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Magnesium intake has inverse association with type 2 diabetes and total stroke: An updated systematic review and meta-analysis

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Abstract

Objective: The detailed associations between type 2 diabetes (T2D) and total stroke and magnesium intake should be timely updated. And, we keep requiring evidence of significant prevention of the two diseases. We conducted a systematic review and meta-analysis to quantify the association and to determine the dose-response relationships between magnesium intake and T2D and stroke.

Design: Systematic review search, methodology and meta-analyses.

Data sources: PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov.

Eligibility criteria: Prospective cohort studies about magnesium intake and risk of T2D or stroke.

Data synthesis: Relative risk (RR) and 95% confidence intervals (95% CI) were pooled for inclusion in random-effects models to calculate risk on T2D and stroke.

Results: Forty-one studies involving 53 cohorts were included. The magnitude of the risk was significantly reduced by 22% for T2D (RR, 0.78 [95% CI, 0.75-0.81]; $P<$ 0.001), 11%for total stroke (RR, 0.89 [95% CI, 0.83-0.94]; $P<$ 0.001), and 12% for ischemic stroke (RR, 0.88 [95% CI, 0.81-0.95];P = 0.001) comparing the highest magnesium intake to the lowest. The inverse association still existed when studies on T2D were adjusted for cereal fiber (RR, 0.79 [95% CI, 0.73-0.85]; $P<$ 0.001) and those on total stroke were adjusted for calcium (RR, 0.89 [95% CI, 0.80-0.99]; P = 0.040). Subgroup analyses suggested risk for total and ischemic stroke was significantly decreased in females, participants with ≥ 25 mg/m^2 body mass index,

and those with ≥ 12y follow-up, the reduced risk in Asia was not so conspicuous as in North America and Europe.

Conclusions: Magnesium intake has significantly inverse associations with T2D and total stroke in a dose-dependent manner. Specific populations may receive more benefits from magnesium–rich dietary pattern. Feasible costless dietary approach needs to be highlighted in the primary prevention of T2D and total stroke by the public.

Strength and limitation

1. We conducted a quantitative analysis suggesting that magnesium intake has a strong inverse association with T2D and total stroke.
2. Magnesium-rich food consumption should be recommended for high-risk individuals in dietary guidelines.
3. Highlighting early management of T2D and stroke requires various efforts and strategies.
4. This study, which includes a considerable amount of evidence, assists with innovation of the global dietary pattern.
5. Although strong inverse associations for T2D and total stroke were reported, individual-level studies having more detection power are required.

Keywords: Magnesium Intake; Type 2 Diabetes; Stroke; Meta-Analysis.

Introduction

Diabetes is a global burden with an alarming increasing rate throughout the world[1,2]. Stroke is an independent disorder and a typical macrovascular complication of type 2 diabetes (T2D) treated as the second leading cause of death after ischemic heart disease[3,4]. These pandemic health problems require more primary prevention strategies.

Magnesium, common cellular ion, acts as critical cofactor for hundreds of enzymes involved in glucose metabolism, protein production, and nucleic acid synthesis[5,6]. Low levels of magnesium have been associated with many chronic and inflammatory diseases, such as Alzheimer's disease, asthma, attention deficit hyperactivity disorder, insulin resistance, T2D, hypertension, cardiovascular disease (e.g., stroke), migraine headaches, osteoporosis and cancer[1,5,7,8].

Actually, many adults in developed countries do not successfully meet the recommended daily consumption of magnesium-rich foods such as whole grains, nuts, and green leafy vegetables, and magnesium is less mentioned in dietary guidelines and in studies about T2D or stroke prevention[9,10]. With this regard, we chose T2D and stroke as our outcome of interest (cardiovascular disease (CVD) was not elaborated because there are so many items relating to CVD and the definitions about CVD varied a lot among searched studies, which would enhance heterogeneity in the pooled process and impair our interpretation of the final conclusion).And, emerging studies[11-51] on this topic are limited, and the results still remain mixed possibly due to the limitations of small simple sizes and differences in intervention duration, study

design, characteristics of participants. Moreover, consecutive meta-analyses[52,53] have used less rigorous inclusion, the statistics were inadequate, the results were incomprehensive, and they did not completely address the influence of other confounders (i.e., body mass index (BMI), cereal fiber, calcium, potassium) on the relationship. Accordingly, we performed a meta-analysis to (1) establish a comprehensive estimate and update the epidemiological evidence for clinical practice; (2) discuss the results of stroke subtype and the impact of several statistical and epidemiology confounders on the investigated association; and (3) highlight a detailed dose-response pattern for the participants in the studies analyzed.

Methods

This study was reported according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines Checklist and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**) (Registration information: PROSPERO CRD42018092690).

Search Strategy

PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were systematically reviewed through inception to March 15, 2019 for studies about magnesium intake and T2D or stroke without language restrictions. The following key words were used: “Magnesium”, “Type 2 Diabetes Mellitus”, “Type 2 Diabetes”, “Stroke”, “Cerebrovascular Stroke”, “Cohort Studies”, and “Prospective Studies”. We

also manually searched the reference lists of the retrieved literature (including meta-analyses and brief reports), bibliographies and gray literature (including presentations and unpublished literature) for further eligible articles.

Selection Criteria

(1) Eligible populations must be composed of individuals with plausible dietary/energy intake, who had no history of diabetes and/or insulin treatment for T2D analysis and no current stroke for stroke analysis. (2) Their apparent life expectancy was long enough for proper follow-up. (3) We only included prospective cohort studies that reported magnesium intake and T2D and/or various types of stroke. Notably, magnesium intake contained dietary magnesium intake and total magnesium intake (dietary and supplementary magnesium).

Only studies containing the most comprehensive information on the population or endpoints were included to avoid duplication. We excluded reviews, basic studies, meta-analyses, etc.

Data Extraction and Quality Assessments

Two researchers independently extracted the following information: the first author, publication year, period of cohort studies, duration of persistent exposure, basic characteristics of the enrolled participants (weight, age, region, BMI, drinking and smoking habits (previous plus current), etc.), median magnesium intake for each quantile (tertile, quartile, or quintile), diabetes and total stroke cases, subtypes of total

stroke, dietary and case assessments, adjusted confounding covariates. Importantly, total stroke is classified as clinical ischemic stroke (87%), hemorrhagic stroke (13%) and undetermined stroke[54]. Hemorrhagic stroke is classified as subarachnoid hemorrhage and intracerebral hemorrhage according to anatomical site or presumed etiology[55].In cases of continuing disagreement, a final decision was reached after discussion with a third member of the panel.

Methodological quality was described by the Newcastle-Ottawa Scale (NOS), which was validated for assessment of the quality of nonrandomized controlled trials in meta-analyses[56]. As for 0-10 scale, each study was categorized as low (0-5), medium (6-7), of high (8-10) quality.

Statistical Analysis

Articles providing data separately for men and women or black and white or different types of disease within an article were treated as independent studies. Multivariate relative risk (RR) and corresponding 95% confidence intervals (CI) for measuring the quantitative associations between exposure and T2D, total stroke and other wanted outcomes, particularly for the highest vs. the lowest categories of magnesium intake were estimated by DerSimonian-Laird random effects model because the assumptions involved account for the presence of within-study and between-study variability. Statistical heterogeneity was determined with the Cochran Q chi-square test and the I^2. An $I^2 > 50\%$ or a P value for the Q test < 0.1 was considered to indicate significant heterogeneity[57]. We performed sensitivity analyses to test the robustness and

post-subgroup analyses to detect source of heterogeneity. In addition, a random-effects meta-regression analysis on BMI, sex, participants region, and dietary assessments with RR for each trial was performed to obtain an understanding of the reasons for heterogeneity. RR and 95% CI might begin to significantly change as publication years increased in T2D and total stroke etc., which would be validated by cumulative meta-analyses.

The dose-response analyses for all outcomes were proposed by Greenland and Longnecker[58] and Orsini[59] et al. The categories of magnesium intake, distributions of cases and person-year, RR and 95 CI were extracted. Once the number of cases and/or person-years was not available, variance-weighted least squares regression was used to pool the risk estimate. For most studies, the median intake for each quantile (tertile, quartile or quintile) of magnesium intake was assigned as the representative dose. For continuous intake reported as category data with a range in some studies, we assigned the mid-point category of the lower and upper bound to the RR in these studies; when the highest category was open ended, we assumed the length of the open ended interval to be 1.5 times as the adjacent interval; when the lowest category was open, we assigned the adjacent interval of the category to be 1.5 times as the length of the open ended interval. We determined generalized least squares regression models to calculate study-specific RR estimates per 50 mg/day, 100 mg/day, and 150 mg/day of magnesium intake increment if there was evidence for linear relationships. In addition, the non-linear relationships between magnesium intake and all outcomes were evaluated using restricted cubic splines with four knots located at the 5th, 35th, 65th,

and 95th percentiles of the distribution. The P value for curve linearity or non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. All results were presented using two-stage dose-response model plots (including linear and nonlinear relationships).Some results were demonstrated in forest plots for < 50 mg/day, ≥ 50 and < 100 mg/day, ≥ 100 and < 150 mg/day, ≥ 150 mg/day increments.

