Circulating and dietary magnesium and risk of cardiovascular disease: a systematic review and meta-analysis of prospective studies[1–3]

Liana C Del Gobbo, Fumiaki Imamura, Jason HY Wu, Marcia C de Oliveira Otto, Stephanie E Chiuve, and Dariush Mozaffarian

ABSTRACT

Background: Clinical hypomagnesemia and experimental restriction of dietary magnesium increase cardiac arrhythmias. However, whether or not circulating or dietary magnesium at usual concentrations or intakes influences the risk of cardiovascular disease (CVD), including fatal ischemic heart disease (IHD), is unclear.

Objective: We performed a systematic review and meta-analysis to investigate prospective associations of circulating and dietary magnesium with incidence of CVD, IHD, and fatal IHD.

Design: Multiple literature databases were systematically searched without language restriction through May 2012. Inclusion decisions and data extraction were performed in duplicate. Linear dose-response associations were assessed by using random-effects meta-regression. Potential nonlinear associations were evaluated by using restricted cubic splines.

Results: Of 2303 articles, 16 studies met the eligibility criteria; these studies comprised 313,041 individuals and 11,995 CVD, 7534 IHD, and 2686 fatal IHD events. Circulating magnesium (per 0.2 mmol/L increment) was associated with a 30% lower risk of CVD (RR: 0.70; 95% CI: 0.56, 0.88 per 0.2 mmol/L) and trends toward lower risks of IHD (RR: 0.83; 95% CI: 0.75, 1.05) and fatal IHD (RR: 0.61; 95% CI: 0.37, 1.00). Dietary magnesium (per 200-mg/d increment) was not significantly associated with CVD (RR: 0.89; 95% CI: 0.75, 1.05) but was associated with a 22% lower risk of IHD (RR: 0.78; 95% CI: 0.67, 0.92). The association of dietary magnesium with fatal IHD was nonlinear ($P < 0.001$), with an inverse association observed up to a threshold of ~250 mg/d (RR: 0.73; 95% CI: 0.62, 0.86), compared with lower intakes.

Conclusion: Circulating and dietary magnesium are inversely associated with CVD risk, which supports the need for clinical trials to evaluate the potential role of magnesium in the prevention of CVD and IHD. *Am J Clin Nutr* 2013;98:160–73.

INTRODUCTION

Observational and experimental studies have shown that magnesium can exert beneficial effects on the cardiovascular system by enhancing endothelium-dependent vasodilation, improving lipid metabolism, reducing inflammation, and inhibiting platelet function (1). As a key electrolyte involved in regulation of cation flux across cardiomyocytes through direct binding and allosteric effects on potassium and calcium channels, magnesium is also required for normal cardiac electrophysiology (2). Abnormally low circulating magnesium (hypomagnesemia, <0.65 mmol/L) is a known risk factor for cardiac arrest (3). Two small randomized, controlled, crossover interventions in healthy postmenopausal women showed that restriction of dietary magnesium to less than half (101–130 mg) of the Recommended Dietary Allowance (RDA)[4] induced atrial arrhythmias and supraventricular beats, which were relieved by magnesium supplementation (4, 5). Severe dietary magnesium restriction also adversely affects oxidative metabolism, glucose homeostasis, and retention and excretion of other electrolytes (4–6). Although marked reductions in magnesium concentrations or intakes produce adverse effects, whether cardiovascular disease (CVD) risk differs across the normal physiologic concentration range of circulating magnesium or dietary magnesium intake is unclear. A meta-analysis examining the associations of circulating magnesium with incident CVD and ischemic heart disease (IHD) across populations has not, to our knowledge, been previously performed. A 2005 pooled analysis of prospective cohorts found no significant association between dietary magnesium and IHD (RR: 0.87; 95% CI: 0.67, 1.10) (7); however, since that time, additional large prospective studies examining this relation have been conducted. Evaluation of both circulating and dietary magnesium is important, because circulating magnesium reflects not only diet but also gastrointestinal absorption and renal regulation, and circulating compared with dietary magnesium could differentially influence CVD risk (8). To investigate potential effects of circulating and dietary magnesium on CVD risk at usual physiologic ranges, we performed a systematic review and meta-analysis of prospective studies examining the associations of circulating magnesium and dietary

[1] From the Departments of Nutrition (LCD, SEC, and DM) and Epidemiology (FI, JHYW, MCdOO, and DM), Harvard School of Public Health, Boston MA, and the Division of Preventive Medicine (SEC) and Division of Cardiovascular Medicine (DM), Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA (DM).

[2] Supported by the National Heart, Lung, and Blood Institute (NHLBI), NIH (R21 HL 109924). LCD was supported by a doctoral fellowship from the Canadian Institutes for Health Research. FI was supported by an NHLBI Administrative Supplement Award (3R01-HL085710-03S1). MCdOO was supported by the Harvard-Bunge Fellowship Program in Nutrition & Health, an unrestricted educational grant from Bunge LLC.

[3] Address correspondence and reprint requests to LC Del Gobbo, 655 Huntington Avenue, Building 2-349, Boston, MA 02115. E-mail: ldelgobb@hsph.harvard.edu.

[4] Abbreviations used: CVD, cardiovascular disease; IHD, ischemic heart disease; RDA, Recommended Dietary Allowance; SCD, sudden cardiac death.

Received October 16, 2012. Accepted for publication April 1, 2013.

First published online May 29, 2013; doi: 10.3945/ajcn.112.053132.

magnesium with CVD, IHD, and fatal IHD. On the basis of available mechanistic evidence, we hypothesized that both circulating magnesium and dietary magnesium would be inversely associated with CVD and that associations would be strongest for fatal IHD.

METHODS

Search and screening

We followed Meta-analysis of Observational Studies in Epidemiology guidelines (9) during all stages of design, implementation, and reporting of this meta-analysis. We performed a systematic search for all prospective studies examining the association of circulating and/or dietary magnesium with CVD, IHD, or fatal IHD. Electronic searches of PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Ovid (EMBASE, AMED/AGRICOLA; http://gateway.ovid.com), the Cochrane Library (http://www.thecochranelibrary.com/view/0/index.html), Web of Knowledge (Biosis, Web of Science, ISI proceedings; http://wokinfo.com), Commonwealth Agricultural Bureau abstracts (http://www.cabdirect.org), CINAHL (http://www.ebscohost.com/academic/cinahl-plus-with-full-text/), Faculty of 1000 (http://f1000.com), and gray literature sources [Scirus (http://www.scirus.com/), the System for Information on Grey Literature in Europe (http://www.opengrey.eu/), and Epidemiology and Prevention/Nutrition, Physical Activity and Metabolism conference abstracts (http://my.americanheart.org/professional/Sessions/EPINPAM/EPINPAM_UCM_316904_SubHomePage.jsp)] were conducted without language restriction from the earliest available online indexing year to May 2012. Key search terms included magnesium, CVD, heart disease, myocardial infarction, heart attack, sudden death, sudden cardiac death (SCD), IHD, ischemic heart disease, cohort, prospective, longitudinal, case-control, incident, and incidence; full search queries for each database are available on request. Non-English records were translated into English for assessment.

Eligibility criteria

All prospective studies (cohort, nested case-control) that provided a multivariate-adjusted effect estimate with an accompanying measure of uncertainty (CI, SE, or other data to calculate variance) for circulating or dietary magnesium and incident CVD, IHD, or IHD death (including SCD) were eligible for inclusion. CVD was defined as any CVD, including cardiovascular or IHD incidence or death, and stroke or angina as part of a broader composite CVD outcome. IHD was defined as IHD incidence or death. IHD death was defined as any fatal IHD, including SCD. We excluded studies reporting stroke as a distinct outcome, because a meta-analysis of dietary magnesium and stroke was recently published (10). We also excluded studies that focused on children or that evaluated only drinking water magnesium or water hardness, dietary patterns/food groups, intracellular free magnesium, or extracellular ionized magnesium. Ionized magnesium studies were excluded because of the limited reliability of available estimates (11). Because our focus was on magnesium exposure in the normal physiologic range, we excluded studies focused on populations with disturbed mineral homeostasis (eg, patients with chronic kidney disease or heart failure). Studies presenting only crude risk estimates, ecologic studies, case reports, cross-sectional studies, retrospective case-control studies, editorials/commentaries, letters, and reviews were not eligible. For any findings published only in abstract form, we contacted the authors to determine whether results were still considered valid. When multiple manuscripts with the same cohort were published (12, 13), the analysis including the largest numbers of events was included.

Selection of articles

One investigator screened all identified titles and abstracts (n = 2303) for potential eligibility, including additional hand-searching of citation lists of relevant review articles (**Figure 1**). Among the 48 full-text articles reviewed independently and in duplicate by 2 investigators, 32 studies were excluded because of not being prospective (n = 14); not including the exposures or outcomes of interest (n = 9); focusing on a population sample with prevalent disease affecting mineral homeostasis (n = 6); reporting only crude estimates (n = 1); or being duplicate publications (n = 2). Details of these exclusions are presented as Supplemental material (*see* "Supplemental data" in the online issue). Citation lists and related citations in PubMed of all final included text articles were hand-searched for additional eligible studies; no new studies were identified. In sum, 16 prospective studies (7, 12–26) met the inclusion criteria and were included in the meta-analysis.

