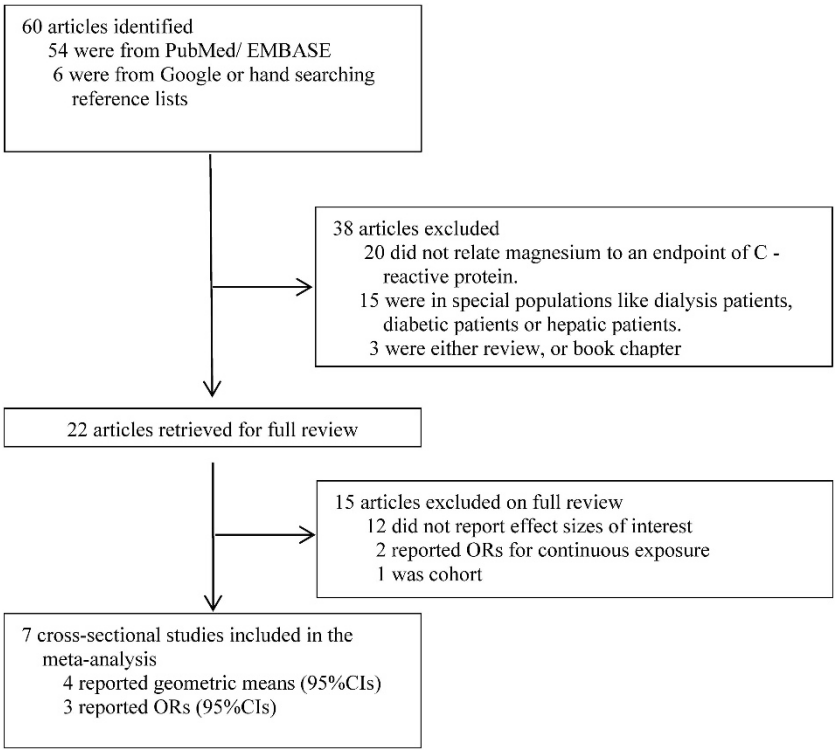

Figure 1. Process of study selection for the meta-analyses.

Table 1. Characteristics of nine cross-sectional analyses and one longitudinal analysis included in the study