Publication bias was assessed graphically by Begg's adjusted rank correlation funnel plots[60] and Egger's linear regression tests[61]. All analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA); two-sided $P < 0.05$ was considered statistically significant except where otherwise specified.

Patient and Public Involvement:

We did not involve patients or the public in this research at any stage.

Results

Study Characteristics and Quality Assessment

Of the total 8713 studies, 107 studies were considered for eligibility after screening of titles and abstracts (**Figure 1**). And a total of 41[11-51] prospective cohort studies involving 53 cohorts, 1 912 634 participants and 76 678 cases were eligible for current systematic review and meta-analysis (**Table S2**). Hodge et al[18] only recorded 500 mg/day increment of magnesium for further pooled analyses; 2 studies[33,51] failed to clearly distinguish the diabetes type, but the great majority of cases had T2D. We

computed the subtype data in three studies[14,27,36] after the extraction of total stroke, and we considered ischemic stroke in three other studies[28,30,42] as total stroke given ischemic stroke accounting for nearly 87% of total stroke. Participants were predominately middle-age at baseline, with mean magnesium intake for the highest category of 370 mg/day, mean for the lowest category of 232 mg/day. The mean duration of all eligible studies was 10.7 years. Nineteen studies were conducted in North America (America); 5 studies were in Europe (Sweden, the Netherlands and Britain); 13 studies in Asia (China and Japan and Taipei); 4 studies enrolled individuals in multiple nations. Most of the studies included used food frequency questionnaires (FFQs) or semi-quantitative FFQs (SFFQs) to assess individual dietary intake. Eighteen studies used dietary magnesium intake, and 21 studies recorded total magnesium intake (dietary and supplementary magnesium intake). Of note, supplementary magnesium intake was assessed from the use of magnesium or multivitamin supplements; nevertheless, dietary magnesium accounted for the majority of magnesium intake. Adjusted confounders were mostly similar; however, adjusted dietary confounders such as cereal fiber, potassium, and calcium still varied across individual studies. It was unclear whether included studies had adjusted for sodium because they did not provide the information. All these studies were written in English.

After the quality assessments of the studies according to NOS, the average score was 8.85 (**Table S3**) and all studies were of high quality (NOS score 8-10).

Magnesium Intake and T2D Incidence

Thirty-five cohorts from 26 publications[11,12,15,20,22-26,29,31-35,37,39,41,43,48,49,51](1 219 636 participants and 56 540 T2D cases) reported the magnitude of the risk of T2D was reduced by 22% (RR, 0.78 [95% CI, 0.75-0.81]; $P < 0.001$) comparing the highest category of magnesium intake to the lowest with a little evidence of heterogeneity ($I^2 = 35.6\%$; $P = 0.021$). The dose category-specific analysis suggested that for < 50 mg/day magnesium increment, the risk of T2D was reduced by 10% (RR, 0.90 [95% CI, 0.88-0.93]; $P< 0.001$); for ≥ 50 and < 100 mg/day, the risk was decreased by 16% (RR, 0.84 [95% CI, 0.82-0.87]; $P < 0.001$); for ≥ 100 and < 150 mg/day, the risk was reduced by 22% (RR, 0.78 [95% CI, 0.74-0.83]; $P < 0.001$); and for ≥ 150 mg/day, the risk was reduced by 21% (RR, 0.79 [95% CI, 0.74-0.84]; $P < 0.001$) (**Figure 2)**. Little evidence of publication bias was found (Egger's test: $P = 0.088$) (**Figure S1A**).

Magnesium Intake and Stroke Incidence

Eighteen cohorts from 15 publications[13,14,21,27,28,30,36,38,40,42,44-47,50] (692 998 participants and 20 138 total stroke cases) reported the magnitude of the risk of total stroke was decreased by 11% (RR, 0.89 [95% CI, 0.83-0.94]; $P < 0.001$) with no heterogeneity ($I^2 = 0\%$; $P = 0.529$) in the highest category of magnesium intake VS. the lowest. Dose category-specific analysis identified no significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and < 150 mg/day of increments. For the ≥ 150 mg/day increment, the risk of total stroke was decreased by 15% (RR, 0.85 [95% CI, 0.79-0.91]; $P< 0.001$) (**Figure S2)**. Publication bias was evaluated for

stroke subtypes respectively.

Fifteen cohorts from 12 publications[14,21,27,28,30,36,38,40,42,45,46,50] reported ischemic stroke. The magnitude of the risk of ischemic stroke was reduced by 12% (RR, 0.88 [95% CI, 0.81-0.95]; $P = 0.001$) with no significant heterogeneity ($I^2 = 16.9\%$; $P = 0.265$). Dose category-specific analysis identified no significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and < 150 mg/day increments. A trend to decrease existed but remained insignificant. The original risk was reduced by 16%in the analysis of the ≥ 150 mg/day increment (RR, 0.84 [95% CI, 0.78-0.91]; $P< 0.001$) (**Figure S3)**. No publication bias was observed in terms of ischemic stroke (Egger's test: $P = 0.937$) (**Figure S1B**).

Ten cohorts from 8 studies[14,21,27,36,38,45,46,50] reported that hemorrhagic stroke was not significantly associated with magnesium intake (RR, 0.93 [95% CI, 0.82-1.06]; $P = 0.282$).Dose category-specific analysis identified no significant association (**Figure S4)**. No significant heterogeneity or publication bias were identified with regard to hemorrhagic stroke (Egger's test: $P = 0.809$) (**Figure S1C**).

Three publications involving 3 cohorts[14,27,36] showed that high magnesium intake had no significant efficacy in reducing subarachnoid hemorrhage risk (RR, 0.99 [95% CI, 0.71-1.39]; $P = 0.963$). Dose category-specific analysis identified no significant association (**Figure S5)**.

With respect to intracerebral hemorrhage, the pooled results from 3 cohorts[14,27,36] in 3 publications revealed no significant advantages of intracerebral hemorrhage (RR, 0.92 [95% CI, 0.71-1.20]; $P = 0.540$). Dose category-specific analysis identified no

significant association (**Figure S6)**.

Meta-Regression and Cumulative Meta-Analysis

Meta-regression identified no evidence of BMI, sex, participant region and dietary assessment for each individual trial bias in T2D (**Figure S7**), total stroke (**Figure S8**), ischemic stroke (**Figure S9**) and hemorrhagic stroke events (**Figure S10**). The male subgroup (P = 0.041) in the sex category might cast little heterogeneity on total stroke; however, the sex category (P = 0.112) had no association with total stroke incidence.

Analyses on T2D (**Figure S11)**, total stroke (**Figure S12)** and ischemic stroke demonstrated that the RRs of the final results became robust within a narrow range and remained significant as publication years increased and as recent high quality studies were included. After inclusion of the Iso et al[14] study, the RR and 95% CI for ischemic stroke decreased to less than 1 and became stable (**Figure S13).** Although there was no significantly reduced risk in hemorrhagic stroke, clear evidence showed that the confidence interval was becoming narrow, which had a trend toward significance (**Figure S14**). Thus, risk for hemorrhagic stroke might be reduced, and further studies are still needed.

Sensitivity Analysis

When three[24-26] studies were excluded in T2D analysis, the summary RR changed from 0.78 ([95% CI, 0.75-0.81]) to 0.78 ([95% CI, 0.75-0.82]) with the heterogeneity declining from (I^2 = 35.6%; P = 0.021) to (I^2 = 24.0%; P = 0.112). Among T2D

analysis, eight studies[19,22,23,26,33,39,48,49] adjusted for cereal fiber intake yield an RR of 0.79 ([95% CI, 0.73-0.85]; $P< 0.001$) and two studies[15,35] for calcium yielded an RR of 0.87 ([95% CI, 0.73-1.04]; $P = 0.128$). While among total stroke analysis, the summary RR was 0.92 ([95% CI, 0.82-1.02]; $P = 0.097$) in five studies[13,44-46,50] adjusted for potassium intake and was 0.89 ([95% CI, 0.80-0.99]; $P = 0.040$) in five studies[14,44-46,50] adjusted for calcium. Only one study[15] adjusted for potassium intake in T2D, one study[36] for cereal fiber in total stroke.