Data extraction

Data were independently extracted in duplicate by 2 investigators with the use of a standardized electronic form (Microsoft Excel). Information on study design, location, follow-up, age, sex, BMI, race, baseline disease (CVD, kidney disease, diabetes mellitus), and use of multivitamins and magnesium supplements was recorded. For dietary magnesium, data on the assessment method used (food-frequency questionnaire, 24-h dietary recall, other) and whether the data were energy-adjusted (yes, no) were obtained; for circulating magnesium studies, data on the assessment method used (atomic absorption spectroscopy, colorimetric assays, other) and on the blood fraction (serum, plasma) were obtained. For each category of exposure, we extracted the median exposure level, the multivariate-adjusted risk estimate and its variance measure, the number of cases, and the number of participants (nested case-control) or person-years (cohorts). Risk estimates for exposures as continuous variables (n = 2 studies) were also extracted (16, 20). If estimates for more than one multivariate model were presented, we extracted estimates with greatest adjustment for potential confounders without inclusion of potential time-varying mediators or covariates having high collinearity with magnesium (ie, dietary potassium). If the only available multivariable model presented included such variables, this was selected in preference to crude estimates or minimally adjusted models. For cohorts presenting multiple cardiovascular outcomes with shared cases, the outcome with the most cases was used for the pooled estimates for outcomes. Among 8 authors contacted for missing information (12, 16, 17, 20, 21, 23–25), we received responses from 5 authors (12, 16, 18, 23, 24) who provided unpublished data on exposure categories (eg, exposure levels, number of cases) or covariates.

Whereas no standardized quality score for observational studies exists (9), we evaluated and scored studies independently and in duplicate on a 6-point scale based on guidelines adapted from (27). The criteria (1 point each) included reporting of study

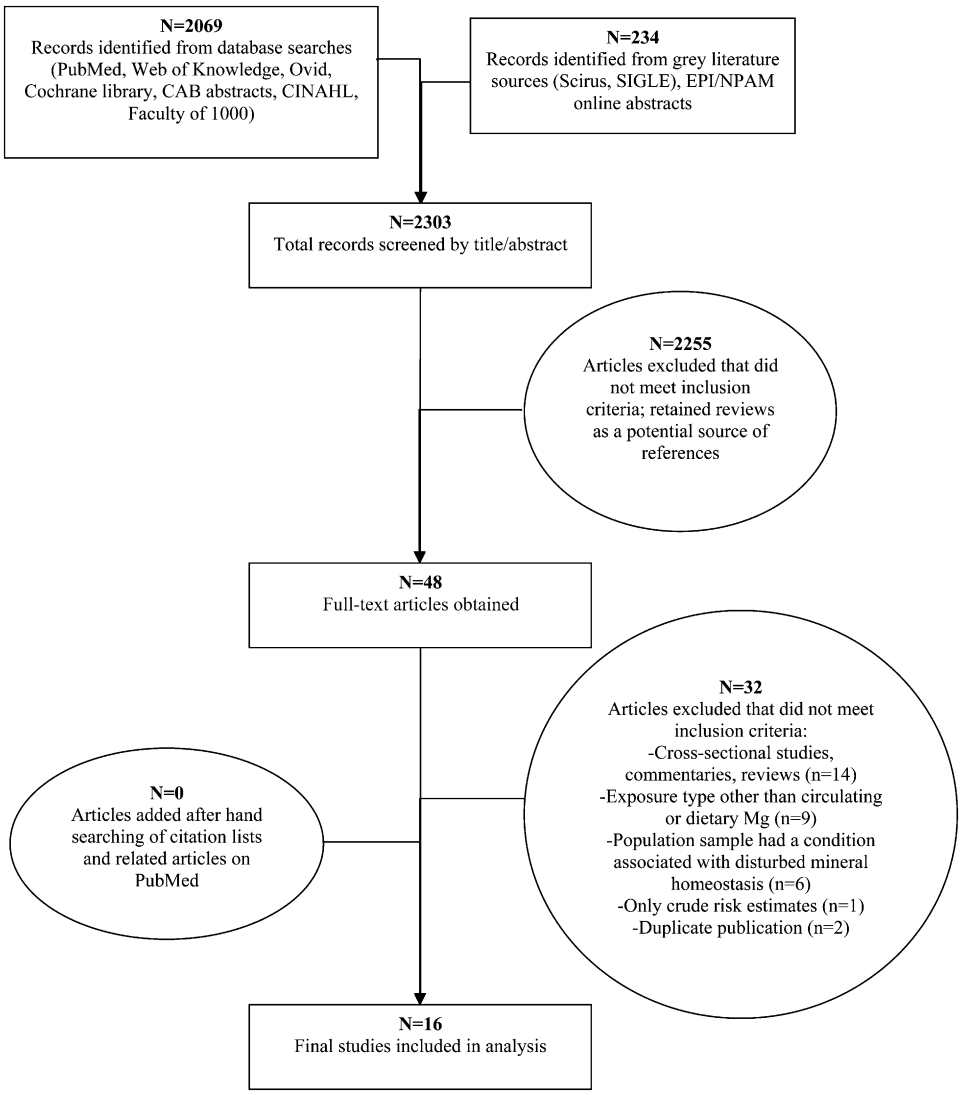

FIGURE 1. Screening and selection of articles on circulating and dietary magnesium and risk of cardiovascular diseases. Records were identified by electronic searches of PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Web of Knowledge (http://wokinfo.com), Ovid (http://gateway.ovid.com), Cochrane library (http://www.thecochranelibrary.com/view/0/index.html), Commonwealth Agricultural Bureau abstracts (http://www.cabdirect.org), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (http://www.ebscohost.com/academic/cinahl-plus-with-full-text/), and Faculty of 1000 (http://f1000.com). Gray literature sources searched included Scirus (http://www.scirus.com/), the System for Information on Grey Literature in Europe (SIGLE) (http://www.opengrey.eu/), and Epidemiology and Prevention/Nutrition, Physical Activity and Metabolism (EPI/NPAM) conference abstracts (http://my.americanheart.org/professional/Sessions/EPINPAM/EPINPAM_UCM_316904_SubHomePage.jsp).

participation, attrition, assessment of exposure and outcome, control of confounding, and appropriateness of the analysis for the study design. Points were summed for each study, and studies with quality scores of 0 to 3 were considered to be of lower quality, and of 4–6 of higher quality. Interrater reliability was reasonable (Cohen κ 0.72).

Statistical analysis

To maximize all data for calculation of the pooled dose-response, risk estimates were meta-analyzed with the use of the 2-step generalized least-squares trend estimation model (28). This method constructs a covariance estimate for dose-specific log RRs within each study and then estimates the dose-response relation, accounting for between- and within-study variation. Study-specific log-linear dose-response slopes are calculated for each study based on category risk estimates, SE, median exposure, number of cases, person-years of follow-up (cohorts) or number of subjects (nested case-control studies). The study-specific risk estimates are then pooled with the use of inverse-variance weighted meta-analysis to derive an overall dose-response. For studies directly reporting risk estimates for continuous exposure, these data were used and added to the analysis at the second step.

Reported HRs and ORs were assumed to approximate RRs (29). If median exposure levels in each category were not reported, values were imputed based on the reported range or obtained by direct author contact. Dose responses of circulating magnesium and dietary magnesium were standardized across studies to 0.2 mmol/L (0.486 mg/dL, 0.4 mEq/L) and 200 mg/d, respectively, based on unweighted median differences between the highest and lowest quartile category medians across all studies of 0.21 mmol/L for circulating magnesium and 190 mg/d for dietary magnesium; RRs for different increments can be calculated from our data. Nearly all studies of circulating magnesium used serum measures; the lone study using plasma (16) was pooled with these,

because the serum and plasma magnesium reference ranges are similar.

Heterogeneity was quantified by using the I^2 statistic (30), with >30% considered at least moderate heterogeneity. The primary analysis used a random-effects model if I^2 >30%. Because random effects may overestimate the influence of small studies in the presence of heterogeneity, fixed-effects models were evaluated in secondary analyses. Prespecified sources of potential heterogeneity were explored by using meta-regression, with significance tested by the Wald test for a cross-product term (circulating or dietary magnesium multiplied by the potential source of heterogeneity < compared with ≥ median, unless otherwise noted). Sources included location (United States, other), design (cohort, nested case-control), length of follow-up, age, sex, BMI, dietary assessment method (24-h recall), circulating magnesium assessment method (atomic absorption spectroscopy, colorimetric assay), circulating magnesium fraction (serum, plasma), outcome (CVD, IHD) proportion of prevalent disease (baseline CVD, type 2 diabetes, kidney disease), and study quality score (0–3, 4–6). Power was insufficient to examine heterogeneity by using multivariable meta-regression. Publication bias was assessed by visual inspection of funnel plots and Egger's and Begg's tests (31, 32). In the presence of potential publication bias, we used Duval and Tweedie's nonparametric "trim and fill" method, which estimates the number and effect estimates of hypothetically missing studies, to adjust the pooled estimates (33). Potential nonlinear relations were examined by using restricted cubic spline models with 3 kn at the 25th, 50th, and 75th percentiles. All analyses were performed by using STATA 12 (StataCorp), with 2-tailed $\alpha = 0.05$.

