Dose-response relationship between dietary magnesium intake and cardiovascular mortality: A systematic review and dose-based meta-regression analysis of prospective studies

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ARTICLE INFO

ABSTRACT

Background: Although epidemiology studies have reported the relationship, including a dose-response relationship, between dietary magnesium intake and risk of cardiovascular disease (CVD), the risk for CVD mortality is inconclusive and the evidence for a dose-response relationship has not been summarized.
Objective: We conducted a systematic review and meta-analysis of prospective studies to summarize the evidence regarding the association of dietary magnesium intake with risk of CVD mortality and describe their dose-response relationship.
Design: We identified relevant studies by searching major scientific literature databases and grey literature resources from their inception to August 2015, and reviewed references lists of retrieved articles. We included population-based studies that reported mortality risks, i.e. relative risks (RRs), odds ratios (ORs) or hazard ratios (HRs) of CVD mortality or cause-specific CVD death. Linear dose-response relationships were assessed using random-effects meta-regression. Potential nonlinear associations were evaluated using restricted cubic splines.
Results: Out of 3002 articles, 9 articles from 8 independent studies met the eligibility criteria. These studies comprised 449,748 individuals and 10,313 CVD deaths. Compared with the lowest dietary magnesium consumption group in the population, the risk of CVD mortality was reduced by 16% in women and 8% in men. No significant linear dose-response relationship was found between increment in dietary magnesium intake and CVD mortality across all the studies. After adjusting for age and BMI, the risk of CVD mortality was reduced by 24–25% per 100 mg/d increment in dietary magnesium intake in women of all the participants and in all the US participants.
Conclusion: Although the combined data confirm the role of dietary magnesium intake in reducing CVD mortality, the dose-response relationship was only found among women and in US population.

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Contents

1. Introduction

Magnesium, an essential mineral for the human body, affects many cellular functions, including signal transduction, energy metabolism and cell proliferation. Acting as a coenzyme in ATP-dependent reactions and in the production and transport of energy and proteins, it regulates diverse biochemical reactions in the body, including protein synthesis, muscle and nerve function, blood glucose control, and blood pressure regulation [1–3]. Magnesium is naturally present in many foods such as vegetables, fruits, legumes and nuts. In the United States (US), the recommended daily intake of magnesium for adults is 310–320/360–400 mg for women/pregnant women and 400–420 mg for men [4]. Recently, an observational study conducted in adults in North America suggested that the recommendations for women should be the same as for men [5]. However, dietary surveys conducted in the United States consistently show that intake of magnesium is lower than recommended [6]. Habitually low intake of magnesium induces changes in biochemical pathways that can increase the risk of illness such as hypertension and cardiovascular disease, type 2 diabetes, osteoporosis, and migraine headaches [7]. The important role of magnesium in the etiology of cardiovascular pathology has been pointed out by a considerable number of experimental [8–10], epidemiological [11–14] and clinical studies [15–17]. Increased magnesium intake appears to have a favorable influence on heart disease and its risk factors, including diabetes mellitus [18], hypertension [19], and metabolic syndrome [20], but also in heart disease [11]. However, controversy still remains as to whether there is an inverse relationship of magnesium intake with cardiovascular disease (CVD) mortality. A pooled analysis shows that magnesium intake does not have an inverse relationship with CVD mortality [21]. But a protective effect of magnesium intake against CVD mortality risk was observed in females (RR = 0.71; 96% CI = 0.60, 0.84) in another meta-analysis for prospective cohort studies [22]. Taken together, the epidemiologic evidence on the relationship between dietary magnesium intake and risk of CVD mortality has not yet been conclusive, and the dose-response relations have not yet been summarized. Therefore, we performed a systematic review and meta-analysis of prospective population-based studies to assess the association of dietary magnesium intake with risk of CVD mortality. On the basis of available mechanistic evidence, we hypothesized that there would be an inverse dose-response relation between dietary magnesium and CVD mortality.

2. Methods

2.1. Search and screening

We followed the standard criteria PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) and MOOSE (Meta-analysis of Observational Studies in Epidemiology) [23,24]. The review was registered in PROSPERO-international prospective register of systematic reviews http://www.crd.york.ac.uk/prospero/ (registration number. CRD42015023447). We conducted a systematic review for all prospective population-based studies that evaluated the dose-response association of dietary magnesium intake with CVD mortality. We searched Pubmed (http://www.ncbi.nlm.nih.gov/), Web of Science (http://webofscience.com/), ScienceDirect (http://www.sciencedirect.com/) and China Knowledge Resource Integrated Database (http://oversea.cnki.net/kns55/default.aspx), Epidemiology and Prevention/Lifestyle and Cardiometabolic Health conference abstracts (http://circ.ahajournals.org/content/131/Suppl_1) and the Cochrane Library (http://www.cochranelibrary.com/) from their inception to August 2015. The later cut-off date was subsequently revised to include the latest published studies. To avoid publication bias, we also used the Resources for Searching the Grey Literature provided by the Duke University (http://guides.mclibrary.duke.edu/c.php?g=158169&p=1035999), the System for Information on Grey Literature in Europe (http://www.opengrey.eu/), Grey Literature Report (www.greylit.org) to find potential unpublished relevant studies. Key search terms included dietary, magnesium intake, cardiovascular disease, CVD, heart disease, cohort, nested case-control, case cohort, prospective, longitudinal, combined with death, and mortality. These searches were supplemented by hand-searching of the reference lists of identified research articles or relevant reviews. No language restrictions were imposed.