Subgroup Analysis

Stratified analyses by characteristics of the population and study design were conducted on T2D (**Table 1**), total stroke, ischemic stroke and hemorrhagic stroke (**Table 2**). The inverse association with T2D remained robust across all subgroups with little evidence of heterogeneity. As for stroke incidence, a decreased risk of total stroke and ischemic stroke was found in female participants (RR, 0.91 [95% CI, 0.83-0.99] for total stroke; 0.89 [95% CI, 0.79-1.00] for ischemic stroke) and individuals with ≥ 25 kg/m^2 mean BMI (RR, 0.89 [95% CI, 0.82-0.96] for total stroke; 0.88 [95% CI, 0.81-0.96] for ischemic stroke). When restricted to a ≥ 12 y follow-up, the risk of total stroke and ischemic stroke could be significantly reduced (RR, 0.89 [95% CI, 0.83-0.95] for total stroke; 0.88 [95% CI, 0.81-0.95] for ischemic stroke). These risks were more reduced in North American and European individuals than Asians. Cardiovascular events (CV events, coronary heart disease, heart failure, atrial fibrillation, and self-reported heart disease etc. other than stroke),

hypercholesterolemia and diabetes would blunt the effect of magnesium on total and ischemic stroke. However, magnesium intake could still, or at least, demonstrate the trend to decrease total and ischemic stroke in individuals even with those risk factors. Similarly, CV events, hypercholesterolemia and family diabetes history had no substantial impact on the inverse association between T2D incidence and magnesium intake. We did not find significantly reduced risk in hemorrhagic stroke across the subgroup analyses.

Dose-Response Analysis

In this part, both linear and nonlinear relationships were found in T2D (**Figure 3A)**, in total stroke (**Figure 3B)**, and in ischemic stroke (**Figure 3C).** However, no linear or non-linear dose-response relationship was observed in hemorrhagic stroke (**Figure 3D)** along with the subtypes including subarachnoid hemorrhage and intracerebral hemorrhage (**Figure S15)**.

Specifically, we calculated RR for the magnesium increments if there was linear relationship found. The calculated RR was 0.94 ([95% CI, 0.93-0.95]) for the 100 mg/day increment for T2D. For total stroke, the summary RR was0.98 ([95% CI, 0.97-0.99]) related to 100 mg/day increment in magnesium intake, RR for ischemic stroke was 0.98 ([95% CI, 0.97-0.99]) related to 100 mg/day increment in magnesium intake. Magnesium intake showed an inverse dose-response relationship with T2D, total stroke and ischemic stroke. Moreover, a more substantial reduction on risks was observed with more magnesium intake.

Discussion

This paper used a general and up-to-date search strategy to identify some additional studies that were missed in prior meta-analyses under real-world conditions. Our results support a significant inverse association between magnesium consumption and T2D, total stroke and ischemic stroke at the highest level vs. the lowest. No significant association for hemorrhagic stroke, subarachnoid hemorrhage and intracerebral hemorrhage was detected. Female obese participants (mean BMI ≥ 25 kg/m^2) with longer follow-up period (≥ 12 y) might obtain a greater benefit from magnesium intake for preventing total and ischemic stroke. Enhancing magnesium intake seemed to be more effective for North American and European individuals to get lower stroke risks. Significant risk reduced by 6%, 2%, and 2% for T2D, total stroke and ischemic stroke respectively at per 100 mg/day increment in magnesium intake level. Overall, the correction of magnesium deficiencies and enhancement of magnesium intake appears to be useful for T2D and total stroke high-risk participants; our study supports the guidelines to address the role of magnesium intake for T2D and stroke early prevention. Even though, we still require more randomized controlled trials (RCTs) in the future to validate the causality.

Dietary nutrients are hot topics for current clinical medicine, folic acid, vitamin D, and ω-3 fatty acids have been specifically recommended to pregnant women, infants and children, and the elderly[62,63], however, magnesium has been less extensively discussed. This is a noteworthy study for the following reasons. First, this

study focused on an important and timely topic related to correlations between two chronic diseases and magnesium. Preventing T2D and stroke still requires high-quality evidence. Current study reinforces the possible role of magnesium in the prevention and management of these illnesses and causes new considerations on the avoidance of other chronic disease with potential diet strategy. Second, this comprehensive study with nearly two million individuals and abundant statistical power provides confirming evidence for medical practitioners, health educators and policy makers. Third, until this study, no related paper has discussed such detailed stratified analyses, which helps physicians to amplify the dietary benefits through individualized strategies. Interestingly, we detected North American and European participants seemed to receive more benefits from magnesium intake than Asians. Fourth, to our knowledge, this is the first study in which cumulative meta-analysis was performed to forecast the changing tendency of main risk estimates. Based on past and current cutting edge evidence about nutrition and T2D prevention, the US Diabetes Prevention Program (DPP) conducted a study that demonstrated that proper lifestyle modification (exercise and Mediterranean diet) significantly reduced T2D risks irrespective of population baselines, and the benefit expanded with increased follow-up[64]. The UK national health service (UK NHS) will launch an intervention program including weight loss, nutrition, monitoring and peer support targeting up to 10 000 people prone to develop T2D[65].

2018 American Diabetes Association (ADA) guidelines[66] recommend to enhance intake of nuts, berries, yogurt, coffee and tea in individuals who are at high risk of

diabetes. The latest guidelines by the American Heart Association (AHA)/American Stroke Association (ASA)[9] also validate considerable status of early management of stroke (ischemic stroke). In deed, a poor outcome on hemorrhagic stroke was observed in a RCT, however, high serum magnesium might be better for intracerebral hemorrhage prognosis[67]. Most specific nutrients especially macronutrients are correlated with total energy intake. In included free-living human studies, variation of total energy intake is originated from physical activity, differences in body size, and differences in energy efficiency[68]. Thus total energy intake can weaken the investigated association with considerable nutrients intake if this covariable is not properly removed. Epidemiologists should assess reproducibility and validity of energy-adjusted nutrients as well as absolute nutrients intake. Though micronutrient as magnesium is, inverse association could be still found in T2D, total stroke and ischemic stroke outcomes after total energy intake adjustment. As for other nuttrients, potassium intake is proposed to lower blood pressure (BP) and improve vascular outcomes (including stroke); dietary potassium may also be influential in glucose control and limiting the risk of diabetes[69]. Vitamin D and calcium may negatively influence glycemia, but the evidence is limited for mostly being based on cross-sectional observational studies[70]. Calcium may be inversely associated with stroke in populations with low to moderate calcium intakes, but no significant association was found between calcium and CVD[71]. All things considered, magnesium-rich food such as nuts (151-567 mg/100g edibles), fruits (132-448 mg/100g edibles), vegetables (132-1257 mg/100g edibles), legumes (138-243

mg/100g edibles), fish (143-303 mg/100g edibles) and total grain (134-306 mg/100g edibles) should be recommended to populations with insufficient magnesium intake from T2D and total stroke.

This seminar has several differences with previous studies. Dong et al[52] found magnesium intake had an inverse association with T2D incidence (RR, 0.78 [95% CI, 0.73-0.84]), and with an intake of 100 mg/day magnesium, the risk was reduced by 14%. In fact, they failed to include adequate studies, and standard quality assessments of eligible studies were absent. Individuals from multiple nations in some studies[18,25,26,32] were incorrectly assigned to Asia or the U.S. in the subgroups, and minor imperfections existed in the selection criteria because it was unclear whether they excluded participants with subclinical diabetes. BMI was not a potential modifier for T2D in our study due to the inclusion of more evidence which had longer follow-up period. Fang et al[72] revealed dietary magnesium had a smaller effect on cardiovascular disease but significantly reduced T2D (RR, 0.74 [95% CI, 0.69-0.80]) and stroke (RR, 0.88 [95% CI, 0.82-0.95]) risks. The results were comparable, but they just focused on dietary magnesium intake rather than overall magnesium intake (total or dietary), and subtypes of total stroke were missed. To our overall knowledge, BMI, follow-up, family diabetes history, etc. were crucial confounders for evaluating the association, which were not addressed in their study. Moreover, researchers had better investigate the likelihood of linear association in the dose-response pattern (using methods by Greenland and Orsini et al). Fang et al[73] found that the 100 mg/day intake of dietary magnesium was associated with an 8-13% reduction in T2D risk, and

while a nonlinear relationship did not exist, a minor publication bias was present. Twenty-five studies were eligible; however, some of them focused not on dietary but on total magnesium intake. Moreover, there were two included studies focusing on red meat intake instead of magnesium intake. After excluding actual ineligible studies, we found no evidence of publication bias. Additionally, both linear and nonlinear relationships existed for T2D, because the RRs of the highest category of magnesium intake VS. the lowest in our pooled study were still used. A study by Larsson et al[53]including 7 studies supported a modest but statistically significant inverse association between dietary magnesium intake and stroke. The sample size was quite small, and there was no useful information for stroke subtypes (e.g., ischemic stroke, hemorrhagic stroke) in the main analysis. In our opinion, a well-designed subgroup analysis is a compulsory undertaking, and a pooled stroke result restricted by potassium and calcium adjustment is recommended. The current study found magnesium intake was strongly inversely associated with total stroke and ischemic stroke, which still existed in the dose-response pattern.