Source	*Participants (n)*	*Males (%)*	*Age, years*	*Exposure assessment*	*Exposure categories*	*Outcome assessment*	*Adjusted variables*	*Reported measures of association*
Cross-sectional analysis								
King *et al.*, 2005, NHANES (1999–2000), USA[18]	5021	25.4	⩾17	Dietary Mg intake was derived from the 24-h recall information for each respondent using the NHANES computer-assisted dietary interview (CADI) system	Four groups based on RDA[a]: <50% RDA; 50–74% RDA; 75–99% RDA; ⩾100% RDA	CRP was analyzed using a high sensitivity assay technique that quantifies CRP by latex-enhanced nephlometry	BMI, smoking, income level, alcohol consumption, exercise, and medical conditions like congestive heart failure, coronary heart disease, angina, heart attack, diabetes and hypertension.	ORs with 95% CIs
Song *et al.*, 2005, WHS, USA[4]	11 686	0	⩾45	Dietary Mg was assessed by semiquantitative FFQ.	Quintiles (median, mg/day): 252; 293; 324; 359; 422.	CRP was measured by a validated high-sensitivity assay (Denka Seiken, Nigata, Japan).	Age, BMI, smoking, exercise, alcohol, total calorie intake, multivitamin use, diabetes, hypertension, high cholesterol, and parental history of MI before 60 years of age and dietary intakes of total fat, cholesterol, folate, glycemic load and fiber.	Geometric Means with 95% CIs
Bo *et al.*, 2006, Italy[17]	1653	47.2	54.6 ± 5.7	Dietary Mg was assessed by semi quantitative FFQ.	Tertiles (Median intake with 95% CIs, mg per day): 241.29(38.6–278); 308.2(269.1–338.6); 397.9(337.5–1052.3).	Serum CRP was measured with a high-sensitivity CRP latex agglutination method on HITACH 911 Analyzer (Sentinel Ch., Milan, Italy).	Age, sex, BMI, smoking, level of physical activity, alcohol consumption, dietary total energy intake, and percentage of total fat and fiber intake.	ORs with 95% CIs, Medians with 95% CIs, and beta coefficients
King *et al.*, 2007, NHANES (1999–2002), USA[10]	5007	51.4	6–17	Secondary data on dietary Mg intake was from NHANES 1999–2002.	Three groups based on RDA[a]: <75% RDA; 75–99% RDA; ⩾100% RDA.	High sensitivity CRP was measured as part of the NHANES 1999–2002 physical and laboratory examination.	Age, sex, race, income level, exercise, BMI and dietary intakes of fiber and total energy.	ORs with 95% CIs
Song *et al.*, 2007, NHS, USA[15]	657	0	56 (43–69)	Dietary Mg was assessed by semi quantitative FFQ.	Quintiles (median, mg per day): 225; 262; 289; 316; 356.	Blood CRP was measured with a latex-enhanced turbidimetric assay on a Hitachi 911.	Age, smoking status, physical activity, alcohol consumption, total energy intake, menopausal status, postmenopausal hormone use, and BMI.	Geometric means with 95% CIs, and beta coefficients with SEs
Chacko *et al.*, 2010, WHI-OS, USA[13]	3713	0	50–79	Dietary Mg, was assessed by semi quantitative FFQ.	Quintiles (median, mg per day): 168.5; 204.4; 233.2; 263.1; 310.2.	hs-CRP was measured on a chemistry analyzer (Hitachi 911; Roche Diagnostics, Indianapolis, IN, USA) using an immunoturbidimetri-c assay with reagents and calibrators (Denka Seiken, Niigata, Japan).	Age, race, ethnicity, clinical center, time of blood draw, smoking, alcohol, energy expenditure from recreational physical activity /week, total energy intake, BMI, case-control status and dietary intakes of fiber, fruit and vegetable, folate, saturated and trans fat.	Geometric means with 95% CIs, beta coefficients with SEs
de Oleivera Otto *et al.*, 2011, MESA, USA[14]	5181	47.6	45–84	Dietary Mg measured by MESA FFQ.	Quintiles (mg/day): ⩽206; 207–237; 238–262; 263–298; ⩾299	Plasma CRP was measured with a particle enhanced immunephelometric assay by a BNII nephelometer (high-sensitivity CRP; Dade Behring).	Age, sex, race-ethnicity, total energy intake, field center, education, physical activity, alcohol consumption, smoking, fiber intake and dietary supplement use.	Geometric Means with 95%CIs
Guerrero-Romero *et al.*, 2002, Mexico[11]	371	27	23–52	Serum Mg was measured by colorimetric method.	Serum Mg quartiles (mg/dl) Lowest, 2nd and 3rd and Highest	CRP was measured by automated micro particle enzyme immunoassay (Imx, Abbot Laboratories, Minneapolis, MN, USA).	Age, sex, BMI and Glucose Tolerance status	Correlation coefficient (r), and OR on continuous scale with 95% CIs

Table 1. (Continued)

Source	*Participants* (n)	*Males (%)*	*Age, years*	*Exposure assessment*	*Exposure categories*	*Outcome assessment*	*Adjusted variables*	*Reported measures of association*
Rodriguez-Morán *et al.*, 2008, Mexico[23]	488	50.8	10–13	Serum Mg concentrations were measured using a colorimetric method.	Tertiles Mg (mg/dl) mean (s.d.): 1.3(0.3); 1.8(0.03); 2.2(0.4).	High sensitive CRP was measured by automated micro particle enzyme immunoassay (Imx, Abbot Laboratories).	BMI and body fat percentage.	OR with 95% CI, and mean with SD
Longitudinal analysis								
Kim *et al.*, 2010, USA[24]	4497	42.9	18–30	Dietary Mg intake was assessed by using a validated interview - administered CARDIA Diet History Questionnaire.	Quintiles of Mg intake (mg/day): 178.68; 275.18; 351.25; 455.74; 669.30.	High sensitive CRP was measured at years 7,15 and 20 with a nephelometry-based high throughput assay.	Age, sex, ethnicity, study center, education, smoking status, alcohol consumption, physical activity, family history of diabetes, BMI, systolic Blood pressure, energy intake, dietary intake of saturated fat, and crude fiber.	Log transformed median, beta coefficients with 95% CIs