RESULTS

Study characteristics

The 16 identified studies provided 25 estimates of circulating or dietary magnesium and risk of CVD, including 313,041 individuals and 11,995 CVD, 7,534 IHD, and 2686 fatal IHD events (**Table 1**). Most studies used cohort designs; 3 estimates were derived from prospective nested case-control studies (16, 25). Two studies provided data on both circulating and dietary magnesium (12, 16).

Of the 9 studies examining circulating magnesium, 5 were from the United States and the remainder from Europe. Participants were predominately middle-aged at baseline, with a median BMI (in kg/m^2) across studies of 25.8; 8 of 9 cohorts included ≤10% patients with diabetes, 4 studies excluded participants with prevalent CVD at baseline, and none reported prevalent chronic kidney disease. Circulating magnesium distributions generally fell within the normal reference range [0.75–0.96 mmol/L (34)] or the wider range used in some laboratories (0.65–1.10 mmol/L) (35). Studies used standard analytic approaches for circulating magnesium determination, atomic absorption spectroscopy, or colorimetric assays, with no record of hemolyzed samples or EDTA use.

Participants in the 9 studies evaluating dietary magnesium analyses were generally similar; most (8 of 9) excluded individuals with prevalent CVD at baseline. Dietary magnesium was most often assessed by using validated food-frequency questionnaires. The median consumption level across all studies was 289 mg—lower than the RDA of 420 mg for men and 320 mg for women >30 y (36). Most studies did not report on potential contribution of multivitamins or supplements to magnesium intake; in 2 cohorts describing such use (15, 16), <14% of participants reported taking magnesium supplements, generally contributing <100 mg total Mg/d in these participants (15).

Most studies validated outcomes by using medical records, autopsy records, and/or endpoint committees, frequently classified by using International Classification of Diseases diagnosis coding (17–19, 21, 24–26). The degree of covariate adjustment varied, with about half of studies adjusting for both sociodemographic and lifestyle variables including age, sex, race, BMI, waist circumference, smoking, alcohol, and physical activity (7, 12, 14–16, 18, 19, 21, 23). Overall, most of the studies (15 of 16) were judged to be of high quality (quality score: 4–6).

Circulating magnesium

Nine studies provided 11 estimates of circulating magnesium and incident CVD, comprising 4106 CVD, 3215 IHD, and 1528 fatal IHD events.

CVD

Circulating magnesium (per 0.2 mmol/L increment) was associated with a 30% lower risk of CVD (RR: 0.70; 95% CI: 0.56, 0.88; **Figure 2**, top), with evidence of moderate between-study heterogeneity (I^2 = 49.5%). Findings were similar in secondary analyses by using fixed-effects models. In a meta-regression, study location, percentage baseline CVD, and event type (incidence compared with death) significantly modified the association between circulating magnesium and CVD (P-heterogeneity = 0.04, 0.02, and 0.02, respectively). A stronger association with lower risk was observed in non-US countries, in studies including some participants with prevalent CVD, and in studies evaluating death rather than incidence as an event type (**Table 2**). In a post hoc subgroup analysis, no significant difference by diuretic use was observed (P = 0.84).

IHD

Five studies evaluated circulating magnesium and IHD. Circulating magnesium was not significantly associated with IHD (RR: 0.83; 95% CI: 0.65, 1.05; I^2 = 49.5%) (Figure 2; middle); findings were similar in secondary analyses with the use of fixed-effects models (RR: 0.88; 95% CI = 0.76, 1.02). No significant sources of between-study heterogeneity were identified, although a trend was seen toward a stronger association with lower risk in studies with mostly (≥50%) female participants (P-heterogeneity = 0.06).

Fatal IHD

Four studies comprising 27,293 unique individuals and 1528 cases evaluated circulating magnesium and fatal IHD. A trend toward lower risk was evident (RR: 0.61; 95% CI: 0.37, 1.00), with substantial between-study heterogeneity (I^2 = 80.2%) (Figure 2; bottom). In secondary analyses using fixed effects, circulating magnesium was associated with a significantly lower risk of fatal IHD (RR: 0.77; 95% CI: 0.64, 0.93). Meta-regression did not identify any statistically significant sources of heterogeneity, although statistical power to identify heterogeneity was

TABLE 1
Characteristics of 16 prospective studies providing 25 risk estimates in 313,041 individuals for circulating or dietary magnesium and risk of total CVD and IHD[1]

First author	Study (country)	Cases/total individuals	Age range	Men	CVD[2]	Exposure assessment[3]	Disease outcome	Disease ascertainment[4]	Follow-up (maximum)	Adjustment[5]	Quality score[6]
		n	*y*	%	%				*y*		
Circulating magnesium											
Reunanen et al (case-control), 1996 (25)	Finnish men (Finland)		15–69	100	22.6	AAS (serum)			10 (mean)	++	4
		220/507					CVD death	ICD-8-CM codes 390.97–458.99			
		160/381					IHD death	ICD-8-CM codes 410.00–414.99			
Marniemi et al, 1998 (22)	Finnish elderly (Finland)	142/344	≥65	52.9	19	AAS (serum)	CVD death	National death register; select cases confirmed at autopsy	13	++	5
Liao et al, 1998 (12)	ARIC (USA)	223/13,922; 96/13,922	45–64	1000	0	Colorimetric (serum)	IHD total	Minnesota Code, death certificates with next of kin interviews and physician questionnaires; deaths validated by autopsies	7	++	5
Ford, 1999 (18)	NHEFS (USA)		25–74	40	0	AAS (serum)			19	++	5
		2637/12,340					IHD total	ICD-9-CM codes 410–414			
		1005/12,340					IHD death	Death certificates listing codes above			
Leone et al, 2006 (21)	PPS II (France)	56/4035	30–60	100	1.4	AAS (serum)	CVD death	ICD-10-CM codes I00–199	21	++	5
Peacock et al, 2010 (13)	ARIC (USA)	264/14,232	45–64	45	0	Colorimetric (serum)	SCD	Fatal IHD cases classified by physician committee as definite or possible sudden arrhythmic death	12	++	4
Khan et al, 2010 (20)[7]	FHS offspring (USA)	554/3531	44.3 (mean)	48	0	Colorimetric (serum)	CVD total	Panel review of hospital, medical, and Framingham clinic visit notes by using standardized criteria	20	++	5.5
Chiuve et al (case-control), 2011 (16)	NHS (USA)	99/390	44–69	0	40	Colorimetric (plasma)	SCD	Medical records or next of kin report of death or cardiac arrest within 1 h of symptom onset, arrhythmic death as defined by Hinkle and Thaler	16	+++	6
Reffelmann et al, 2011 (24)	SHIP (Germany)	79/3910	20–79	49	5.8	Colorimetric (serum)	CVD death	ICD-10-CM codes I10–I79	12	++	5.5
Dietary magnesium											
Elwood et al, 1996 (17)	Caerphilly cohort (Wales)		45–59	100	17	FFQ			10	+	3
		269/2172					IHD total	ICD-9-CM codes 410–414			
		96/2172					IHD death	ICD-9-CM code 410			
Liao et al, 1998 (12)	ARIC (USA)	223/13,744; 96/13,744	45–64	1000	0	FFQ	IHD total	Minnesota Code, death certificates with next of kin interviews and physician questionnaires; deaths validated by autopsies	7	+++	5
Abbott et al, 2003 (14)	HHS (USA)	548/7172	45–68	100	0	24-h recall	IHD total	ECG or cardiac enzyme evidence, SCD, heart failure or arrhythmic death in patients with IHD history, and/or autopsy findings	15	+++	5
Al-Delaimy et al, 2004 (15)	HPFS (USA)	1449/39,633	40–75	100	0	FFQ	IHD total	Next of kin/coworker reports or National Death Index; confirmation with medical/autopsy reports or death certificates; SCD	12	+++	5

(Continued)

TABLE 1 (*Continued*)

First author	Study (country)	Cases/total individuals	Age range	Men	CVD[2]	Exposure assessment[3]	Disease outcome	Disease ascertainment[4]	Follow-up (maximum)	Adjustment[5]	Quality score[6]
Song et al, 2005 (7)	WHS (USA)		39–89	0	0	FFQ			11	++	5.5
		1027/35,601					CVD total	Myocardial infarction symptoms with ECG changes or cardiac enzyme elevation; hospital record of angioplasty or coronary bypass graft; stroke determined by endpoints committee			
		672/35,601					IHD total	Same as CVD incidence, excluding stroke and final CVD			
Kaluza et al, 2010 (19)	CSM (Sweden)	819/23,366	45–79	100	0	FFQ	CVD death	ICD-10-CM codes I00–I79	10	+++	5
Chiuve et al, 2011 (16)	NHS (USA)	505/88,375	34–59	0	0	FFQ	SCD	Medical records or next of kin report of death or cardiac arrest within 1 h of symptom onset, arrhythmic death as defined by Hinkle and Thaler	26	+++	6
Otto et al, 2012 (23)	MESA (USA)	263/5285	45–84	47	0	FFQ	CVD total	Self-reported diagnoses, death certificates, autopsy reports, medical records reviewed by endpoints committee	7	+++	5
Zhang et al, 2012 (26)	JACC (Japan)	1347/35,532	40–79	0	0	FFQ	CVD death	ICD-10-CM codes I01–I99	17	+++	5.5
		1343/23,083		100			CVD death	Same as above			
		246/35,532		0			IHD death	ICD-10-CM codes I20–I25			
		311/23,083		100			IHD death	Same as above			

[1] AAS, atomic absorption spectrophotometry; ARIC, Atherosclerosis Risk in Communities; CM, clinical modification; CSM, Cohort of Swedish Men; CVD, cardiovascular disease; ECG, electrocardiogram; FFQ, food-frequency questionnaire; FHS offspring, Framingham Heart Study, offspring cohort; HHS, Honolulu Heart Study; HPFS, Health Professionals Follow-Up Study; ICD-CM, International Statistical Classification of Disease Clinical Modification; IHD, ischemic heart disease; JACC, Japan Collaborative Cohort Study; MESA, Multi-Ethnic Study of Atherosclerosis; NHEFS, NHANES I Epidemiologic Follow-Up Study; NHS, Nurses' Health Study; PPS II, Paris Prospective Study II; SCD, sudden cardiac death; WHS, Women's Health Study.