Future studies still have something to be addressed. At first, no significant efficacy was found in hemorrhagic stroke, however, the beneficial trend was observed in the cumulative meta-analysis, which addresses needs for more updated prospective studies and RCTs. Second, there is a key question regarding the optimal time to start prevention and methods to screen severe complications. Cardiovascular events occur in more than 50% and diabetic kidney disease occurs in 20-40% of patients with diabetes. Actually, cardiovascular events increase the risk of death three to four times

compared with patients without such complications. A sustained period of intensive glucose control early in T2D has been confirmed to reduce complication rates[74]. Most importantly, to the public, educators and guideline makers, boosting magnesium-rich food consumption brings considerable benefits to T2D and total stroke prevention, especially in high-risk populations.

Several limitations deserve further discussion. First, this group-level meta-analysis is insufficient. Although strong inverse associations for T2D and total stroke were reported, individual-level studies having more detection power are required. Second, several variations cannot be totally understood, for example, we cannot exclude the possibility that other nutrients and/or dietary components correlated with dietary magnesium may have been responsible, either partially or entirely, for the observed associations. Based on eligible studies, we could not quantify the impact of supplementary magnesium (not combined with dietary intake) on T2D and stroke incidence. The real effect of some dietary supplements on T2D or cardiovascular disease seems very interesting to a number of medical experts, clinicians and nutrition educators. Third, FFQs/validated FFQs mostly used in primary studies could not characterize all the nutrients, which misclarified plausible associations. Finally, besides prospective cohort studies, we still required further RCTs, because observational studies might only reach the same conclusion (i.e., magnesium intake is inversely associated with T2D incidence) but could not prove causality. However, there has been some evidence suggesting that magnesium achieves glucose and insulin metabolism through tyrosine kinase activity of the

insulin receptor; magnesium also helps to eliminate calcium cation cytotoxicity and has vasodilatory effect[75].

Conclusion

Magnesium intake has a substantial inverse association with T2D and total stroke. Among these populations, magnesium consumption can be recommended as an optimization for T2D, total stroke and ischemic stroke primary prevention or early management. In particular, the greater the magnesium intake, the more the risk is reduced. As patients, physicians, policy makers and legislators debate on these issues, such a cost-effective alternative is needed to inform policy decisions and assist reform in global dietary health care.

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None declared

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Table 1 Subgroup Analysis relating to Magnesium Intake and Type 2Diabetes (T2D)

Group	T2D					
	No. of studies	RR (95% CI)	P_{ES}	$P_{heterogeneity}$	I^2 (%)	$P_{interaction}$
Total	26	0.78 (0.75-0.81)	< 0.001	0.021	35.6	NA
Participants region	26					0.905
North America	13	0.77 (0.73-0.82)	< 0.001	0.048	39.5	
Europe	0	NA	NA	NA	NA	
Asia	9	0.78 (0.71-0.87)	< 0.001	0.165	21.7	
Multiple nations	4	0.79 (0.71-0.88)	< 0.001	0.048	58.3	
Sex[a]	34					0.284
Male	9	0.81(0.76-0.87)	< 0.001	0.337	11.7	
Female	17	0.77 (0.73-0.81)	< 0.001	0.055	37.5	
Both[b]	8	0.70 (0.57-0.85)	< 0.001	0.067	45.3	
BMI (kg/m^2)	26					0.716
≥ 25	12	0.75 (0.69-0.81)	< 0.001	0.135	31	
< 25	11	0.78 (0.74-0.83)	< 0.001	0.022	45.4	
Unknown	3	0.81 (0.76-0.86)	< 0.001	0.586	0	
Follow-up duration (y)	26					0.150
≥ 10	12	0.80 (0.76-0.84)	< 0.001	0.047	38.8	
< 10	14	0.74 (0.68-0.80)	< 0.001	0.164	25.2	
Dietary assessment	26					0.281
FFQ/validated FFQ	15	0.77 (0.73-0.82)	< 0.001	0.159	23.7	
SFFQ/validated SFFQ	9	0.79 (0.74-0.84)	< 0.001	0.017	52.5	
Other	2	0.55 (0.36-0.83)	0.005	0.826	0	
Magnesium intake type[c]	28					0.335
Total magnesium intake[d]	15	0.79 (0.75-0.84)	< 0.001	0.035	39.8	
Dietary magnesium intake	13	0.77 (0.72-0.82)	< 0.001	0.166	25.0	
Total energy adjustment	26					0.396
Yes	17	0.79 (0.74-0.84)	< 0.001	0.027	40.4	
No	9	0.76 (0.72-0.81)	< 0.001	0.225	21.6	
Difference between top and bottom intake (mg/day)[e]	27					0.671
≥ 140	13	0.78 (0.74-0.83)	< 0.001	0.020	45.3	
< 140	14	0.77 (0.72-0.82)	< 0.001	0.209	21.0	
Current CV events status[f]	26					0.536
Yes	13	0.79 (0.74-0.83)	< 0.001	0.049	37.9	
Unknown	13	0.77 (0.71-0.82)	< 0.001	0.082	35.1	
Hypercholesterolemia status[g]	26					0.625
Yes	5	0.79 (0.73-0.85)	< 0.001	0.021	57.5	
Unknown	21	0.77 (0.73-0.82)	< 0.001	0.096	27.3	
Family diabetes history	26					0.168
Yes	17	0.76 (0.72-0.80)	< 0.001	0.021	41.8	
Unknown	9	0.81 (0.76-0.87)	< 0.001	0.258	14.3	

Abbreviation: T2D, type 2 diabetes; BMI, body mass index; FFQ, food frequencyquestionnaire; SFFQ, semi-quantitative food frequent questionnaire; RR, relative risk; ES, effect size; CV events, cardiovascular events.

[a], Male and female of T2D outcome were treated as independent cohorts within eight studies;

[b], Male and female participants were in independent cohorts;

[c], Two studies reported total magnesium and dietary magnesium intake outcome;

[d], Total magnesium intake (milligrams per day) included the total amount of magnesium from both food (diet) and supplement;

[e], Subtract the lowest category intake from the highest. Oba el al (M) was in < 140 group, while Oba el al (F) was in ≥ 140 group;

[f], Grouped by whether participants with or without CV events. CV events in this part include coronary heart disease, heart failure, stroke, atrial fibrillation, and self-reported heart disease etc;

[g], Grouped by whether participants with or without hypercholesterolemia. Hypercholesterolemia in this part means cholesterol concentration ≥ 240 mg/dL.

Table 2. Subgroup Analyses Relating to Magnesium Intake and Total Stroke, Ischemic Stroke, Hemorrhagic stroke.