Abbreviations: BMI: body mass index, CARDIA, coronary artery risk development in young adults; CI, confidence interval; CRP, C-reactive protein; MESA, multi-ethnic study of atherosclerosis; NHANES, National Health and Nutritional Examination Survey; NHS, Nurse Health Study; OR, odds ratio; RDA, recommended dietary allowance; s.e., standard error; WHI-OS, Women's Health Initiative- Observational Study; WHS, Women Health Study. [a]Mg RDA (mg/day) for both males and female: 130 for those aged 6–8 years, 240 for those aged 9–13 years; for males: 410 for those aged 14–18 years, for females: 360 for those aged 14–18 years.

Table 2. Randomized controlled trials investigating the effect of Mg supplementation on CRP in humans

Study	*Country*	*Intervention group*				*Control group*				*Duration*	*Outcome measure*
		n/N	*Male, %*	*Age, year*	*Treatment*	n/N	*Male, %*	*Age, year*	*Treatment*		
Almoznino-Sarafian *et al.*, 2007[25]	Israel	17/17	52.9	71.0 ± 7.8	Oral Mg citrate: 300 mg/day	18/18	55.6	72.38	Untreated controls	5 weeks	ln(CRP) ± s.d.; Pearson's correlation coefficient
Chacko *et al.*, 2010[27]	USA	13/14	71	44.4 ± 13.0	Oral Mg citrate: 500 mg/day	13/14	71	44.4 ± 13.0	Placebo	4 weeks	Geometric mean (95% CI)
Nielsen *et al.*, 2010[26]	USA	46/50	22	51–85	Oral Mg citrate: 320 mg/day	49/50	22	51–85	Placebo (sodium citrate)	8 weeks	Change in mean CRP (increase/decrease)
Rodriguez-Hernandez *et al.*, 2010[33]	Mexico	15/20	0	30–65	Oral solution containing 50 ml of 5% Mg chloride (equivalent to 450 mg/day elemental Mg)	15/18	0	30–65	Control	4 months	Mean CRP ± s.d.; OR for reduction in CRP
Mosleh *et al.*, 2012[32]	Iran	35/37	0	46.3 ± 4.2	Oral Mg oxide: 250 mg/day	34/37	0	46.3 ± 4.2	Placebo	8 weeks	Median (IQR) for CRP

Abbreviations: CRP, C-reactive protein; IQR, interquartile range. *n/N*, is the number of participants who completed the study in each arm/number of participants who started the study in each arm.

Two cross-sectional studies[11,23] and one prospective cohort study[24] were not included in the meta-analyses because the exposure measurement, effect size or the study design was different. The two cross-sectional studies found that serum Mg level was significantly inversely associated with serum CRP levels. In a study[23] conducted in Mexican children aged 10–13 years old, a continuous decrease in mean CRP levels from the lowest tertiles (2.45 mg/l, s.d. = 10.6) to the highest tertile (0.8 mg/l, s.d. = 0.5) of serum Mg level was observed. In a similar study[11] conducted in adults aged from 23 to 52 years old, it was found that serum Mg level was significantly inversely correlated to serum CRP levels ($r = -0.39$, $P < 0.002$). In a prospective cohort study[24] conducted among young adults aged 18–30 years, the researchers found a significant inverse association between dietary Mg intake and serum CRP levels, β-coefficient (95% CI) in the highest quintile of Mg intake was −0.160 (−0.262 to −0.058, $P_{trend} < 0.01$).