2.2. Inclusion criteria

We only included original research in this meta-analysis. Reviews, editorials, commentaries, letters were not eligible. All prospective studies (cohort, nested case-control, case cohort or community-based interventional studies) were included if they fulfilled the following criteria: (1) had a population-based study design (2) the dietary magnesium intake was reported (3) the endpoint of interest included all kinds of CVD death or cause-specific CVD death (4) the mortality risk was reported such as relative risk (RR), odds ratio (OR) or hazard ratio (HR), as well as the corresponding 95% confidence interval (CI) or other data to estimate the variance or accuracy (standard deviation or standard

error) were reported (5) the risk assessment had to be adjusted for potential confounding variables or by other forms of standardization (if applicable). For multiple studies using the same population, only the study with the largest number of events or with additional diagnostic categories was included. We excluded the studies that focused on the populations with disrupted mineral homeostasis (such as patients with heart failure or kidney disease). We also excluded the studies that focused on children, evaluated magnesium only in drinking water or had no reliable magnesium estimates. For included studies only in abstract form, we tried to contact with authors to get necessary estimates or risks and relevant accuracy.

2.3. Identification of articles

Computerized bibliographic searches of pre-determined literature databases used an optimized version of the Cochrane Collaboration search strategy [25]. Three investigators (XF, CL and ML) screened all the identified titles and abstracts for relevance (n = 3,002). Full papers were downloaded for all the abstracts judged potentially relevant (n = 18). All papers identified through the screening process were assessed for relevance independently by two investigators (CL and ML) using standardized study assessment and sorting form. The studies were evaluated and scored based on the guidelines adapted from the tools for assessing quality and susceptibility to bias in observational studies in epidemiology [26]. Points were summed for the quality criteria and inter-rater agreement was substantial (Cohen κ > 0.6) [27].

No new studies were identified among the cited references of all included articles. Of 18 full-text articles reviewed independently, 9 studies were excluded because no dose of magnesium intake was reported (n = 3); dietary magnesium was measured in water (n = 3), or they were reviews (n = 3). No studies were excluded by the quality assessment. In total, 9 studies met the inclusion criteria and were included in the meta-analysis. Initial searches were completed for the period up to and including August 31, 2015. Pubmed and other literature databases were searched again in October, 2015 for any studies that could have appeared since our final analyses were completed. No new studies were identified.

2.4. Data extraction

Full papers were obtained for all abstracts judged potentially relevant. Data extraction was conducted independently by 2 investigators (XF and ML) with the use of a standardized electronic form in Microsoft Excel.

The following data were extracted from each study: first author's last name, study design, location, years of study started, finished and published, age, sex, ethnicity, sample size (number of cases, controls, exposed, unexposed and total participants), baseline disease (CVD, kidney disease or diabetes mellitus), magnesium intake modes and doses, and covariates adjusted for in multivariable analysis. For dietary magnesium, data on assessment method used (food frequency questionnaire, dietary recall, other) and whether the data were energy-adjusted (yes, no) were obtained.

For each study, the median magnesium intake for each category was assigned to each corresponding RR/HR/OR. When the median intake per category was not provided, we assigned the midpoint of lower and upper boundaries in each category as the average intake. If the lower or upper boundary for the lowest or highest category, respectively, was not reported, we assumed that the boundary has the same amplitude as the closest category.

For each level of exposure, we extracted the median dose and RR/OR/HR with its measure of uncertainty (standard error) or variance (95% CI). Risk estimates for continuous exposure were also extracted. If estimates were presented for more than one multivariate model, we only extracted estimates from the model with adjustment for fewer factors to avoid potential collinearity between covariates and allow for the homogeneity of included studies. For studies presenting multiple cardiovascular outcomes with shared cases, the outcomes with the most cases was used for the pooled analysis.

2.5. Statistical analysis

Mathematically, when event rates are small, and the relative risks are close to unity, the HR, OR and RR approximate one another and usually the HR falls between the RR and OR. Thus, we used ORs and RRs as HRs in our pooled analysis [28,29]. HRs for different increments of magnesium intake can be calculated from our data. We estimated a pooled risk with 95% CI for a 100 mg/day increase in dietary magnesium intake for the studies. To maximize all the data for calculating the pooled dose-response, the restricted maximum likelihood (REML) approach proposed by Harbord, which provides improved estimation of the between-study variance, was used to compute the linear trend of the log transformed risk estimates across magnesium intake doses [30].

We performed subgroup analysis for different magnesium intake levels, sex and geographic area. We calculated combined HRs for subtype-specific CVDs, i.e. coronary heart disease (CHD), heart failure and stroke, given in individual studies to assess potential effect modification. If the study reported both total and subtype CVD mortality, total mortality was used in the main analysis while subtype mortality was used in subgroup analysis. If the study only reported subtype mortality, it was used in both main and subgroup analysis. We also conducted a sensitive analysis to investigate the influence of a single study on the overall risk estimate by dropping one study in each turn.