Group	Total Stroke				Ischemic Stroke				Hemorrhagic stroke			
	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$
Total	15	0.89 (0.83-0.94)	0.00	NA	12	0.88 (0.81-0.95)	16.90	NA	8	0.93 (0.82-1.06)	0.461	NA
Participants region	15			0.733	12			0.584	8			0.873
North America	6	0.87 (0.79-0.96)	0.00		5	0.85 (0.76-0.95)	0.00		4	0.90 (0.71-1.15)	0.00	
Europe	5	0.87 (0.77-0.98)	14.80		3	0.86 (0.78-0.95)	0.00		2	0.99 (0.79-1.25)	0.00	
Asia	4	0.90 (0.78-1.05)	32.80		4	0.93 (0.75-1.14)	45.50		2	0.89 (0.66-1.21)	53.40	
Multiple nations	0	NA	NA		0	NA	NA		0	NA	NA	
Sex[a]	18			0.031	14			0.134	10			0.425
Male	6	0.95(0.86-1.05)	0.00		4	0.99 (0.82-1.19)	52.80		4	0.97 (0.75-1.26)	35.50	
Female	7	0.91 (0.83-0.99)	0.00		6	0.89 (0.79-1.00)	0.00		6	0.88 (0.74-1.06)	0.00	
Both[b]	5	0.74 (0.64-0.85)	0.00		4	0.76 (0.65-0.88)	0.00		0	NA	NA	
Mean BMI (kg/m^2)	15			0.606	12			0.631	8			0.418
≥ 25	8	0.89 (0.82-0.96)	0.00		6	0.88 (0.81-0.96)	0.00		5	0.97 (0.81-1.17)	0.00	
< 25	5	0.89 (0.78-1.01)	30.00		5	0.87 (0.73-1.03)	44.00		3	0.88 (0.69-1.12)	39.30	
Unknown	2	0.80 (0.63-1.02)	0.00		1	0.76 (0.57-1.07)	NA		0	NA	NA	
Follow-up duration (y)	15			0.798	12			0.811	8			0.808
≥ 12	11	0.88 (0.82-0.94)	5.30		10	0.87 (0.80-0.95)	19.10		7	0.93 (0.81-1.08)	7.70	
< 12	4	0.90 (0.77-1.05)	0.00		2	0.86 (0.62-1.20)	48.40		1	0.88 (0.57-1.36)	NA	
Dietary assessment	15			0.578	12			NA	8			NA
FFQ/validated FFQ	14	0.89 (0.83-0.95)	3.80		12	0.88 (0.81-0.95)	16.90		8	0.93 (0.82-1.06)	0.00	
SFFQ/validated SFFQ	0	NA	NA		0	NA	NA		0	NA	NA	
Other	1	0.81 (0.61-1.09)	0.00		0	NA	NA		0	NA	NA	
Magnesium intake type	15			0.865	12			0.831	8			0.831
Total magnesium intake[c]	8	0.89 (0.82-0.96)	0.00		6	0.87 (0.80-0.94)	0.00		5	0.94 (0.79-1.12)	0.00	
Dietary magnesium		0.88	0.44			0.89	35.40			0.91 (0.70-1.18)	39.40	

intake	7	(0.81-0.96)			6	(0.77-1.03)			3		
Total energy adjustment	15			0.888	12			0.689	8		0.538
Yes	5	0.87 (0.77-0.99)	27.00		2	0.86 (0.78-0.94)	0.00		2	0.93 (0.82-1.06)	0.00
No	10	0.89 (0.83-0.96)	0.00		10	0.88 (0.79-0.99)	26.60		6	0.90 （0.76-1.07）	11.40
Difference between top and bottom intake (mg/day)[d]	15			0.107	12			0.180	8		0..244
≥ 180	7	0.83 (0.76-0.91)	0.00		5	0.83 (0.76-0.91)	0.00		6	1.07 (0.83-1.37)	0.00
< 180	8	0.93 (0.86-1.00)	0.00		7	0.92 (0.81-1.03)	26.20		2	0.89 (0.76-1.03)	0.00
Current CV events status[e]	15			0.074	12			0.393	8		NA
Yes	12	0.90 (0.85-0.96)	0.00		11	0.88 (0.81-0.96)	18.20		8	0.93 (0.82-1.06)	0.00
Unknown	3	0.75 (0.63-0.90)	0.00		1	0.76 (0.57-1.01)	NA		0	NA	NA
Hypercholesterolemia status[f]	15			0.480	12			0.565	8		0.651
Yes	7	0.91 (0.83-0.99)	0.00		6	0.90 (0.80-1.01)	6.90		5	0.90 (0.76-1.08)	0.00
Unknown	8	0.86 (0.79-0.95)	13.10		6	0.86 (0.77-0.97)	32.40		3	0.94 (0.72-1.22)	40.30
Current diabetes status[g]	15			0.039	12			0.159	8		NA
Yes	10	0.91 (0.82-0.97)	0.00		10	0.89 (0.82-0.97)	13.50		8	0.93 (0.82-1.06)	0.00	0.00
Unknown	5	0.75 (0.64-0.88)	0.00		2	0.72 (0.56-0.92)	0.00		0	NA	NA	NA

Abbreviation: BMI, body mass index; FFQ, food frequency questionnaire; SFFQ, semi-quantitative food frequency questionnaire; CV events, cardiovascular events; RR, relative risk; NA, not available.

[a], several studies reported stroke outcome of male and female participants in different cohorts;

[b], male and female participants were in the same cohort;

c, total magnesium intake (milligrams per day) included the total amount of magnesium from both food (diet) and supplements;

[d], subtract the lowest category intake from the highest;

[e], grouped by whether participants with or without CV events. CV events in this part include coronary heart disease, heart failure, atrial fibrillation, and self-reported heart disease etc., stroke is not included;

[f], grouped by whether participants with or without hypercholesterolemia. Hypercholesterolemia in this part means cholesterol concentration ≥ 240 mg/dL;

[g], grouped by whether participants with or without diabetes.

Figure Legends

Figure 1. Flow Chart for Literature Search and Screening Process

Figure 2. Forest Plots for Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure 3. Two-Stage Dose-Response Effect on the Relationships betweenMagnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).

Supplementary material online:

Table S1. PRISMA 2009 Checklist

Table S2. Summary of Baseline Characteristics of Included Studies

Table S3. Methodological Quality Assessments Of Studies Included With Newcastle-Ottawa Scales

Figure S1. Funnel Plots for Magnesium Intake and Type 2 Diabetes (A), Ischemic Stroke (B) and Hemorrhagic Stroke (C).

Figure S2. Forest Plots for Risk of Total Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure S3. Forest Plots for Risk of Ischemic Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure S4. Forest Plots for Risk of Hemorrhagic Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure S5. Forest Plots for Risk of Subarachnoid Hemorrhage for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E)

Figure S6. Forest Plots for Risk of Intracerebral Hemorrhage for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E)

Figure S7. Meta-Regression of Relative Risk for Type 2 Diabetes According to Body Mass Index (A, $P = 0.716$), Sex (B, $P = 0.284$), Participant Region (C, $P = 0.904$) and Dietary Assessment (D, $P = 0.521$).

Figure S8. Meta-Regression of Relative Risk for Total Stroke According to Body Mass Index (A, $P = 0.606$), Sex (B, $P = 0.112$), Participant region (C, $P = 0.891$) and Dietary Assessment (D, $P = 0.891$).

Figure S9. Meta-Regression of Relative Risk for Ischemic Stroke According to Body Mass Index (A, $P = 0.631$), Sex (B, $P = 0.134$), Participant Region (C, $P = 0.584$) and Dietary Assessment (D, no regression *P*-value due to limited data).

Figure S10. Meta-Regression of Relative Risk for Hemorrhagic Stroke According to Body Mass Index (A, $P = 0.418$), Sex (B, $P = 0.872$), Participant Region (C, $P = 0.872$) and Dietary Assessment (D, no regression P-value due to limited data).

Figure S11. Cumulative Meta-Analysis Related to Magnesium Intake and Type 2 Diabetes (T2D)

Figure S12. Cumulative Meta-Analysis Related to Magnesium Intake and Total Stroke

Figure S13. Cumulative Meta-Analysis Related to Magnesium Intake and Ischemic Stroke

Figure S14. Cumulative Meta-Analysis Related to Magnesium Intake and Hemorrhagic Stroke

Figure S15. Dose-Response Effect on the Relationships between Magnesium Intake and Subarachnoid Hemorrhage (A) and Intracerebral Hemorrhage (B).