In addition, five Mg intervention studies (Table 2) reported significant inverse association between Mg supplementation and serum CRP levels. Two of the studies were conducted in the USA and the rest were conducted in Mexico, Israel and Iran, respectively. The age of participants ranged from 30 to 85 years. The duration of the studies ranged from 4 weeks to 4 months. One of the intervention studies[25] measured CRP at baseline and at the end of study, and reported it in natural logarithmic scale. The ln(CRP) decreased significantly after the intervention. Another study[26] showed that CRP levels decreased by 1.6 mg/l in the Mg intervention group, whereas it increased by 1.5 mg/l in the placebo group ($P < 0.002$). Two other studies did not find a significant association between Mg supplementation and CRP levels. Of note, one study[27] found that CRP levels increased after 500 mg elemental Mg supplementation in the form of Mg citrate for 4 weeks, whereas it decreased in the placebo group. The difference in changes between groups was not significant ($P = 0.50$).

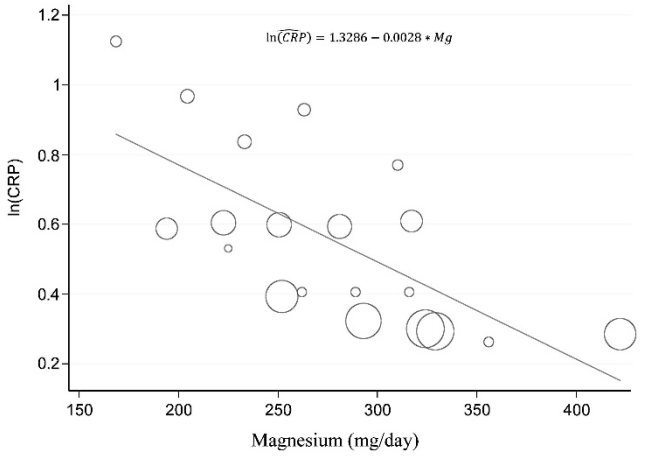

Figure 2. Meta-regression for modeling ln(CRP) levels against dietary Mg intake from four cross-sectional studies. The dots represent observations from each quintile relating ln(CRP) to dietary Mg intake. Size of dot is proportional to the inverse of squared standard error of ln(CRP).

DISCUSSION

Evidence from this meta-analysis and systematic review indicates that dietary Mg intake is inversely associated with serum CRP levels. Our findings are robust as the meta-analysis is based on both continuous and binary outcomes, and the results are supportive of each other. In addition, the study participants are comprised of male and female, adults and children with a wide age range, which improve the generalizability of the findings. In addition, the summarization of findings both from observational and intervention studies either in the meta-analyses or in the systematic review makes the available information on the association of Mg and serum CRP levels more aggregated.

Some limitations should also be considered when interpreting the results from this meta-analysis. First, most of the studies had just a single measure of exposure/effect sizes, for example, mean level of CRP, ORs or correlation coefficients. The different measures of exposure and effect size made it difficult or even impossible to pool the results and estimate the overall association. For example, we had to exclude two studies[11,23] from the meta-analysis because they reported mean CRP (s.d.), and/or OR (95% CI) on the basis of a continuous scale of Mg intake. Second, none of the primary studies considered the health impact of high Mg intake (hypermagnesemia, for example, serum Mg > 1.9 mEq/l[28]). Anyway, no sufficient evidence to date indicates any substantial adverse effect of dietary Mg overdose, although two case studies reported that Mg intake above 6 mEq/l, a rare phenomenon in a general population, caused parathyroid gland dysfunction, respiratory, cardiac and CNS dysfunction.[29,30] Of note, an estimated 75% of Americans have daily Mg intakes less than the RDA.[31]

In addition, the possibility of residual confounding from primary studies cannot be completely excluded, although various potential confounders including lifestyle and demographic variables were well adjusted in the primary studies.