[2] Prevalent CVD at baseline.

[3] Dietary exposure was assessed by using FFQs or 24-h dietary recalls; circulating magnesium (serum or plasma) was assessed by using colorimetric assays (colorimetric) or AAS.

[4] The CM number indicates the revision number.

[5] The degree of covariate adjustment is indicated by + (sociodemographic variables), ++ (sociodemographic variables and other risk factors), and +++ (sociodemographic variables, other risk factors, and dietary variables). Circulating magnesium was inversely associated with non-white race, prevalence of hypertension, diabetes, use of diuretics, and other cardiovascular drugs, with weak positive correlations with dietary magnesium intake ($r \leq 0.09$) (15, 16) and serum potassium and calcium ($r \leq 0.18$) (20) and inconsistent associations with BMI, smoking, lipid profiles, and glomerular filtration rate in univariate analyses (13, 16, 20, 21, 24). Two circulating magnesium studies provided estimates, including diabetes and hypertension as time-varying covariates (13, 16); models excluding these variables were used. Most dietary magnesium studies adjusted for intakes of other nutrients (12, 14–16, 19, 23, 26), including potassium (12, 14–16, 26). Few studies have reported the correlation between dietary magnesium and potassium, although $r \geq 0.91$ was reported in references 20 and 26. Multivariate-adjusted estimates excluding dietary potassium were used; if the only available multivariable model presented included dietary potassium, it was selected in preference to crude estimates or minimally adjusted models. Dietary magnesium intake was also associated with intakes of energy, calcium, and fiber ($r \leq 0.75$), higher educational attainment, and greater physical activity and was inversely associated with BMI, hypertension, and diabetes in univariate analyses (7, 14–16, 19, 26).

[6] Study quality was assessed by using 6 criteria (up to 1 point per criterion), including participation (1 point if key characteristics of source population were described, including record of sampling recruitment method, period and location of recruitment, or reference to previously published study detailing source population characteristics), attrition (1 point if participants/nonparticipants did not differ by key study characteristics), exposure determination (1 point if dietary magnesium was measured by using a validated dietary assessment method; for circulating magnesium, 1 point if measured by using a published AAS or colorimetric method, with absence of evidence of the potential for hemolyzed samples or EDTA chelation), validated outcome (lack of reliance on self-report/recall), control of confounding [0.5 points for inclusion of age, sex, race/field center (if multi-ethnic cohort), BMI, smoking, alcohol, physical activity; 0.5 points for adjustment of fiber in dietary magnesium models; 0.5 points for adjustment of diabetes at baseline in circulating magnesium models], and analysis (1 point if risk estimate determination and statistical approaches were appropriate for the study design). Scores were summed; studies with scores from 0 to 3 and 4 to 6 were considered to be of lower and higher quality, respectively.

[7] For Khan et al (20), categorical estimates were used for generalized least-squares trend, because the published continuous estimate for a 0.2-mmol/L dose (RR: 0.55; 95% CI: 0.10, 2.98) was strongly influenced by the presence of a small number of outlying hypomagnesemic individuals (serum magnesium <0.62 mmol/L) who were at markedly elevated CVD risk (RR: 1.99; 95% CI: 1.02, 3.85) compared with the reference group with normal magnesium concentrations (0.62–0.91 mmol/L).

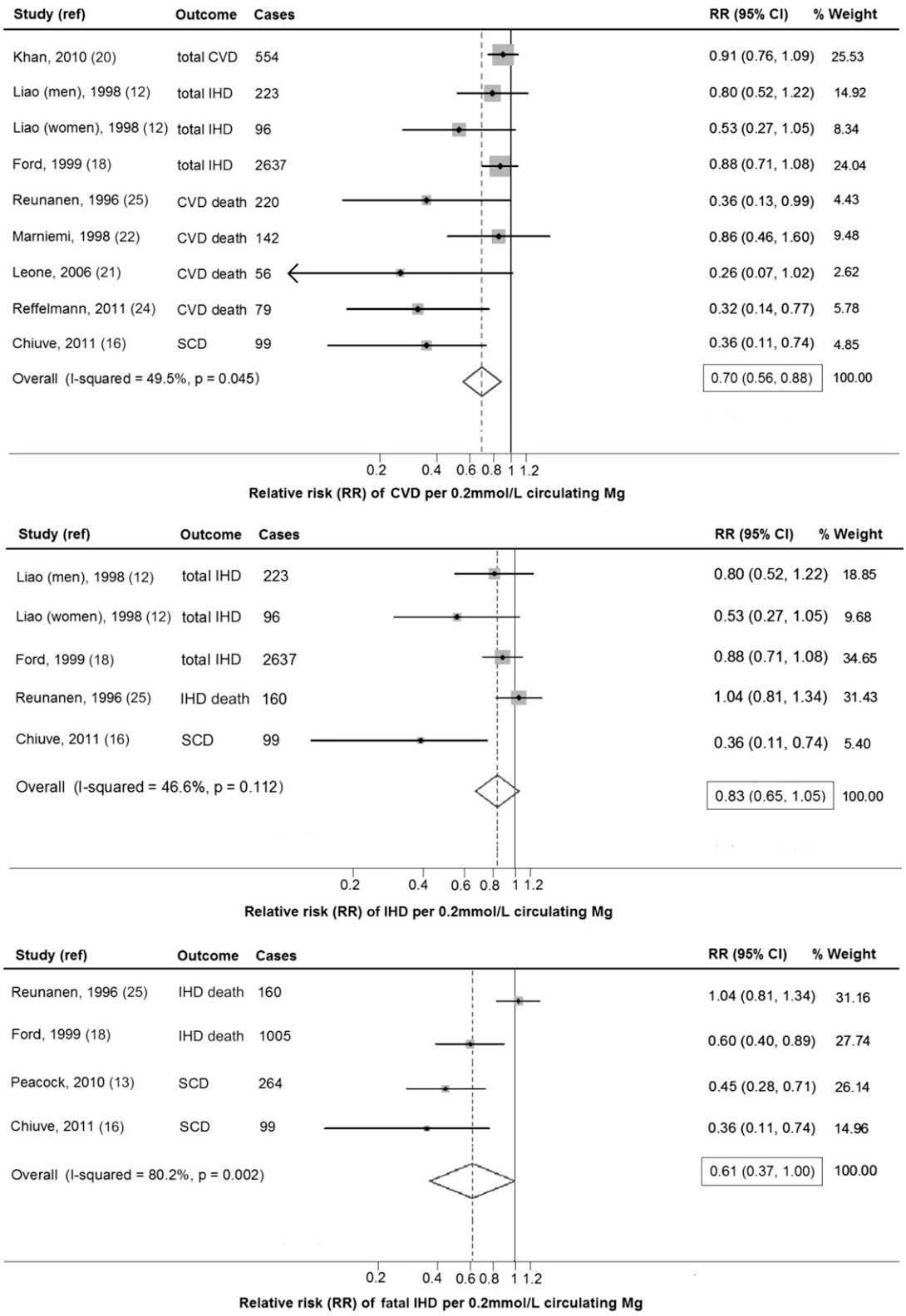

FIGURE 2. RR of CVD, IHD, and fatal IHD associated with a 0.2-mmol/L higher circulating magnesium concentration quantified by using generalized least-squares trend estimation and pooled by using a random-effects meta-analysis (n = 53,212). Circulating magnesium (per 0.2-mmol/L increment) was associated with a 30% lower risk of CVD (RR: 0.70; 95% CI: 0.56, 0.88 per 0.2 mmol/L) and a trend toward lower risks of IHD (RR: 0.83; 95% CI: 0.75, 1.05) and fatal IHD (RR: 0.61; 95% CI: 0.37, 1.00). CVD, cardiovascular disease; IHD, ischemic heart disease; ref, reference; SCD, sudden cardiac death.