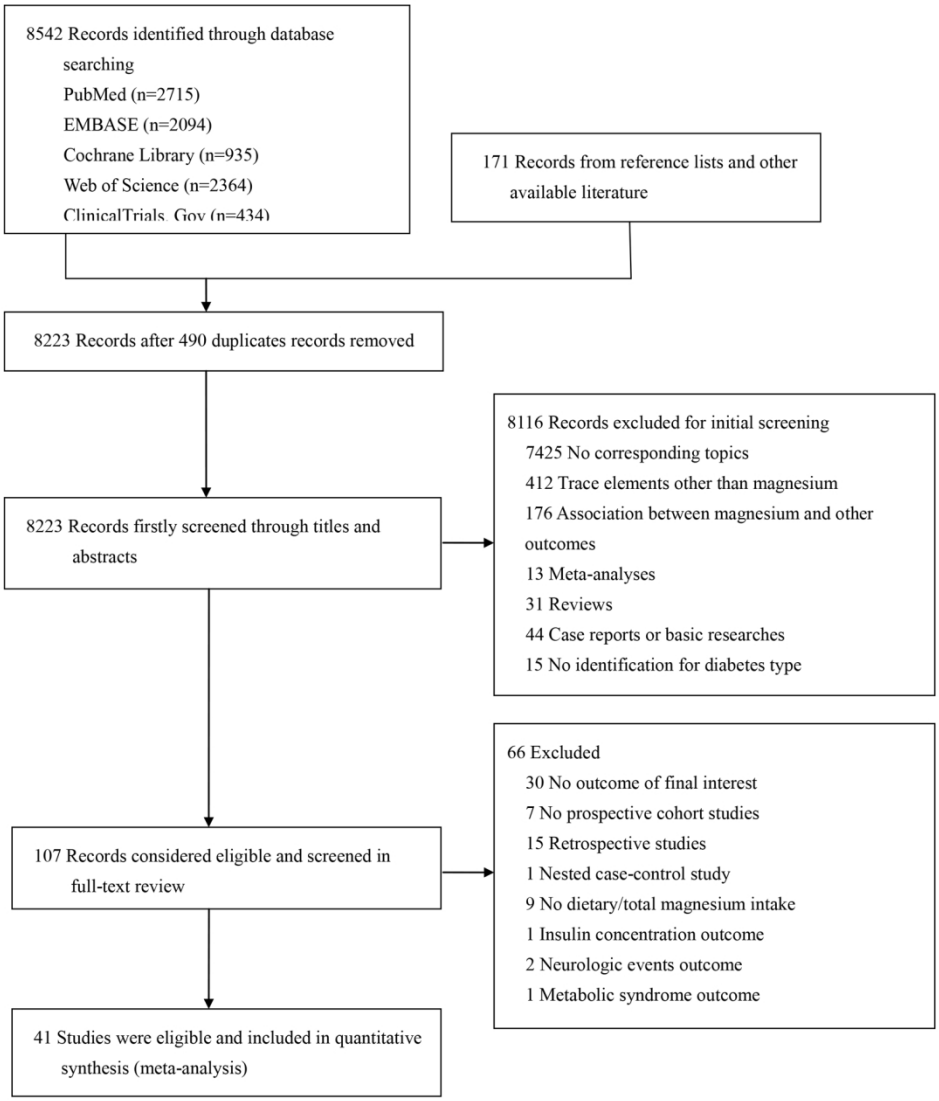


Figure 1. Flow Chart for Literature Search and Screening Process

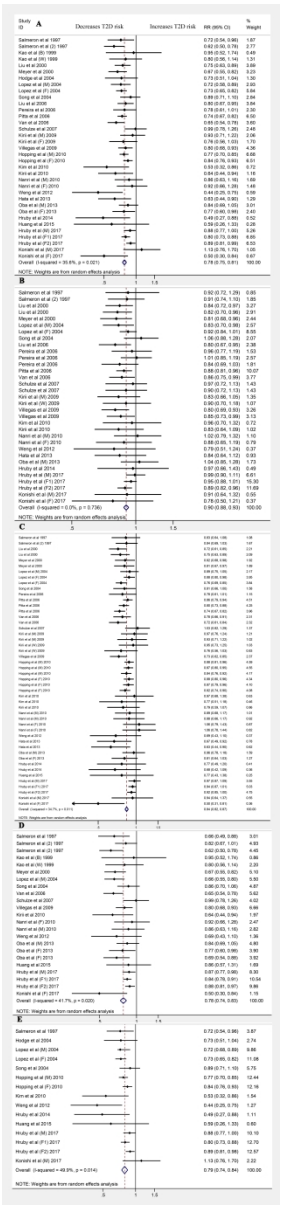


Figure 2. Forest Plots for Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

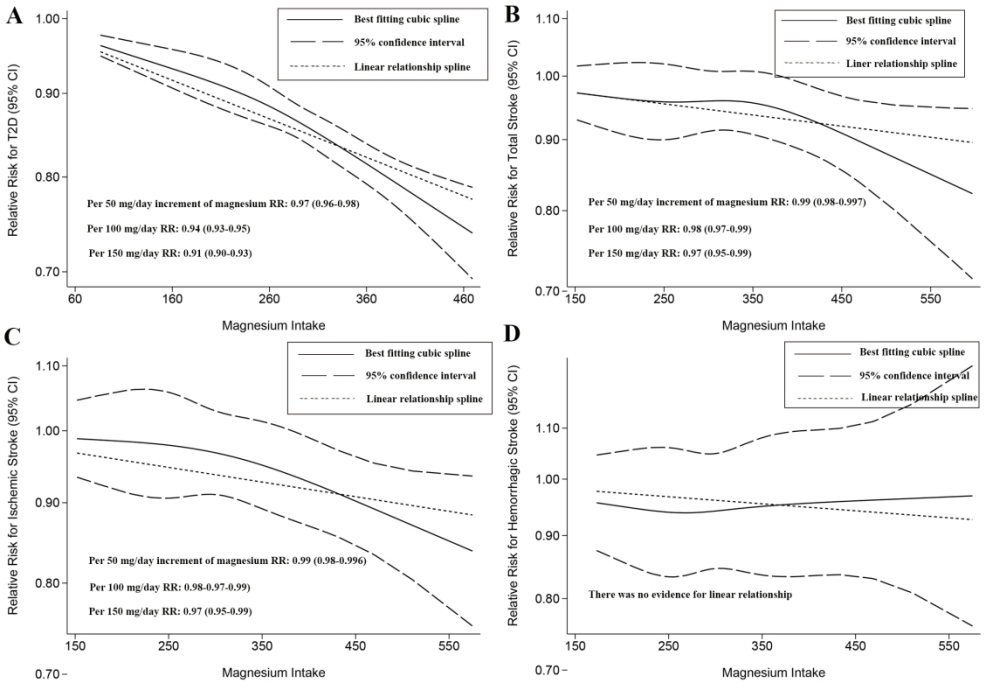


Figure 3. Two-Stage Dose-Response Effect on the Relationships betweenMagnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			2-3
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			4-5
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			5-9
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-10

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			9-16
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-16
DISCUSSION			16-22
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			23
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S2 Summary of Baseline Characteristics of Included Studies

Source	Nation	Period	Population	BMI	Dietary Assessment	Case Ascertainment	Case (Cohort size)	Magnesium intake (mg/day) highest VS. the lowest [Adjusted RR (95% CI)]
Salmeron 1997[11]	USA	1986-1992	M; 40-75 y	25.5	validated SFFQ	self-reported questionnaire	523 T2D (42759)	461 VS. 262 (0.72 (0.54-0.96))
Salmeron 1997(2)[12]	USA	1986-1992	F; 40-65 y	25.1	validated SFFQ	self-reported questionnaire	915 T2D (65173)	338 VS. 222 (0.62 (0.50-0.78))
Ascherio 1998[13]	USA	1986-1994	M; 40-75 y	NA	validated FFQ	self-reported questionnaire	328 stroke (43738)	425 VS. 243 (0.92 (0.58-1.46))
Iso 1999[14]	USA	1980-1994	F; 34-59 y	22.7	FFQ	self-reported questionnaire	690 stroke (85764)	381 VS. 211 (0.80 (0.63-1.01))
Kao 1999[15]	USA	NA	M/F; 45-64 y	27.2	FFQ	self-reported questionnaire	black: 367 T2D (2622) white: 739 T2D (9506)	374 VS. 264 (0.95 (0.52-1.74)) 418 VS. 308 (0.80 (0.56-1.14))
Liu 2000[16]	USA	1976-1984	F; 38-63 y	24.8	validated FFQ	self-reported questionnaire	1879 T2D (75521)	342 VS. 248 (0.75 (0.63-0.89))
Meyer 2000[17]	USA	1986-1992	F; 55-69 y	26.8	validated FFQ	self-reported questionnaire	1141 T2D (35998)	362 VS. 220 (0,67 (0.55-0.82))
Hodge 2004[18a]	multiple	1990-1994	M/F; 45-64 y	26.1	validated FFQ	self-reported questionnaire	365 T2D (31641)	500 increment per day
Lopez 2004[19]	USA	M: 1986-1998 W: 1980-1998	M; 40-75 y F; 30-35 y	25.4 24.3	validated SFFQ	self-reported questionnaire	1333 T2D (42872) 4085 T2D (85060)	457 VS. 314 (0.72 (0.58-0.89)) 373 VS. 222 (0.73 (0.65-0.82))
Song 2004[20]	USA	1993-2001	F; ⩾45 y[c]	26	SFFQ	self-reported questionnaire	918 T2D (38025)	433 VS. 255 (0.89 (0.71-1.10))
Song 2005[21]	USA	1993-2003	F; 39-89 y	26	FFQ	follow-up examination	368 stroke (39876)	433 VS. 255 (0.90 (0.65-1.26))
Liu 2006[22]	USA	1996-2006	F; 47-63 y	25.8	validated SFFQ	self-reported questionnaire	1603 T2D (37183)	340 VS. 307 (0.80 (0.67-0.95))
Pereira 2006[23]	USA	1986-1997	F; 56-66 y	26.7	validated FFQ	self-reported questionnaire	1418 T2D (28812)	334 VS. 281 (0.78(0.61-1.01))
Pittas 2006[24]	USA	1980-2000	F; 30-55 y	24.1	validated SFFQ	self-reported questionnaire	4843 T2D (83779)	352 VS. 258 (0.74 (0.67-0.82))
Van 2006[25]	multiple	1995-2003	F; 21-69 y	27.6	validated FFQ	self-reported questionnaire	1964 T2D (41186)	244 VS. 115 (0.65 (0.54-0.78))
Schulze2007[26]	multiple	1994-2005	M/F; 35-65 y	26.1	validated SFFQ	self-reported questionnaire	844 T2D (25067)	377 VS. 268 (0.99 (0.78-1.26))
Larsson 2008[27]	Sweden	1985-2004	M; 50-69 y	26.4	validated FFQ	follow-up examination	3370 stroke (26556)	575 VS. 382 (0.91 (0.77-1.07))
Weng 2008[28]	Taipei	1989-2002	M/F; ≥40 y	24.5	validated FFQ	Self-reported and cross-checked questionnaire	132 ischemic stroke (1772)	423 VS. 162 (0.69 (0.45-1.06))
Kirii 2009[29]	Japan	1993-1998	M; 40-69 y F; 40-69 y	23.6 23.5	FFQ	self-reported questionnaire	634 T2D (25876) 480 T2D (33919)	331 VS. 245 (0.93 (0.71-1.22)) 314 VS. 248 (0.76 (0.56-1.03))
Ohira 2009[30]	USA	1987-2004	M/F; 45-64 y	27.4	validated FFQ	follow-up examination	577 ischemic stroke (14221)	362 VS. 152 (0.80 (0.75-1.13))
Villegas 2009[31]	China	2000-2006	F; 40-70 y	23.8	validated FFQ	follow-up examination	2273 T2D (64191)	318 VS. 214 (0.80 (0.68-0.93))
Hopping 2010[32]	multiple	1993-2007	M; 45-75 y F; 45-75 y	NA	validated FFQ	self-reported questionnaire	4555 T2D (36256) 4032 T2D (39256)	278 VS. 86 (0.77 (0.70-0.85)) 300 VS. 93 (0.84 (0.76-0.93))
Kim 2010[33]	USA	1985-2005	M/F; 18-30 y	24.5	validated DHQ	self-reported questionnaire	330 T2D (4497)	302 VS. 182 (0.53 (0.32-0.86))
Kirii 2010[34]	Japan	NA	M/F; 40-65 y	22.9	validated FFQ	self-reported questionnaire	459 T2D (17592)	303 VS. 158 (0.64 (0.44-0.94))