Five Mg intervention studies[25–27,32,33] used different doses of Mg supplementation (50–450 mg/day) for relatively short durations (4 weeks to 4 months). These studies cannot be

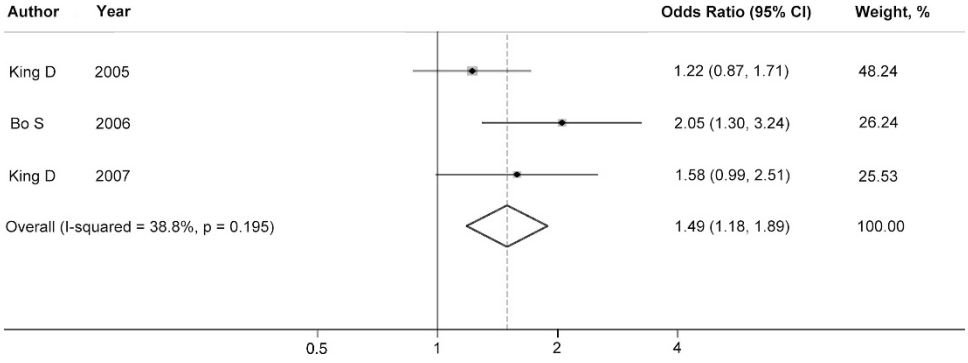

Figure 3. Multivariable adjusted ORs and 95% CIs of having elevated CRP levels (⩾3 mg/l) comparing those in the lowest with those in the highest dietary Mg intake group from three cross-sectional studies. The summary estimate was obtained by using a fixed-effects model. The dots indicate the adjusted ORs. The size of the shaded square is proportional to the weight of each study. The horizontal lines represent 95% CIs. The diamond markers indicate the pooled ORs.

pooled because of the different measures of outcome across studies. Nevertheless, all these intervention studies reported a generally inverse association between Mg supplementation and serum CRP levels, which is consistent with the pooled estimate from observational studies. In addition, a study conducted in patients with cardiac surgery found a moderate inverse correlation between serum Mg concentration and preoperative CRP levels.[34]

Findings from this meta-analysis are biologically plausible. Studies indicate that Mg deficiency may increase CRP production mediated through interlinked chains of the following events. Inadequate dietary Mg intake depletes extracellular Mg ion and consequently leads to the activation of macrophages and influx of calcium ions into cells (adipocytes, neuronal and peritoneal cells). The increased calcium level in the cells causes enhanced Mg need to block the influx of calcium ion, which further leads to the increased stimulation of *N*-methyl-D-aspartic acid or *N*-methyl-D-aspartate receptors. The increased stimulation of *N*-methyl-D-aspartic acid or *N*-methyl-D-aspartate results in the opening of channels nonselective to cations, thus increasing calcium ions in neuronal cells.[9] This leads to the release of neurotromediators (for example, substance P) and inflammatory cytokines. Major pro-inflammatory cytokines including IL-6 and tumor necrosis factor-alpha are released into the bloodstream and act as signaling molecules to promote the release of CRP from the liver as a part of the acute phase response, which further prolongs the inflammatory response in the body.[1] CRP production by liver is regulated by tumor necrosis factor -alpha and IL-6.[9] A well-documented link between Mg deficiency and acute inflammatory response in animal models characterized by leukocyte and macrophage activation, release of inflammatory cytokines and acute phase proteins, and excessive production of free radicals has also been reported in experimental settings.[35,36] Studies based on infrared spectrometry techniques have also demonstrated substantial alteration in secondary structures of human CRP in the presence of Mg ions.[37]

In summary, findings from this meta-analysis and systematic review indicate that dietary Mg intake is inversely associated with serum CRP levels. Our results suggest that the potential beneficial effect of Mg intake on the risk of chronic diseases may be, at least in part, explained by inhibiting inflammation. Because inflammation is a risk factor of various chronic diseases, increasing Mg intake is certainly of great public health significance.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGEMENTS

This study was partially supported by NIH grants (R01HL081572 and R01ES021735).