TABLE 2
RRs (95% CIs) for dietary or circulating magnesium and incidence of CVD, IHD, and fatal IHD according to prespecified potential sources of heterogeneity (n = 313,041)[1]

Sources[2]	Circulating magnesium CVD (n = 9)	IHD (n = 5)	Fatal IHD (n = 4)	Dietary magnesium CVD (n = 11)	IHD (n = 9)	Fatal IHD (n = 4)
Study location						
USA	0.83 (0.69, 0.99)	NA (only one non-US cohort)	NA	0.87 (0.71, 1.06)	0.82 (0.67, 0.99)	NA (only one non-US cohort)
Other	0.46 (0.25, 0.84)			0.91 (0.65, 1.28)	0.68 (0.51, 0.90)	
P-heterogeneity[3]	0.04			0.79	0.44	
Study design						
Cohort	0.78 (0.63, 0.96)	0.83 (0.69, 1.00)	0.53 (0.39, 0.71)	NA (all cohort)	NA	NA
Case-control	0.36 (0.18, 0.72)	0.68 (0.24, 1.89)	0.68 (0.24, 1.89)			
P-heterogeneity[3]	0.32	0.63	0.27			
Follow-up						
<Median	0.54 (0.35, 0.84)	0.71 (0.50, 1.02)	0.70 (0.30, 1.60)	1.07 (0.76, 1.51)	0.90 (0.69, 1.18)	NA (only one below median)
≥Median	0.82 (0.66, 1.03)	0.88 (0.65, 1.18)	0.55 (0.38, 0.80)	0.81 (0.67, 0.97)	0.72 (0.61, 0.85)	0.35
P-heterogeneity[3]	0.46	0.27	0.66	0.30	0.40	
Age						
<Median	0.81 (0.62, 1.05)	0.94 (0.80, 1.12)	0.81 (0.47, 1.00)	0.84 (0.71, 0.98)	0.83 (0.66, 1.04)	0.80 (0.46, 1.39)
≥Median	0.60 (0.42, 0.87)	0.62 (0.40, 0.95)	0.43 (0.28, 0.65)	0.97 (0.69, 1.37)	0.72 (0.57, 0.90)	0.63 (0.41, 0.98)
P-heterogeneity[3]	0.95	0.14	0.25	0.54	0.55	0.56
Sex (% male)						
<Median	0.81 (0.65, 1.02)	0.47 (0.27, 0.81)	0.55 (0.38, 0.80)	0.93 (0.66, 1.31)	0.83 (0.51, 1.33)	0.56 (0.38, 0.83)
≥Median	0.56 (0.35, 0.88)	0.92 (0.79, 1.07)	0.70 (0.30, 1.60)	0.86 (0.71, 1.05)	0.77 (0.68, 0.87)	0.94 (0.69, 1.28)
P-heterogeneity[3]	0.21	0.06	0.66	0.96	0.06	0.12
BMI (kg/m^2)						
<Median	0.32 (0.14, 0.72)	0.94 (0.80, 1.12)	0.81 (0.47, 1.39)	0.73 (0.55, 0.98)	0.63 (0.50, 0.81)	0.63 (0.41, 0.98)
≥Median	0.77 (0.62, 0.95)	0.62 (0.41, 0.95)	0.43 (0.28, 0.65)	1.09 (0.84, 1.42)	0.86 (0.65, 1.13)	0.80 (0.46, 1.39)
P-heterogeneity[3]	0.37	0.62	0.19	0.09	0.41	0.56
Circulating magnesium method						
AAS	0.69 (0.44, 1.07)	0.94 (0.80, 1.12)	0.81 (0.47, 1.39)	NA	NA	NA
Colorimetry	0.64 (0.44, 0.93)	0.62 (0.40, 0.95)	0.43 (0.28, 0.65)			
P-heterogeneity[3]	0.80	0.14	0.25			
Prevalent CVD						
No CVD	0.87 (0.76, 0.99)	0.83 (0.69, 1.00)	0.81 (0.47, 1.39)	NA (only one nonzero baseline %)	NA	NA
>0%	0.45 (0.28, 0.73)	0.68 (0.24, 1.89)	0.43 (0.28, 0.65)			
P-heterogeneity[3]	0.02	0.63	0.25			
Disease type						
CVD	0.58 (0.35, 0.96)	NA	NA	1.06 (0.82, 1.37)	NA	NA
IHD	0.74 (0.55, 0.99)			0.76 (0.66, 0.87)		
P-heterogeneity[3]	0.35			0.07		
Event type						
Incidence	0.87 (0.76, 0.99)	0.83 (0.69, 1.00)	NA	0.88 (0.73, 1.06)	0.83 (0.69, 0.99)	NA
Death	0.45 (0.28, 0.73)	0.68 (0.24, 1.89)		0.89 (0.60, 1.30)	0.61 (0.44, 0.85)	
P-heterogeneity[3]	0.02	0.63		0.88	0.07	

(Continued)

TABLE 2 (*Continued*)

Sources[2]	Circulating magnesium			Dietary magnesium		
	CVD (n = 9)	IHD (n = 5)	Fatal IHD (n = 4)	CVD (n = 11)	IHD (n = 9)	Fatal IHD (n = 4)
Type 2 diabetes (%)						
<Median	0.80 (0.61, 1.05)	0.64 (0.28, 1.47)	0.81 (0.47, 1.39)	1.00 (0.78, 1.30)	0.80 (0.60, 1.06)	0.56 (0.37, 0.83)
≥Median	0.50 (0.25, 0.99)	0.85 (0.61, 1.19)	0.43 (0.28, 0.65)	0.79 (0.64, 0.97)	0.73 (0.62, 0.86)	0.94 (0.69, 1.28)
P-heterogeneity[3]	0.96	0.73	0.25	0.31	0.59	0.12

[1] RRs and 95% CIs for each study were quantified by using generalized least-squares trend estimation and pooled by using random-effects meta-analysis. AAS, atomic absorption spectrophotometry; CVD, cardiovascular disease; IHD, ischemic heart disease; NA, not available.

[2] Median values across the studies for participant characteristics were used to create binary categories. Prespecified sources of heterogeneity—including the method used to determine dietary magnesium (food-frequency questionnaire compared with 24-h recall), circulating magnesium fraction (serum compared with plasma), and quality score (0–3 compared with 4–6)—were not assessed because only one study quantified dietary magnesium with the use of a 24-h recall (14), measured circulating magnesium in plasma (16), or obtained a quality score of 0 to 3 (17). Kidney disease was also not assessed in the heterogeneity analyses, because disease prevalence was not reported in any study.

[3] P-heterogeneity was obtained by adding a cross-product term of the main exposure and the potential source of heterogeneity (binary coded) to models.

limited given only 4 studies. In a post hoc analysis restricted to studies evaluating SCD, circulating magnesium was associated with a 57% lower risk (RR: 0.43; 95% CI: 0.28, 0.65), but this was based on only 2 studies with relatively few endpoints (n = 99; n = 264 cases) (13, 16). A third cohort reported no significant association between serum magnesium and SCD (20), but this study had very few cases (n = 29 cases) and did not provide a specific risk estimate in the manuscript nor after author request.

Dietary magnesium

Eleven studies provided 14 estimates of dietary magnesium and incident CVD, including 7889 CVD, 4319 IHD, and 1158 fatal IHD events.

CVD

Dietary magnesium (per 200-mg/d increment) was not significantly associated with total CVD (RR: 0.89; 95% CI: 0.75, 1.05; **Figure 3**, top), with evidence for between-study heterogeneity (I^2 = 67.7%). In secondary analyses using fixed effects, dietary magnesium was significantly associated with a lower risk of CVD (RR: 0.87; 95% CI: 0.72, 0.89) (*see* Supplemental Figure S1 under "Supplemental data" in the online issue). No statistically significant sources of between-study heterogeneity were identified, but trends were seen toward stronger associations with lower risk among studies with lower median BMI (<25) (P-heterogeneity = 0.09) or evaluating IHD rather than CVD (P-heterogeneity = 0.07) (Table 2).

IHD

Dietary magnesium was associated with 22% lower risk of CHD (RR: 0.78; 95% CI: 0.67, 0.92; Figure 3, middle), with moderate heterogeneity (I^2 = 44.1). The pooled estimate from a fixed-effects model was similar (RR: 0.80; 95% CI: 0.72, 0.89). Trends toward stronger associations in cohorts with more men (P-heterogeneity = 0.06) and studies evaluating fatal IHD death rather than total IHD (P-heterogeneity = 0.07) were observed (Table 2).

Fatal IHD

Dietary magnesium intake (per 200-mg/d increment) was not significantly associated with fatal IHD (RR: 0.73; 95% CI: 0.52, 1.03; Figure 3, bottom) by using linear modeling; however, a significant nonlinear association was observed (**Figure 4**). Between-study heterogeneity was moderate (I^2 = 43.2%). In a secondary fixed-effects model, dietary magnesium was significantly associated with fatal IHD (RR: 0.77; 95% CI: 0.60, 0.98). Meta-regression did not identify any statistically significant prespecified sources of heterogeneity, although the power to identify heterogeneity was limited given the number of studies.