Because the Q statistic has low power as a comprehensive test of heterogeneity when the number of studies is small [31], the I^2 statistic, a quantitative measure of inconsistency, was calculated instead of Q to evaluate the statistical heterogeneity across the studies [32]. $I^2 > 30\%$ was considered at least moderate heterogeneity. In view of substantial heterogeneity being detected, we presented the pooled estimates based on the random effects model.

Potential publication bias was assessed by Egger's test. Because the sample sizes of reference groups and comparative groups were balanced in all the studies, we used Harbord's modification to Egger's test to reduce the false positive rate [33].

Potential nonlinear associations were assessed using restricted cubic splines; we used 3 knots at fixed percentiles 10%, 50% and 90% of the distribution [34]. The dose-specific estimates were pooled by using the REML method in a random-effects meta-analysis [35].

We performed all analyses in Stata (version 13.1; StataCorp). A p value < 0.05 was considered statistically significant, except where otherwise specified.

3. Results

3.1. Study characteristics

Our literature search identified 9 articles from 8 independent studies that met the eligibility criteria (Fig. 1) [11,12,14,21,36–40]. These studies were published between 2005 and 2014 and comprised 449,748 individuals and 10,313 CVD deaths (Table 1). Five studies were conducted in the US, two in Europe and another two in Asia. Most excluded individuals with prevalent CVD (6 of 9) and cancer (6 of 9) at baseline. Five studies also excluded participants with implausible energy intake, and one excluded participants using any type of dietary supplements. Participants were

Table 1

Characteristics of 9 cohort studies providing risk estimates for dietary magnesium intake and CVD death.

| First author, year, study name (country)	No. of deaths (cohort size)	Years of follow-up	Sex, range of age at baseline (M = male, F = female)	Magnesium intake (mg/day) for the highest vs. the lowest category [HR (95% CI)]	Adjustments in basic model
Guasch-Ferré, 2014, PREDIMED, (Spain)	81 (7216)	4.8 y	M and F, 55–80 y	442 vs. 312 [0.51 (0.28, 0.95)]	Age, sex and intervention group
Deng, 2013, NHANES (US)	1615 (12257)	18 y	M and F, >17 y	420 vs. 225 [0.93 (0.84, 1.04)]	Serum vitamin D level
Dai, 2013, SMHS (China)	800 (61414)	5.5 y	M, 40–74 y	367 vs. 258 [0.83 (0.58, 1.20)]	Age, sex, body mass index(BMI), education, marriage status, smoking status, tea drinking,
Dai, 2013, SWHS (China)	1147 (73232)	11.0 y	F, 40–70 y	347 vs. 232 [1.35 (1.03, 1.77)]	Age, sex, BMI, education, marriage status, smoking status, tea drinking,
Levitan, 2013, WHI (US)	1433 (3340)	4.6 y	F, 50–79 y	408 vs. 199 [0.84 (0.72, 0.97)]	Age, total energy intake
Zhang, 2012, JACC (Japan)	1343 (23083)	14.7 y	M, 40–79 y	294 vs. 173 [0.91 (0.76, 1.08)]	Age, BMI, smoking status. Educational status, history of hypertension, menopausal status, etc.
Zhang, 2012, JACC (Japan)	1347 (35532)	14.7 y	F, 40–79 y	275 vs. 175 [0.76 (0.64, 0.90)]	Age, BMI, smoking status. Educational status, history of hypertension, etc.
Kaluza, 2010, Cohort of Swedish Men (Sweden)	819 (23366)	10.0 y	M, 45–79 y	523 vs. 387 [0.95 (0.80, 1.13)]	Age, waist-hip-ratio, education, smoking status, physical activity, alcohol consumption, etc.
Chiuve, 2013, NHS (US)	1103 (86323)	28 y	F, 30–55 y	342 vs. 246 [0.58 (0.48, 0.70)]	Age
Chiuve, 2011, NHS (US)	505 (88375)	26 y	F, 30–55 y	383 vs. 235 [0.62 (0.48, 0.79)]	Age
Song, 2005, WHS (US)	120 (35610)	10 y	F, 39–89 y	433 vs. 255 [1.11 (0.61, 2.00)]	Age, treatment assignment
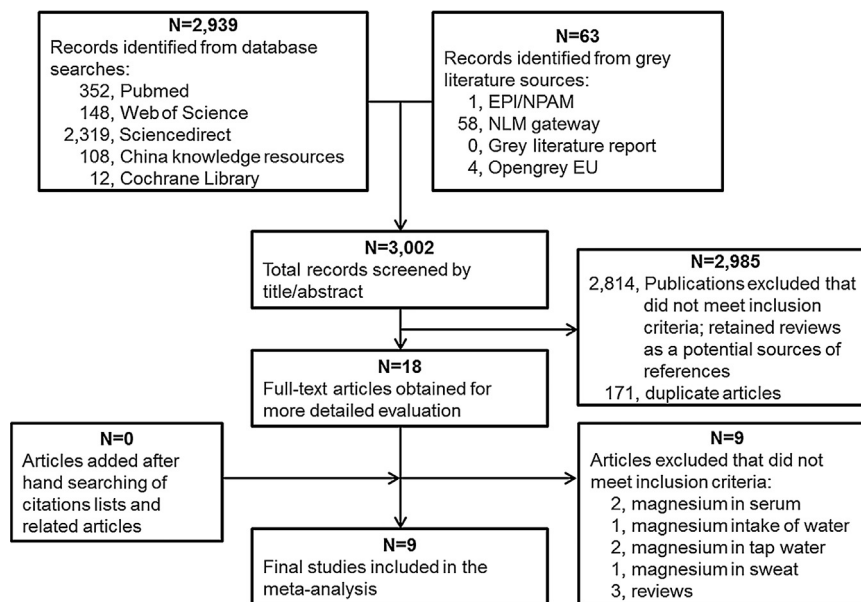
Fig. 1. Screening and selection of articles on dietary magnesium intake and risk of CVD mortality.