REFERENCES

1 Liu S, Chacko S. Dietary Mg intake and biomarkers of inflammation and endothelial dysfunction. In: Watson RR, Preedy VR, Zibadi S eds. *Magnesium in Human Health and Disease*. Humana Press: New York, 2013, pp 35–50.
2 He K, Liu K, Daviglus ML, Morris SJ, Loria CM, Van Horn L *et al.* Magnesium intake and incidence of metabolic syndrome among young adults. *Circulation* 2006; **113**: 1675–1682.
3 Rayssiguier Y, Gueux E, Nowacki W, Rock E, Mazur A. High fructose consumption combined with low dietary magnesium intake may increase the incidence of the metabolic syndrome by inducing inflammation. *Magnes Resi* 2006; **19**: 237–243.
4 Song Y, Ridker PM, Manson JE, Cook NR, Buring JE, Liu S. Magnesium intake, C-reactive protein, and the prevalence of metabolic syndrome in middle-aged and older U.S. women. *Diabetes Care* 2005; **28**: 1438–1444.
5 Song Y, Manson JE, Buring JE, Liu S. Dietary magnesium intake in relation to plasma insulin levels and risk of type 2 diabetes in women. *Diabetes Care* 2004; **27**: 59–65.
6 Abbott RD, Ando F, Masaki KH, Tung KH, Rodriguez BL, Petrovitch H *et al.* Dietary magnesium intake and the future risk of coronary heart disease (the Honolulu Heart Program). *Am J Cardiol* 2003; **92**: 665–669.
7 Al-Delaimy WK, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Magnesium intake and risk of coronary heart disease among men. *J Am Coll Nutr* 2004; **23**: 63–70.
8 Stevanovic S, Nikolic M, Stankovic A. Dietary magnesium intake and coronary heart disease risk: a study from Serbia. *Med Glas* 2011; **8**: 203–208.
9 Nielsen FH. Magnesium, inflammation, and obesity in chronic disease. *Nutr Rev* 2010; **68**: 333–340.
10 King DE, Mainous 3rd AG, Geesey ME, Ellis T. Magnesium intake and serum C-reactive protein levels in children. *Magnes Res* 2007; **20**: 32–36.
11 Guerrero-Romero F, Rodriguez-Moran M. Relationship between serum magnesium levels and C-reactive protein concentration, in non-diabetic, non-hypertensive obese subjects. *Int J Obes Relat Metab Disord* 2002; **26**: 469–474.
12 King DE, Mainous AG, Geesey ME, Egan BM, Rehman S. Magnesium supplement intake and C-reactive protein levels in adults. *Nutr Res* 2006; **26**: 193–196.
13 Chacko SA, Song Y, Nathan L, Tinker L, de Boer IH, Tylavsky F *et al.* Relations of dietary magnesium intake to biomarkers of inflammation and endothelial dysfunction in an ethnically diverse cohort of postmenopausal women. *Diabetes Care* 2010; **33**: 304–310.
14 de Oliveira Otto MC, Alonso A, Lee DH, Delclos GL, Jenny NS, Jiang R *et al.* Dietary micronutrient intakes are associated with markers of inflammation but not with markers of subclinical atherosclerosis. *J Nutr* 2011; **141**: 1508–1515.
15 Song Y, Li TY, van Dam RM, Manson JE, Hu FB. Magnesium intake and plasma concentrations of markers of systemic inflammation and endothelial dysfunction in women. *Am J Clin Nutr* 2007; **85**: 1068–1074.
16 Higgins RMHaJPT. STATA Journal 2008; **8** (Number 4): 493–519.
17 Bo S, Durazzo M, Guidi S, Carello M, Sacerdote C, Silli B *et al.* Dietary magnesium and fiber intakes and inflammatory and metabolic indicators in middle-aged subjects from a population-based cohort. *Am J Clin Nutr* 2006; **84**: 1062–1069.
18 King DE, Mainous 3rd AG, Geesey ME, Woolson RF. Dietary magnesium and C-reactive protein levels. *J Am Coll Nutr* 2005; **24**: 166–171.