Nanri 2010[35]	Japan	1990-1995	M; 40-65 y F; 40-65 y	NA	validated FFQ	self-reported questionnaire	634 T2D (25872) 480 T2D (33919)	348 VS. 213 (0.86 (0.63-1.16)) 333 VS. 213 (0.92 (0.66-1.28))
Larsson 2011[36]	Sweden	1998-2008	F; 49-83 y	25	validated FFQ	follow-up examination	1680 stroke (34670)	373 VS. 297 (1.02 (0.82-1.27))
Weng 2012[37]	Taipei	1993-2002	M/F; ≥30 y	24	validated FFQ	follow-up examination or self-reported questionnaire	141 T2D (1604)	406 VS. 212 (0.44 (0.25-0.75))
Zhang 2012[38]	Japan	1988-2006/	M; 40-79 y F; 40-79 y	22.7 22.9	validated FFQ	follow-up examination	634 stroke (23083) 620 stroke (35533)	294 VS. 173 (1.03 (0.79-1.35)) 274 VS. 175 (0.90 (0.69-1.16))
Hata 2013[39]	Japan	1988-2009	M/F; 40-79 y	22.9	validated SFFQ	self-reported questionnaire	417 T2D (1999)	215 VS. 133 (0.63 (0.44-0.90))
Lin 2013[40]	Taipei	1989-2002	M/F; ≥ 18 y	23.3	validated FFQ	follow-up examination and self-reported questionnaire	123 stroke (2061)	378 VS. 210 (0.62 (0.40-0.97))
Oba 2013[41]	Japan	1990-2000	M; 40-69 y F; 40-69 y	23.6 23.5	validated FFQ	self-reported questionnaire	690 T2D (27769) 500 T2D (36864)	349 VS. 232 (0.84 (0.69-1.05)) 356 VS. 211 (0.69 (0.54-0.88))
Sluijs 2013[42]	Netherland	NA	M/F; 21-70 y	NA	FFQ	NA	361 ischemic stroke (36359)	435 VS. 253 (0.76 (0.57-1.01))
Hruby 2014[43]	USA	1995-2001	M/F; 26-81 y	27	validated FFQ	self-reported questionnaire	179 T2D (2582)	395 VS. 235 (0.49 (0.27-0.88))
Sluijs 2014[44]	Netherland	NA	M/F; 21-70 y	NA	FFQ	follow-up examination	631 stroke (36094)	597 VS. 190 (0.64 (0.44-0.94))
Adebamowo 2015[45]	USA	1986-2010	M; 40-75 y	25.4	validated FFQ	self-reported questionnaire	1547 stroke (42669)	467 VS. 267 (0.89 (0.71-1.11))
Adebamowo 2015(2)[46]	USA	1976-2006 1989-2011	F; 30-55 y F; 25-42 y	26.4 25.7	validated FFQ	self-reported questionnaire	3237 stroke (86149) 543 stroke (94715)	411 VS. 233 (0.93 (0.79-1.08))
Bain 2015[47]	Britain	2002-2008	M; 40-75 y F; 40-75 y	26.5 26.2	7-day diary recall	follow-up examination	364 stroke (2000) 511 stroke (2445)	456 VS. 266 (0.81 (0.53-1.22)) 374 VS. 456 (0.82 (0.54-1.24))
Huang 2015[48]	Taipei	2000-2008	M/F; ≥65 y	NA	24 h dietary recall and SFFQ	follow-up examination	231 T2D (1400)	398 VS. 103 (0.59 (0.26-1.33))
Hruby 2017[49]	USA	1984-2012 1991-2013 1986-2012	F; 30-55 y F; 25-42 y M; mean 53.5 y	24.8 24.6 24.8	validated SFFQ	self-reported questionnaire	7620 T2D (69176) 6080 T2D (91471) 3430 T2D (42096)	390 VS. 229 (0.80 (0.73-0.88)) 424 VS. 249 (0.89 (0.81-0.99)) 469 VS. 280 (0.88 (0.77-1.00))
Kokubo 2017[50b]	Japan	1990-2009 1993-2010	M; 40-69 y F; 40-69 y	23.6 23.6	FFQ	follow-up examination	2576 stroke (39505) 1846 stroke (45788)	348 VS. 213 (1.07 (0.86-1.33)) 333 VS. 213 (0.88 (0.67-1.14))
Konishi 2017[51]	Japan	1992-2002	M; ≥35 y F; ≥35 y	22.6 22.1	validated FFQ	self-reported questionnaire	266 T2D (5885) 172 T2D (7640)	469 VS. 310 (1.13 (0.76-1.70)) 432 VS. 285 (0.50 (0.30-0.84))

Abbreviations: FFQ, food-frequency questionnaire; SFFQ, semi-quantitative food-frequency questionnaire; BMI, body mass index; T2D, type 2 diabetes; NA, not available.