predominately middle-aged at baseline, with a mean age of 49.5 years and a mean BMI of 24.3 kg/m² across the studies (the average BMI of Swedish adult men was imputed by 24.1 [41]). The length of the follow-up period ranged from 5 to 28 years.

Dietary intake of magnesium was evaluated by food frequency questionnaires (FFQs) in all the studies. Five studies reported on sources of magnesium intake from multivitamin or supplements but did not report on the contribution of the supplemental intake to the total intake. The median magnesium intake of the different dose groups ranged from 173 mg/d in Japanese men (much lower than the US Recommended Dietary Allowance of 400 mg/d for men and 310 mg for women >30 years [4]) to 523 mg/d in Swedish men.

All the studies adopted international classification of disease (ICD) in outcome assessment. Six studies provided risk estimates for all CVD deaths whereas two studies only provided the risk estimates for deaths from coronary heart disease (CHD), heart failure and sudden cardiac death. All the studies except one provided risk estimates that were adjusted for age in the basic model. Although the degree of covariate and confounder adjustment varied in advanced models, most studies adjusted for body mass index (BMI) or waist-to-hip ratio, total energy intake, smoking, alcohol intake, physical activity and education attainment in the multivariate model; fewer studies adjusted for intake of calcium and other nutrition supplement.

3.2. Dietary magnesium intake and CVD mortality

The heterogeneity was found across the doses. The overall combined HR was 0.86 (95% CI: 0.81, 0.91) with $I^2 = 62.4\%$ (p < 0.001). However, the approximately symmetric Egger's funnel plot indicates a moderate homogeneity among the doses categories (Fig. 2), and no evidence of publication bias among studies was observed (Egger's p = 0.547, Begg's p = 0.126 and Harbord's p = 0.167). We divided the increment of dietary magnesium intake compared with the reference doses into three categories: <50 mg/d, 50–100 mg/d and >100 mg/d. The estimated HRs for CVD mortality of the included studies within each magnesium increment category and the combined HRs are shown in Fig. 3. The combined HRs for CVD mortality are 0.84 (95% CI: 0.74, 0.96), 0.84 (95% CI: 0.76, 0.92) and 0.90 (95% CI: 0.81, 0.99) for <50 mg/d, 50–100 mg/d and >100 mg/d
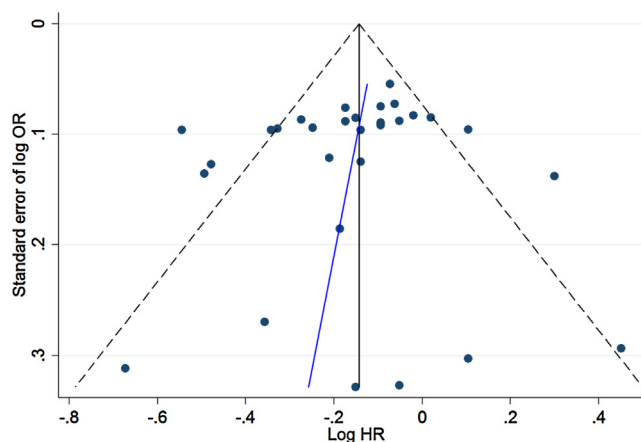

Fig. 2. Egger's funnel plot with pseudo 95% confidence limits.

subgroups respectively. In general, increased dietary magnesium was associated with reduced risk of CVD mortality by 10–16%.

The results of subgroup analyses are presented in Table 2. Statistically non-significant associations between dietary magnesium and risk of CVD mortality were found in two studies including both men and women (n = 19,437, combined HR = 0.77, 95% CI: 0.54, 1.09) and two studies conducted in Europe (n = 30,582, combined HR = 0.89, 95% CI: 0.74, 1.07). Inverse associations of dietary magnesium intake with CVD mortality were observed in sex-separated groups, US and Asian countries, and all CVD subtypes (Table 2).