19 Bowden J, Tierney JF, Copas AJ, Burdett S. Quantifying, displaying and accounting for heterogeneity in the meta-analysis of RCTs using standard and generalised Q statistics. *BMC Med Res Methodol* 2011; **11**: 41.
20 Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002; **21**: 1539–1558.
21 Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj* 1997; **315**: 629–634.
22 Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994; **50**: 1088–1101.
23 Rodriguez-Moran M, Guerrero-Romero F. Serum magnesium and C-reactive protein levels. *Archives of disease in childhood* 2008; **93**: 676–680.
24 Kim DJ, Xun P, Liu K, Loria C, Yokota K, Jacobs Jr DR *et al.* Magnesium intake in relation to systemic inflammation, insulin resistance, and the incidence of diabetes. *Diabetes Care* 2010; **33**: 2604–2610.
25 Almoznino-Sarafian D, Berman S, Mor A, Shteinshnaider M, Gorelik O, Tzur I *et al.* Magnesium and C-reactive protein in heart failure: an anti-inflammatory effect of magnesium administration? *Eur J Nutr* 2007; **46**: 230–237.
26 Nielsen FH, Johnson LK, Zeng H. Magnesium supplementation improves indicators of low magnesium status and inflammatory stress in adults older than 51 years with poor quality sleep. *Magnes Res* 2010; **23**: 158–168.
27 Chacko SA, Sul J, Song Y, Li X, LeBlanc J, You Y *et al.* Magnesium supplementation, metabolic and inflammatory markers, and global genomic and proteomic profiling: a randomized, double-blind, controlled, crossover trial in overweight individuals. *Am J Clin Nutr* 2011; **93**: 463–473.
28 Wong ET, Rude RK, Singer FR, Shaw Jr ST. A high prevalence of hypomagnesemia and hypermagnesemia in hospitalized patients. *Am J Clin Pathol* 1983; **79**: 348–352.
29 McLaughlin SA, McKinney PE. Antacid-induced hypermagnesemia in a patient with normal renal function and bowel obstruction. *Ann Pharmacother* 1998; **32**: 312–315.
30 Uchiyama C, Kato T, Tomida K, Suzuki R, Nakata K, Hamanaka M *et al.* Fatal hypermagnesemia induced by preoperative colon preparation in an elderly woman: report of a case. *Clin J Gastroenterol* 2013; **6**: 105.
31 World Health Organization. *Calcium and Magnesium in Drinking-water: Public Health Significance*. Geneva, Switzerland: World Health Organization, 2009, xi, 180 pp.
32 Moslehi N, Vafa M, Rahimi-Foroushani A, Golestan B. Effects of oral magnesium supplementation on inflammatory markers in middle-aged overweight women. *J Res Med Sci* **17**: 607–613.
33 Rodriguez-Hernandez H, Cervantes-Huerta M, Rodriguez-Moran M, Guerrero-Romero F. Oral magnesium supplementation decreases alanine aminotransferase levels in obese women. *Magnes Res* 2010; **23**: 90–96.

34 Svagzdiene M, Rupsa T, Sirvinskas E, Baranauskiene D, Abdrachmanovas O. P-74 Relation of magnesium level in serum, erythrocytes, and cardiac tissue and C-reactive protein. *J Cardiothorac Vasc Anesth* 2011; **25**: S64.

35 Bussiere FI, Tridon A, Zimowska W, Mazur A, Rayssiguier Y. Increase in complement component C3 is an early response to experimental magnesium deficiency in rats. *Life Sci* 2003; **73**: 499–507.

36 Mazur A, Maier JA, Rock E, Gueux E, Nowacki W, Rayssiguier Y. Magnesium and the inflammatory response: potential physiopathological implications. *Arch Biochem Biophys* 2007; **458**: 48–56.

37 Dong A, Caughey WS, Du Clos TW. Effects of calcium, magnesium, and phosphorylcholine on secondary structures of human C-reactive protein and serum amyloid P component observed by infrared spectroscopy. *J Biol Chem* 1994; **269**: 6424–6430.