Nonlinear associations

We found no evidence of nonlinear associations between circulating magnesium and CVD (P = 0.64), IHD (P = 0.42), or fatal IHD (P = 0.67) or between dietary magnesium and CVD (P = 0.56) or IHD (P = 0.26) (Figure 4). These findings suggest that pooling of dose-response estimates from linear trend estimation (generalized least-squares trend) for these exposures and outcomes was appropriate. In contrast, we identified

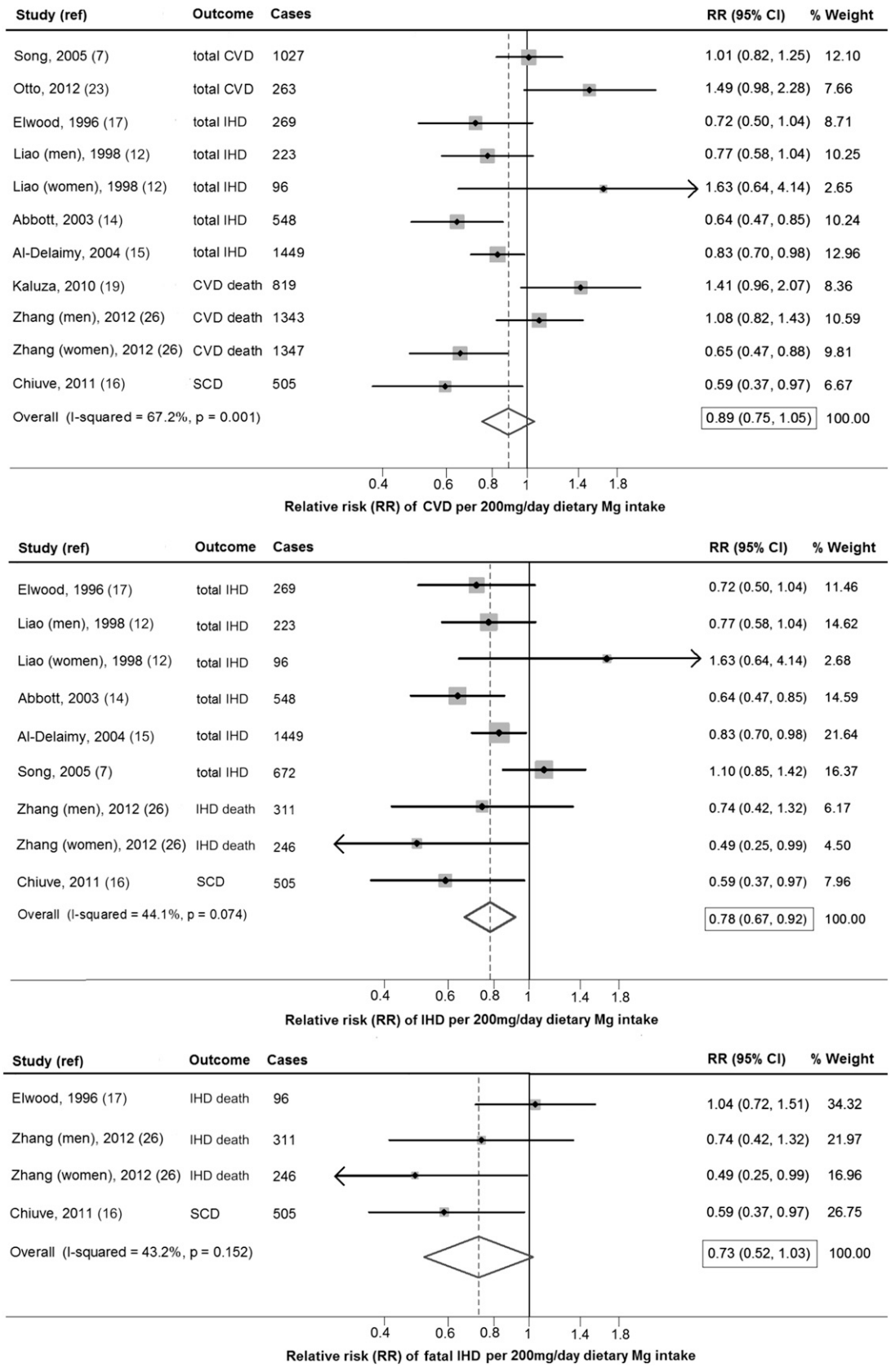

FIGURE 3. RR of CVD, IHD, and fatal IHD associated with a 200-mg/d higher dietary magnesium intake quantified by using generalized least-squares trend estimation and pooled by using a random-effects meta-analysis (n = 273,963). Dietary magnesium (per 200-mg/d increment) was not significantly associated with CVD (RR: 0.89; 95% CI: 0.75, 1.05) but was associated with a 22% lower risk of IHD (RR: 0.78; 95% CI: 0.67, 0.92). Dietary magnesium intake was not significantly associated with fatal IHD (RR: 0.73; 95% CI: 0.52, 1.03) with linear modeling; however, a significant nonlinear association was observed (Figure 4). CVD, cardiovascular disease; IHD, ischemic heart disease; ref, reference; SCD, sudden cardiac death.

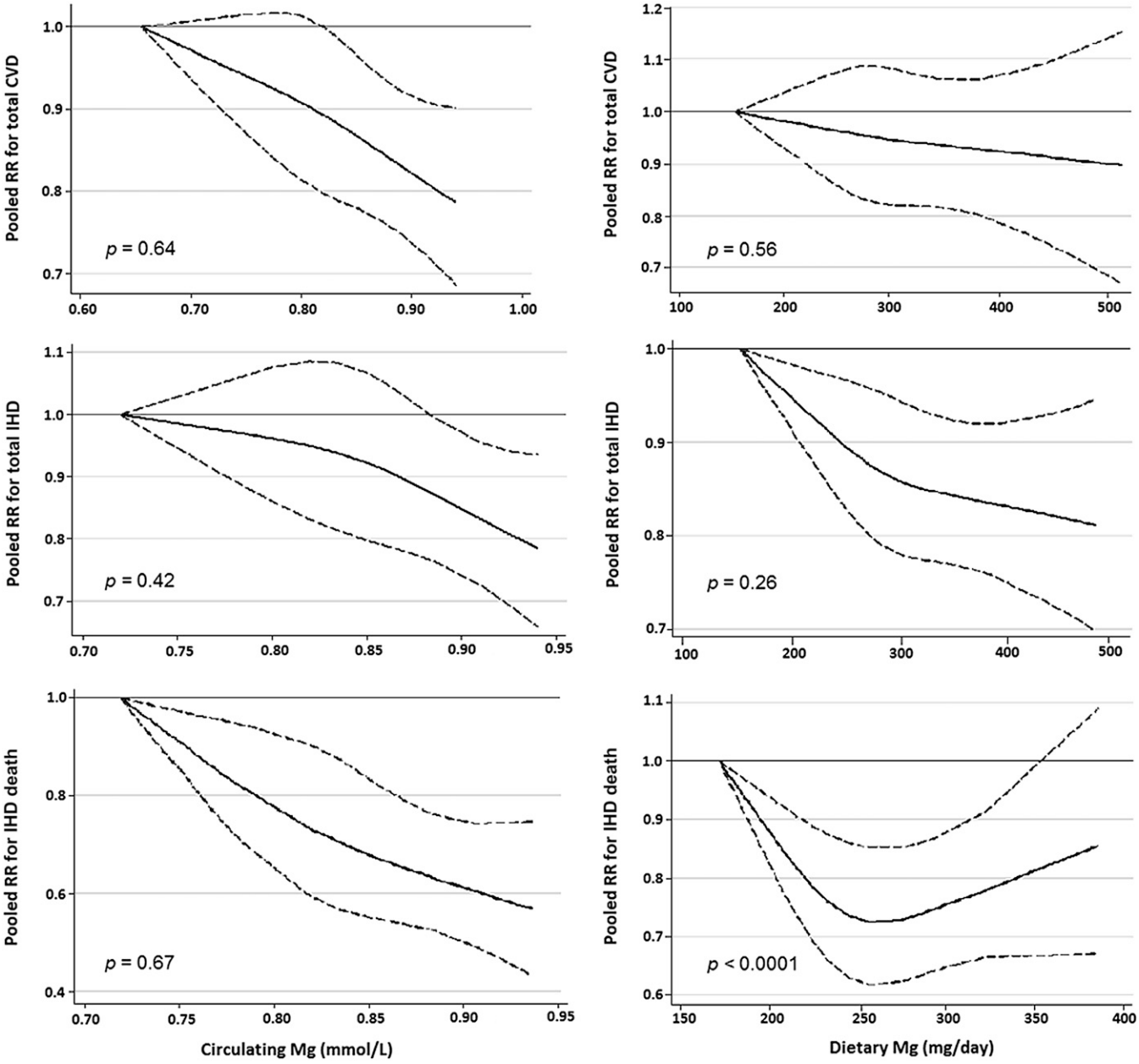

FIGURE 4. Prospective associations between circulating and dietary magnesium and RR of CVD, IHD, and fatal IHD estimated by random-effects meta-analysis with the use of restricted cubic splines (n = 313,041). Each reference value represents the lowest median value of included studies. P values for nonlinear associations are presented. The association between dietary magnesium and fatal IHD was nonlinear (P-nonlinear < 0.001). In comparison with lower intakes, a 27% lower risk of fatal IHD was observed up to a threshold of ~250 mg/d (RR: 0.73; 95% CI: 0.62, 0.86). CVD, cardiovascular disease; IHD, ischemic heart disease.

a significant nonlinear association between dietary magnesium and fatal IHD (P-nonlinearity < 0.001). Compared with lower intakes, a 27% lower risk of fatal IHD was seen up to a threshold of ~250 mg/d (RR: 0.73; 95% CI: 0.62, 0.86) (Figure 4, bottom right).