No significant linear dose-response relationship between increased dietary magnesium intake and CVD mortality was found across the studies (see Fig. 4). The HRs of per 100 mg increment in dietary magnesium intake per day for CVD mortality were 0.98 (0.85, 1.13), 0.95 (0.75, 1.19) and 1.04 (0.82, 1.32) for all participants, women and men, respectively, and 1.00 (0.88, 1.14) and 1.01 (0.78, 1.29) for all CVD deaths and cause-specific deaths (heart failure, CHD or sudden cardiac death), respectively. After adjusting for age, BMI and other covariates, the statistically non-significant association was not modified for all studies (see Table 3). However, we found an inverse linear dose-response relationship among women (Table 3, Fig. 5) and in the US population (Table 3, Fig. 6).
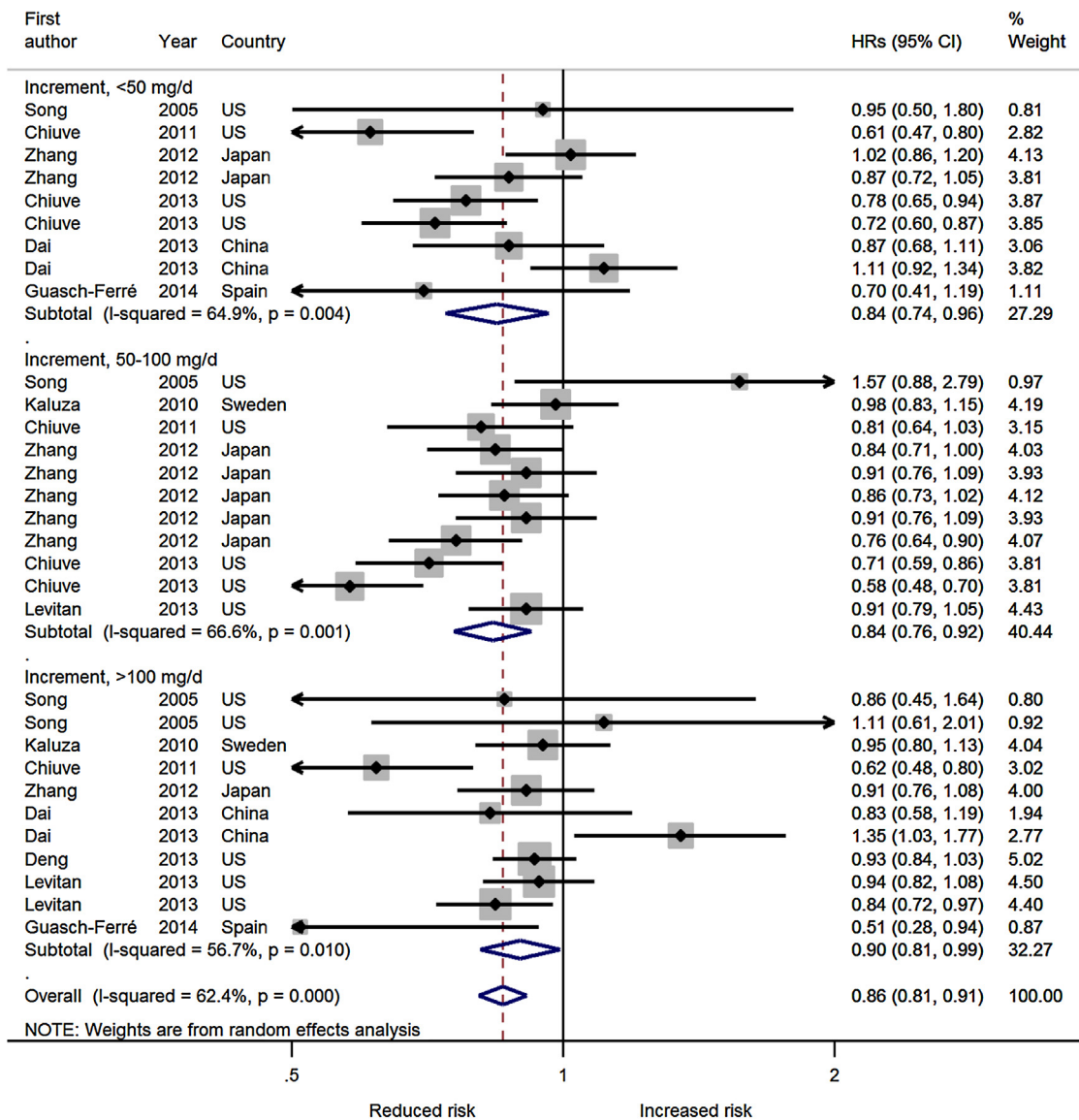
Fig. 3. Dose-based HRs for risk of CVD mortality for the higher vs. the lowest dietary magnesium intake group.

Table 2
Dose-based pooled HRs for increased dietary magnesium intake with risk of CVD mortality by sex, area and CVD subtypes.

Subgroup	No. of dose categories	HR (95% CI)	I² (%)	Heterogeneity-p
Sex				
Women	26	0.84 (0.77, 0.92)[a]	72.2	<0.001
Men	11	0.92 (0.86, 0.98)	0	0.979
Both women and men	5	0.77 (0.54, 1.09)[a]	56.0	0.103
Area				
US	20	0.80 (0.72, 0.88)[a]	68.2	<0.001
Europe	6	0.89 (0.74, 1.07)[a]	43.2	0.152
Asia	16	0.92 (0.85, 0.99)[a]	46/0	0.041
CVD subtypes				
All CVDs	29	0.92 (0.87, 0.98)[a]	32.2	0.078
Subtype-specific CVDs	13	0.74 (0.68, 0.84)[a]	69.6	0.001
CHD	5	0.69 (0.61, 0.79)[a]	42.6	0.156
Heart failure	4	0.90 (0.83, 0.98)	0	0.549
Sudden cardiac death	4	0.68 (0.56, 0.82)[a]	38.4	0.197

[a] Random effects model was used.

Table 3
Dose-based pooled HRs for risk of CVD mortality with an incremental increase of 100 mg/d in dietary magnesium intake, adjusted for age and BMI.

	No. of doses categories	I^2	HR (95% CI)	p-value
All studies[a]	38	69.55	1.01 (0.81, 1.26)	0.91
Women	20	50.25	0.75 (0.58, 0.99)	0.04
Men	11	0	0.98 (0.72, 1.34)	0.90
US	14	6.23	0.76 (0.59, 0.98)	0.04
Asia	16	0	1.15 (0.85, 1.55)	0.31
Europe[b]	6	0	0.83 (0.09, 7.53)	0.47
All CVDs	27	35.94	0.95 (0.79, 1.14)	0.56
Cause-specific CVDs	9	0	1.23 (0.54, 2.80)	0.49

[a] One study was excluded for both age and BMI were missing.
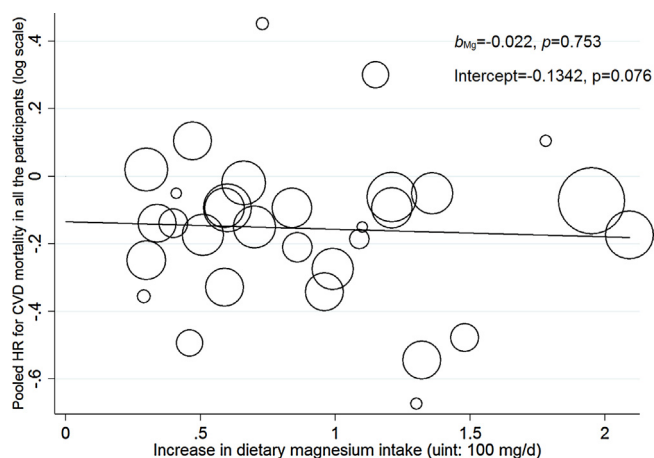[b] Only adjusted by age.

Fig. 4. Dose-response relationship between risk of CVD mortality and incremental increase in dietary magnesium intake (the size of the bubble reflects the study-specific analytical weight, i.e. the inverse of the variance).
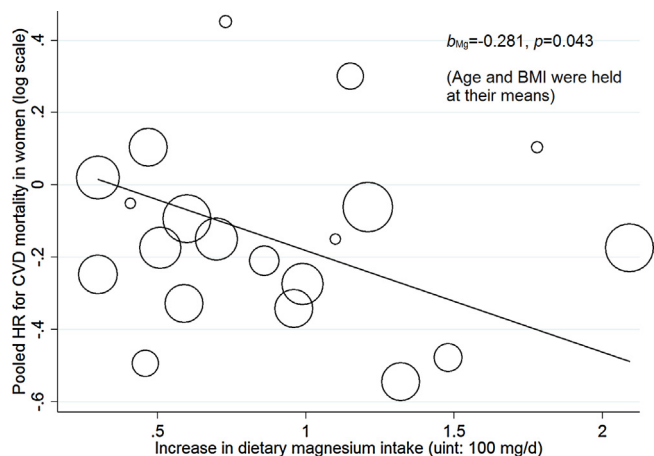

Fig. 6. Dose-response relationship between risk of CVD mortality and incremental increase in dietary magnesium intake in US population (the size of the bubble reflects the study-specific analytical weight, i.e. the inverse of the variance).

Fig. 5. Dose-response relationship between risk of CVD mortality and incremental increase in dietary magnesium intake in women (the size of the bubble reflects the study-specific analytical weight, i.e. the inverse of the variance).

Compared with the lowest intakes, we observed a 25–26% lower risk of CVD mortality per 100 mg increment in dietary magnesium up to 433 mg/d in women of all the participants and in all the US participants.