Evaluation of publication bias

Egger's and Begg's tests suggested no evidence of publication bias for associations of circulating magnesium with CVD or fatal IHD ($P > 0.05$). Egger's test was significant for circulating magnesium and IHD ($P = 0.01$); meta-regression did not identify any statistically significant sources of heterogeneity for this outcome, but power was limited. Visual inspection of funnel plots showed asymmetry for the association of circulating magnesium with CVD (*see* Supplemental Figure S2 under "Supplemental data" in the online issue), explained by heterogeneity due to stronger associations ($P = 0.02$) in studies that included participants with prevalent CVD at baseline and that evaluated fatal IHD (*see* Supplemental Figure S3 under "Supplemental data" in the online issue). For dietary magnesium, no evidence of publication bias was seen for IHD or fatal IHD ($P > 0.05$). Egger's test was significant for dietary magnesium and CVD ($P < 0.001$), consistent with observed funnel plot asymmetry (*see* Supplemental

Figure S4 under "Supplemental data" in the online issue). Duval and Tweedie's rank-based "trim and fill" method identified a "missing" small beneficial study. Addition of this hypothetical missing study (*see* Supplemental Figure S5 under "Supplemental data" in the online issue) did not appreciably alter the results, with a corrected pooled RR for dietary magnesium and CVD of 0.87 (95% CI: 0.74, 1.03) in comparison with the original pooled RR of 0.89 (95% CI: 0.75, 1.05).

DISCUSSION

This systematic review and meta-analysis identified significant associations of both circulating and dietary magnesium and risk of CVD events. Circulating magnesium (per 0.2-mmol/L increment) was associated with a 30% lower risk of CVD, with trends toward a lower risk of IHD and fatal IHD. Dietary magnesium was associated with a 22% lower risk of IHD and showed a nonlinear association with fatal IHD, with a 27% lower risk up to a threshold of ~250 mg/d, compared with lower intakes. This investigation, which included a total of 313,041 individuals in whom 4106 CVD, 3215 IHD, and 1528 fatal IHD events were documented for circulating magnesium and 7889 CVD, 4319 IHD, and 1158 fatal IHD events for dietary magnesium, provides the most robust evidence to date of the associations between circulating and dietary magnesium across their usual physiologic ranges and CVD risk.

Circulating magnesium

Our finding of a significantly inverse association between circulating magnesium and incident CVD is supported by evidence from observational studies and small intervention trials showing that magnesium may improve vascular tone and endothelial function, reduce platelet aggregation, increase HDL, improve glucose homeostasis (1, 37), and lower the risk of stroke (38, 39). On the basis of the key role of magnesium in ion channel function and arrhythmias, we hypothesized that associations of circulating magnesium concentrations would be strongest for fatal IHD events. Consistent with this, we identified a trend toward a 39% lower risk of fatal IHD, and, in post hoc analyses, a 57% lower risk of SCD. Whereas the number of studies were limited for fatal IHD, these findings suggest that circulating magnesium may influence arrhythmic risk at concentrations above the clinically low range (hypomagnesemia, <0.65 mmol/L) (3). Because observational studies cannot establish causality, randomized controlled trials are needed to test this hypothesis.

Our results also indicate a need to better understand the determinants of magnesium concentrations in blood. Circulating magnesium is under close homeostatic regulation, primarily through renal reabsorption and excretion (8), although the determinants of variation within the normal physiologic range are not well understood. For example, genetic variations in single nucleotide polymorphisms may account for <2% of the variance in serum magnesium concentrations (40), and our understanding of the influence of endocrine factors on magnesium homeostasis is incomplete (41). Circulating concentrations are responsive to supplementation and long-term changes in intakes (4, 5, 37); however, the correlation between dietary intake and circulating concentrations is low (12, 16), which highlights the importance of other important regulatory and homeostatic mechanisms.

Dietary magnesium

Our meta-analysis of dietary magnesium and total IHD updates a previous pooled estimate published by Song et al in 2005 (7) by including estimates from the Japan Collaborative Cohort Study and Nurses' Health Study cohorts and, for the first time, reports on the association between dietary magnesium and total CVD and fatal IHD. Findings from 2 small randomized controlled trials showing development of arrhythmias at low dietary magnesium intakes (4, 5) are broadly consistent with our meta-analysis result of a significantly lower risk of fatal IHD up to a dietary magnesium intake threshold of ~250 mg/d. In these trials, restriction of dietary magnesium in healthy postmenopausal to less than half (101–130 mg) of the RDA induced atrial arrhythmias and supraventricular beats. During the magnesium-restriction phase, calcium, potassium, copper, and other nutrients were supplemented to determine the direct effect of low magnesium intake, and arrhythmias were relieved by provision of 200 mg Mg/d through supplementation.

Dietary magnesium was not significantly associated with CVD in our analysis, although a recent meta-analysis of prospective studies showed a modest significant inverse association between dietary magnesium and risk of stroke, particularly ischemic stroke (10). Taken together, these results may suggest mechanistic pathways specific to stroke that are not captured in a more heterogeneous endpoint of CVD. Evidence from large prospective studies examining the association of dietary magnesium with incident hypertension have been inconsistent (42), and additional experimental evidence is needed to elucidate the potential effects of inadequate magnesium intake, at usual consumption levels, on components of CVD risk.

Overall, our findings support the importance of adequate dietary magnesium for lowering IHD risk. Dietary magnesium intakes among most American adults are low; the estimated magnesium intake from food sources in 2005–2006 was 261 mg in women and 347 mg in men (43), which is well below the RDA (320 mg for women and 420 mg for men). In elderly Americans (>70 y), 70% of men and 80% of women consume less than the Estimated Average Requirement for magnesium (43). Because nearly all the dietary magnesium in the identified studies was from foods, our findings support recommendations to increase consumption of magnesium-rich foods rather than to take supplements. An increased consumption of magnesium-rich foods, such as whole grains, nuts, and vegetables (by 1 serving/d for whole grains and vegetables and by 2 servings/wk for nuts), has been estimated to lower the risk of cardiovascular mortality by 28% (44).

Strengths

In the absence of any large randomized controlled trials to increase circulating magnesium concentrations or magnesium intake for the prevention of cardiovascular events, our data derived from a systematic search and meta-analysis of prospective studies provide the best available evidence of how circulating and dietary magnesium may influence CVD risk. Our comprehensive search methods and contacts with authors made it unlikely that any major published report was missed. By combining all available data across all categories of exposure in each study, we increased the validity of the dose-response estimates, maximized statistical

power, and were able to evaluate potential nonlinear associations. We separately evaluated CVD, IHD, and fatal IHD, which mechanistically differ and on which magnesium may plausibly have different effects. We limited our analysis to prospective cohorts or case-control studies nested within such cohorts, which greatly limited the possibility of selection bias or recall bias. We also limited our analysis to studies that used established analytic methods for measuring circulating magnesium. Disease outcomes in these studies were typically classified by using standardized algorithms and detailed records, which reduced the likelihood of misclassified outcomes. The findings were generally consistent regardless of whether random effects or fixed models were used and in various sensitivity analyses accounting for potential publication bias.

Limitations

Our findings were constrained by the availability of published or unpublished data on magnesium-CVD associations. Although we contacted many authors to obtain potential unpublished risk estimates, none were recovered. For several outcomes, the number of separate studies were limited to examine heterogeneity. Misclassification, residual confounding, and reverse causation may bias observational studies. Dietary magnesium was assessed by using food-frequency questionnaires or 24-h dietary recalls, which do not capture magnesium intake from drinking water and thereby underestimate total magnesium intake. However, this source of nondifferential misclassification would likely attenuate findings toward the null and underestimate the magnitude of the true associations. Only a few circulating magnesium studies (16, 20, 24) adjusted for glomerular filtration rate; although most participants in these cohorts were generally healthy, unrecognized differences in renal function could be a source of residual confounding for circulating magnesium. Furthermore, because of the high correlation between dietary magnesium and dietary potassium in some studies (12, 26), we cannot exclude the possibility of residual confounding by dietary potassium in our dietary magnesium analyses. The potential for reverse causation should be considered because circulating magnesium concentrations can be influenced by intake of specific medications that were not adjusted for in cohort analyses (eg, omeprazole) (45). Finally, we did not examine associations of magnesium and stroke as a distinct outcome. Circulating and dietary magnesium in some ways represent relatively distinct exposures, given the homeostatic regulation of the former and their low intercorrelation; thus, the significant associations observed for both biomarker and dietary magnesium with cardiovascular outcomes was reassuring. Nonetheless, randomized trials are needed to definitively elucidate whether magnesium is causally related to CVD risk.

Conclusions

Circulating magnesium was significantly associated with a lower risk of CVD, with trends toward a lower risk of IHD and fatal IHD. Dietary magnesium was associated with a significantly lower risk of IHD and showed a nonlinear association with fatal IHD. Our findings support the importance of dietary recommendations to increase magnesium-rich foods, including whole grains, nuts/seeds, and vegetables, which are also good sources of other nutrients. Additional experimental studies and randomized trials are needed to elucidate the roles of circulating and dietary magnesium, at usual physiologic concentrations and intakes, on CVD risk.

We thank the following authors for clarifying data in their published manuscripts and/or providing additional unpublished data: Earl Ford, Aaron Folsom, Thorston Reffelmann, Christine Albert, and Jennifer Nettleton.