3.3. Sensitivity analysis

The sensitivity analysis omitting one study at a time when estimating the combined risk, yielded a relatively wide range of HRs for all the participants from 0.83 (95% CI: 0.69, 1.01) to 1.06 (95% CI: 0.77, 1.46). After excluding one study conducted in Spain[36],
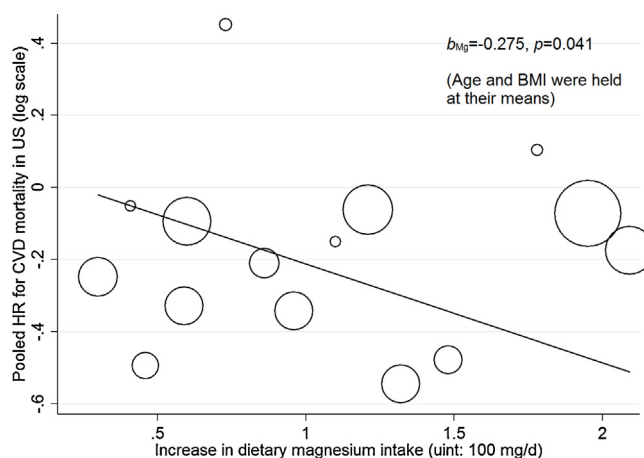
the association between increased dietary magnesium intake and CVD mortality was marginally significant (HR = 0.83, 95% CI: 0.69, 1.01; p = 0.06), which suggested a protective dose-response effect of dietary magnesium intake against CVD mortality. Excluding the study of Spain appears appropriate because the lowest intake was above the recommended dietary allowance. The sensitivity analysis yielded a narrow range of HRs for women from 0.71 (95% CI: 0.54, 0.92) to 0.79 (95% CI: 0.51, 1.23), which supports a constancy of trend in women. However, the findings for the US population were varied with HRs ranging from 0.71 (95% CI: 0.48, 1.03) to 1.22 (95% CI: 0.59, 2.49).

Since the dose-based effect synthesis was mainly based on one study [40], the pooled HR for men was essentially unchanged after excluding dose categories from another study. For non-US populations, the sensitivity analysis constantly resulted in non-significant results with a narrow range of HRs from 1.01 (95% CI: 0.79, 1.30) to 1.06 (95% CI: 0.86, 1.32).

3.4. Nonlinear association

We found no evidence of nonlinear associations between dietary magnesium intake and CVD mortality across all the studies (p = 0.540), in men (p = 0.896) and in non-US populations (p = 0.789). No nonlinear association was further found in women (p = 0.909) or in the US population (p = 0.423), which suggested that pooling of dose-response estimates from linear trend estimation for dietary magnesium and CVD mortality was appropriate.

4. Discussion

This meta-analysis of 9 prospective studies confirmed the inverse association between dietary magnesium intake and risk of

CVD mortality (HR = 0.86; 95%: 0.81, 0.91). Compared with the lowest dietary magnesium consumption groups in the populations, the risk of CVD mortality could be reduced by 16% in women and 8% in men (Table 2). The largest reduction of mortality risk was observed for sudden cardiac death (32%). No significant linear dose-response relationship, however, was found between increment in dietary magnesium intake and CVD mortality across all the studies, with or without adjusting for age and BMI. Still, after adjusting for age and BMI, we did find a statistically significant linear dose-response relationship of increased dietary magnesium intake with CVD mortality risk in women and in the US population. The risk of CVD mortality is associated with a reduction of 24–25% per 100 mg/d increment in dietary magnesium intake. This systematic review, which included a total of 449,748 participants and 10,313 CVD deaths, provides the most robust evidence to date of the dose-response relationship between dietary magnesium intake across its physiological range and risk of CVD mortality.

4.1. Dose-response effect of dietary magnesium intake on CVD mortality

The protective effects of magnesium intake against CVD incidence, mortality or arrhythmias after CVD have long been demonstrated and believed [13,21,42,43]. The inverse association between magnesium intake and CVD mortality may be partially explained by its effects on lowering blood pressure (BP), improving endothelial function, inhibiting inflammation and platelet aggregation [44,45]. Several mechanisms have been proposed for the potential cardiometabolic benefits of magnesium intake, including improvement of glucose and insulin homeostasis; antihypertensive, antiarrhythmic, anti-inflammatory, anticoagulant, or antiplatelet effects; improved lipid metabolism; reduced vascular contractility; and increased endothelium-dependent vasodilation [46]. However, regarding the beneficial dose of dietary magnesium, there is no conclusive evidence. For example, a recent meta-analysis of 3 trials randomizing 277 participants with 24–28 weeks of follow-up found no evidence that magnesium supplementation up to 360 mg/d reduced mortality, morbidity or BP in adults [47]. There is less evidence of dose-response relationship between dietary magnesium and risk of fatal and/or non-fatal CVDs. A pooled analysis indicated that magnesium intake was not associated with total CVD mortality (RR = 0.94, 95% CI: 0.78, 1.12) [22]. There were only three published systematic reviews that investigated the dose-response relationship between dietary magnesium intake and CVD risks. By combining results of 7 prospective studies, Larsson et al. observed a modest but statistically significant inverse association between magnesium intake and risk of stroke, especially of ischemic stroke [48]. An intake increment of 100 mg magnesium/d was associated with an 8% reduction in risk of total stroke. By combining 14 estimates of dietary magnesium of 11 studies, Del Gobbo et al. did not find a significant association between dietary magnesium (per 200 mg/d increment) and total CVD incidence (RR = 0.89, 95% CI: 0.75, 1.05) [49]. By combining 11 studies on dietary magnesium intake, Qu et al. found a statistically significant nonlinear inverse association between dietary magnesium intake and total CVD events risk [50]. However, none of the studies investigated the dose-response relationship between dietary magnesium intake and total CVD mortality, except for Del Gobbo's study, which found a nonlinear dose-response relationship with fatal ischemic heart disease (IHD) (RR = 0.73, 95% CI: 0.62, 0.86).

Although our meta-analysis did not find a statistically significant dose-response relationship between increased dose of dietary magnesium intake and total CVD mortality among all the participants, the dose-dependent inverse association observed in women is consistent with Xu's review [22], and the magnitude of the effect (25% reduction in risk of total CVD mortality) is comparable to those

from Xu's review (29% reduction in risk of total CVD mortality) and Del Gobbo's review (27% reduction in risk of fatal IHD).

The discrepant findings between women and men might be due to the influence of other factors than magnesium intake. For example, the influence of magnesium on CVD mortality in men may be attenuated by potentially higher exposure to other risk factors for CVD death such as smoking, alcohol and/or energy drinking among men; such exposures could accelerate CVD development and counteract the potentially protective influence of magnesium. Moreover, the high starting point of the lowest intake in the two studies in Spain and Sweden probably had an effect on not finding an association, which included many of the men and might affect the association within men. The discrepancy between the US population and non-US population needs further research. However, because the limited number of the included studies, the discrepancy may have been accidental and a chance finding cannot be ruled out.

It should be noted that our sensitivity analysis also revealed a variation in the associations among all the participants and among the US participants. The possible reason might be the relatively high degree of heterogeneity between the studies (I^2 = 69.55%) and the limited number of the studies included.

4.2. Strengths and limitations

The population-based evidence on whether increased magnesium intake may reduce CVD mortality is still sparse and inconsistent. To our knowledge, this study is the first meta-analysis that investigated the dose-response relationship between dietary magnesium intake and overall CVD mortality. It had several strengths. First, our data derived from a systematic review of prospective studies provide the best available evidence of how dietary magnesium intake may influence risk of CVD mortality. Because of the lagged and cumulative effects of exposure on outcome of chronic diseases, the dose-response relationship without reversed causality would be revealed only by prospective studies rather than cross-sectional or retrospective studies. In addition, the prospective studies also minimized recall and selection bias. Second, by combining all available doses in included studies across a wide range of exposure, we increased the validity of the dose-response estimates. Our studies included 42 dietary magnesium doses and 31 risk estimates, which enabled us to estimate the linear dose-response relationship and to model the nonlinear association with a high statistical power. Third, age and BMI were adjusted for in our meta-regression model and stratified analyses were used for sex, geographic areas and CVD subtypes, which reduced the potential confounding from demographic factors. Furthermore, the random-effected model considered the heterogeneity among studies, which resulted in a relatively conservative conclusion rather than exaggerated one. Fourth, disease outcomes in these studies were classified using standard algorithms and detailed medical records, which reduced the likelihood of misclassification.

However, some limitations warrant consideration. First, the preponderance of women and US population in the included studies limits the possible extrapolation of these results to other populations. Second, the magnesium intake in these studies were only assessed by FFQ, which do not capture the magnesium intake from drinking water and nutritional supplementation, and thereby might underestimate total magnesium intake and result in potential misclassification. However, the misclassification would most likely lead to an underestimated association. Third, influence of other nutrients or dietary components such as potassium [39], calcium [12] and vitamin D [37] that are correlated with dietary magnesium could not be excluded; other nutrients may have been responsible for the observed association partly or in whole. Finally, although weighted meta-regression takes account of both within-

study variances and the residual between-study heterogeneity (that is, heterogeneity not explained by the covariates in the regression) by adding random effects in the model, it is not reasonable to assume that all of the heterogeneity is explained [32,51]. Thus, we have to be cautious to interpret the combined results in view of the statistically significant heterogeneity presented in current analyses ($I^2 > 60\%$). Although the problem can be avoided by pre-specification of covariates that will be investigated as potential sources of heterogeneity, in practice this is not easy to achieve [51]. Use of magnesium in the prevention of CVD and related mortality needs to be investigated in further randomized controlled trials.

5. Conclusions

In conclusion, results from this meta-analysis confirm that dietary magnesium intake is associated with a reduced risk of CVD mortality. Although no significant linear dose-response relationship was identified among all the participants, an incremental increase of 100 mg/d in dietary magnesium intake was associated with one fourth reduction in risk of CVD mortality among women and in US population. No nonlinear dose-response relationship was found between increased dose of dietary magnesium intake and risk of CVD mortality. Although it is still premature to recommend the beneficial dose range for magnesium supplementation, recommending increased consumption of magnesium-rich food within the current reference dose of oral magnesium exposure appears prudent [52].

Author contributions

YC and JAa designed the research; YC provided study oversight and took primary responsibility for the final content of the manuscript; XF, CL, ML, undertook literature search, screening and data extraction; XF and YC performed statistical analysis; XF and CL drafted the manuscript; SM and KF revised the article critically; and all authors contributed to the manuscript writing, made critical revision, read and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

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