The authors' responsibilities were as follows—LD and DM: designed the research; LD, FI, JHYW, MCdOO, and SEC: conducted the research; LCD, FI, and JHYW: analyzed the data; LCD: drafted the manuscript; FI, JHYW, MCdOO, SEC, and DM: made critical revisions to the manuscript for important intellectual content; and DM: provided funding. All authors read and approved the final manuscript. DM reported ad hoc consulting fees from McKinsey Health Systems Institute (November 2011) and Foodminds (January 2012) (modest) and ad hoc travel reimbursement and/or honoraria for one-time scientific presentations on diet and cardiometabolic diseases from SPRIM (November 2009), Nutrition Impact (September 2010), the International Life Sciences Institute (12/10), Bunge (November 2011), Pollock Institute (March 2012), and Quaker Oats (April 2012) (modest). DM reported involvement in the Unilever North America Scientific Advisory Board. None of the authors reported a conflict of interest. The supporting agencies had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

REFERENCES

1. Shechter M. Magnesium and cardiovascular system. Magnes Res 2010; 23:60–72.
2. Mubagwa K, Gwanyanya A, Zakharov S, Macianskiene R. Regulation of cation channels in cardiac and smooth muscle cells by intracellular magnesium. Arch Biochem Biophys 2007;458:73–89.
3. AHA (ECC Guidelines). Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care, Part 8: Advanced challenges in resuscitation: Section 1: Life-threatening electrolyte abnormalities. Circulation 2000;102:I217–22.
4. Klevay LM, Milne DB. Low dietary magnesium increases supraventricular ectopy. Am J Clin Nutr 2002;75:550–4.
5. Nielsen FH, Milne DB, Klevay LM, Gallagher S, Johnson L. Dietary magnesium deficiency induces heart rhythm changes, impairs glucose tolerance, and decreases serum cholesterol in postmenopausal women. J Am Coll Nutr 2007;26:121–32.
6. Nielsen FH, Milne DB, Gallagher S, Johnson L, Hoverson B. Moderate magnesium deprivation results in calcium retention and altered potassium and phosphorus excretion by postmenopausal women. Magnes Res 2007;20:19–31.
7. Song Y, Manson JE, Cook NR, Albert CM, Buring JE, Liu S. Dietary magnesium intake and risk of cardiovascular disease among women. Am J Cardiol 2005;96:1135–41.
8. Arnaud MJ. Update on the assessment of magnesium status. Br J Nutr 2008;99:S24–36.
9. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. JAMA 2000; 283:2008–12.
10. Larsson SC, Orsini N, Wolk A. Dietary magnesium intake and risk of stroke: a meta-analysis of prospective studies. Am J Clin Nutr 2012;95: 362–6.
11. Zhang W. Point of care testing of ionized magnesium in blood with potentiometric sensors—opportunities and challenges. Am J Biomed Sci 2011;3:301–12.
12. Liao F, Folsom AR, Brancati FL. Is low magnesium concentration a risk factor for coronary heart disease? The Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 1998;136:480–90.
13. Peacock JM, Ohira T, Post W, Sotoodehnia N, Rosamond W, Folsom AR. Serum magnesium and risk of sudden cardiac death in the Atherosclerosis Risk in Communities (ARIC) Study. Am Heart J 2010;160: 464–70.
14. Abbott RD, Ando F, Masaki KH, Tung KH, Rodriguez BL, Petrovitch H, Yano K, Curb JD. Dietary magnesium intake and the future risk of coronary heart disease (the Honolulu Heart Program). Am J Cardiol 2003;92:665–9.

15. 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.
16. Chiuve SE, Korngold EC, Januzzi JL Jr, Gantzer ML, Albert CM. Plasma and dietary magnesium and risk of sudden cardiac death in women. Am J Clin Nutr 2011;93:253–60.
17. Elwood PC, Fehily AM, Ising H, Poor DJ, Pickering J, Kamel F. Dietary magnesium does not predict ischaemic heart disease in the Caerphilly cohort. Eur J Clin Nutr 1996;50:694–7.
18. Ford ES. Serum magnesium and ischaemic heart disease: findings from a national sample of US adults. Int J Epidemiol 1999;28:645–51.
19. Kaluza J, Orsini N, Levitan EB, Brzozowska A, Roszkowski W, Wolk A. Dietary calcium and magnesium intake and mortality: a prospective study of men. Am J Epidemiol 2010;171:801–7.
20. Khan AM, Sullivan L, McCabe E, Levy D, Vasan RS, Wang TJ. Lack of association between serum magnesium and the risks of hypertension and cardiovascular disease. Am Heart J 2010;160:715–20.
21. Leone N, Courbon D, Ducimetiere P, Zureik M. Zinc, copper, and magnesium and risks for all-cause, cancer, and cardiovascular mortality. Epidemiol 2006;17:308–14.
22. Marniemi J, Järvisalob J, Toikkaa T, Räihä I, Ahotupa M, Sourander L. Blood vitamins, mineral elements and inflammation markers as risk factors of vascular and non-vascular disease mortality in an elderly population. Int J Epidemiol 1998;27:799–807.
23. de Oliveira Otto MC, Alonso A, Lee DH, Delclos GL, Bertoni AG, Jiang R, Lima JA, Symanski E, Jacobs DR Jr, Nettleton JA. Dietary intakes of zinc and heme iron from red meat, but not from other sources, are associated with greater risk of metabolic syndrome and cardiovascular disease. J Nutr 2012;142:526–33.
24. Reffelmann T, Ittermann T, Dörr M, Völzke H, Reinthaler M, Petersmann A, Felix SB. Low serum magnesium concentrations predict cardiovascular and all-cause mortality. Atherosclerosis 2011;219:280–4.
25. Reunanen A, Knekt P, Marniemi J, Mäki J, Maatela J, Aromaa A. Serum calcium, magnesium, copper and zinc and risk of cardiovascular death. Eur J Clin Nutr 1996;50:431–7.
26. Zhang W, Iso H, Ohira T, Date C, Tamakoshi A; JACC Study Group. Associations of dietary magnesium intake with mortality from cardiovascular disease: the JACC study. Atherosclerosis 2012;221: 587–95.
27. Hayden JA, Côté P, Bombardier C. Evaluation of the quality of prognosis studies in systematic reviews. Ann Intern Med 2006;144:427–37.
28. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata J 2006;6: 40–57.
29. Symons MJ, Moore DT. Hazard rate ratio and prospective epidemiological studies. J Clin Epidemiol 2002;55:893–9.
30. Higgins JP, Thompson S. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
31. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–634.
32. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
33. Duval S, Tweedie R. Trim and fill: a simple funnel plot based method of testing and adjusting for publication bias in meta-analysis. Biometrics 2000;56:455–63.
34. Lowenstein FW, Stanton MF. Serum magnesium levels in the United States, 1971-1974. J Am Coll Nutr 1986;5:399–414.
35. Tietz NW. Clinical guide to laboratory tests. Philadelphia, PA: WB Saunders, 1990.
36. Institute of Medicine (IOM). Dietary Reference Intakes for calcium, phosphorus, magnesium, vitamin D, and fluoride. Washington, DC: National Academies Press, 1997.
37. Song Y, He K, Levitan EB, Manson JE, Liu S. Effects of oral magnesium supplementation on glycaemic control in Type 2 diabetes: a meta-analysis of randomized double-blind controlled trials. Diabet Med 2006;23:1050–6.
38. Ohira T, Peacock JM, Iso H, Chambless LE, Rosamond WD, Folsom AR. Serum and dietary magnesium and risk of ischemic stroke: the Atherosclerosis Risk in Communities Study. Am J Epidemiol 2009; 169:1437–44.
39. Amighi J, Sabeti S, Schlager O, Mlekusch W, Exner M, Lalouschek W, Ahmadi R, Minar E, Schillinger M. Low serum magnesium predicts neurological events in patients with advanced atherosclerosis. Stroke 2004;35:22–7.
40. Meyer TE, Verwoert GC, Hwang S-J, Glazer NL, Smith AV, van Rooij FJ, Ehret GB, Boerwinkle E, Felix JF, Leak TS, et al. Genome-wide association studies of serum magnesium, potassium, and sodium concentrations identify six loci influencing serum magnesium levels. PLoS Genet 2010;6:e1001045.
41. Saris NE, Mervaala E, Karppanen H, Khawaja JA, Lewenstam A. Magnesium: an update on physiological, clinical and analytical aspects. Clin Chim Acta 2000;294:1–26.
42. Song Y, Sesso HD, Manson JE, Cook NR, Buring JE, Liu S. Dietary magnesium intake and risk of incident hypertension among middle-aged and older US women in a 10-year follow-up study. Am J Cardiol 2006;98:1616–21.
43. Moshfegh A, Golman J, Auhja J, Rhodes D, Lacomb R. What we eat in America, NHANES 2005-2006: usual intakes from food and water compared to 1997 Dietary Reference Intakes for vitamin D, calcium, phosphorus and magnesium. Washington, DC: US Department of Agriculture, Agricultural Research Service, 2009.
44. Mozaffarian D, Capewell S. United Nations' dietary policies to prevent cardiovascular disease. BMJ 2011;343:d5747.
45. Hess MW, Hoenderop JG, Bindels RJM, Drenth JPH. Systematic review: hypomagnesaemia induced by proton pump inhibition. Aliment Pharmacol Ther 2012;36:405–13.