[a], different ethnicities of participants are in multiple nations cohort;

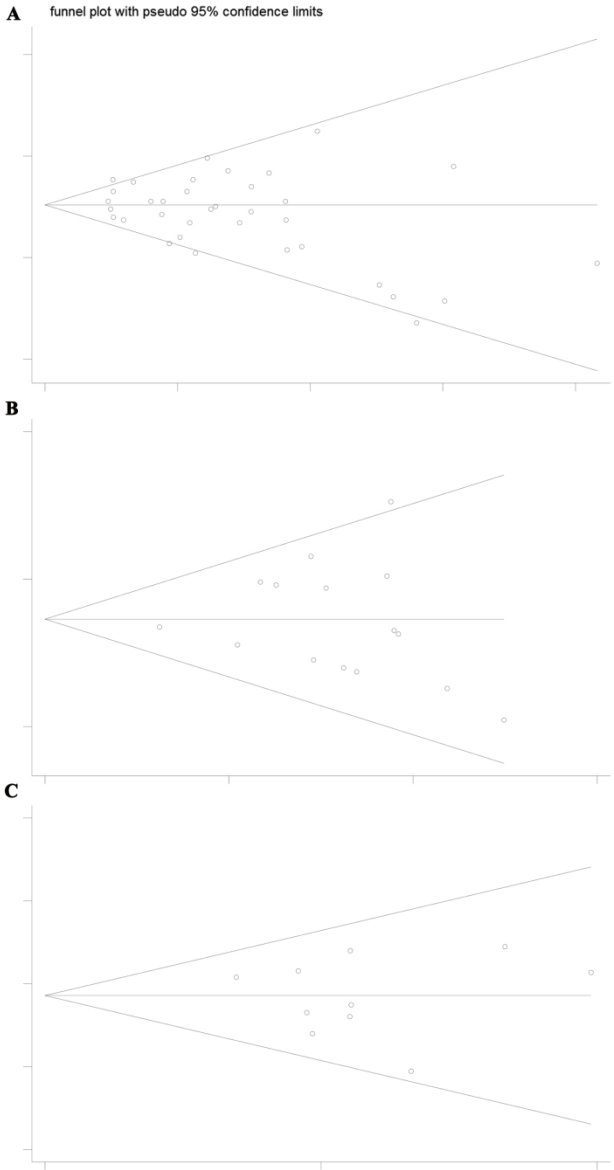
[b], the dose of magnesium intake which is not available in this study is retrieved from the same cohort reported in former publication;

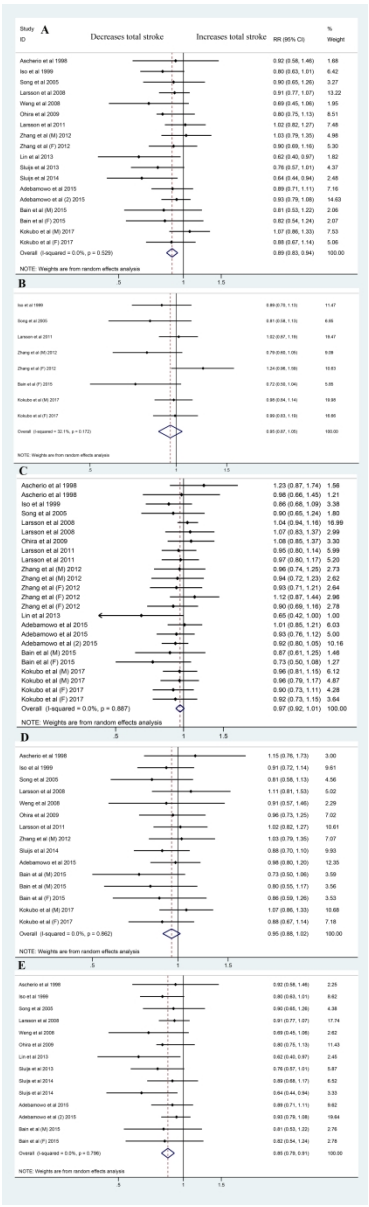
[c] the range of enrolled participants age is not mentioned.

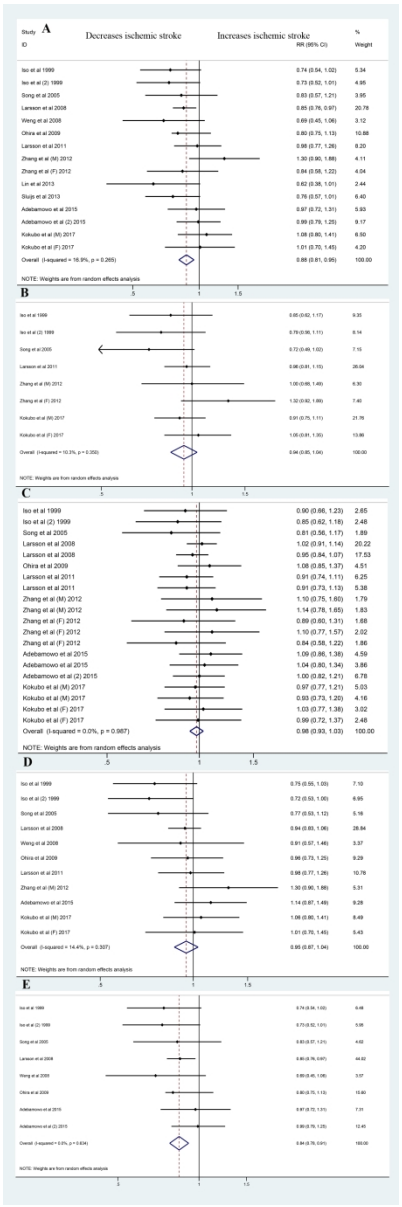
Table S3 Methodological Quality Assessments Of Included Studies With Newcastle-Ottwa Scales

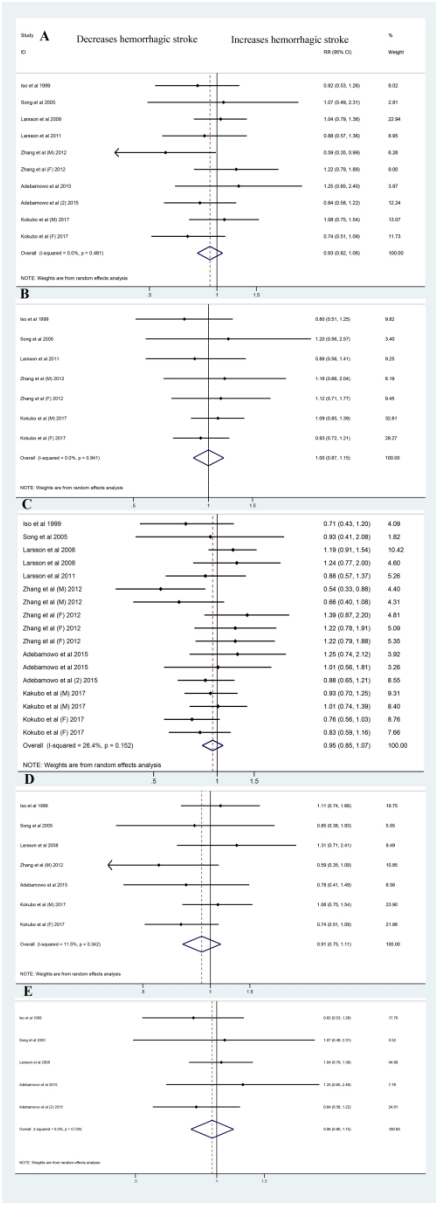
	Study	Selection				Comparability	Outcome			Total score
		Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
1997	Salmeron et al,[11]	*	*	*	*	**	*	*		9
1997	Salmeron et al (2),[12]	*	*	*	*	**	*	*	*	9
1998	Ascherio et al,[13]	*	*	*	*	**	*	*	*	9
1999	Iso et al,[14]	*	*	*	*	**	*	*	*	9
1999	Kao et al,[15]	*	*	*	*	**	*	*	*	9
2000	Liu et al,[16]	*	*	*	*	**	*	*	*	9
2000	Meyer et al,[17]	*	*	*	*	**	*	*	*	9
2004	Hodge et al,[18]	*	*	*	*	*	*	*		7
2004	Lopez et al,[19]	*	*	*	*	**	*	*	*	9
2004	Song et al,[20]	*	*	*	*	**	*	*	*	9
2005	Song et al,[21]	*	*	*	*	**	*	*	*	9
2006	Liu et al,[22]	*	*	*	*	**	*	*	*	9
2006	Pereira et al,[23]	*	*	*	*	**	*	*	*	9
2006	Pittas et al,[24]	*	*	*	*	**	*	*	*	9
2006	Van et al,[25]	*	*	*	*	**	*	*	*	9
2007	Schulze et al,[26]	*	*	*	*	**	*	*	*	9
2008	Larsson et al,[27]	*	*	*	*	**	*	*	*	9
2008	Weng et al,[28]	*	*	*	*	**	*	*	*	9
2009	Kirii et al,[29]	*	*	*	*	**	*	*	*	9
2009	Ohira et al,[30]	*	*	*	*	**	*	*	*	9
2009	Villegas et al,[31]	*	*	*	*	**	*	*	*	9
2010	Hopping et al,[32]	*	*	*	*	**	*	*	*	9
2010	Kim et al,[33]	*	*	*		**	*	*	*	8
2010	Kirii et al,[34]	*	*	*	*	**	*	*	*	9
2010	Nanri et al,[35]	*	*	*	*	**	*	*	*	9
2011	Larsson et al,[36]	*	*	*	*	**	*	*	*	9
2012	Weng et al,[37]	*	*	*	*	**	*	*		8
2012	Zhang et al,[38]	*	*	*	*	**	*	*	*	9

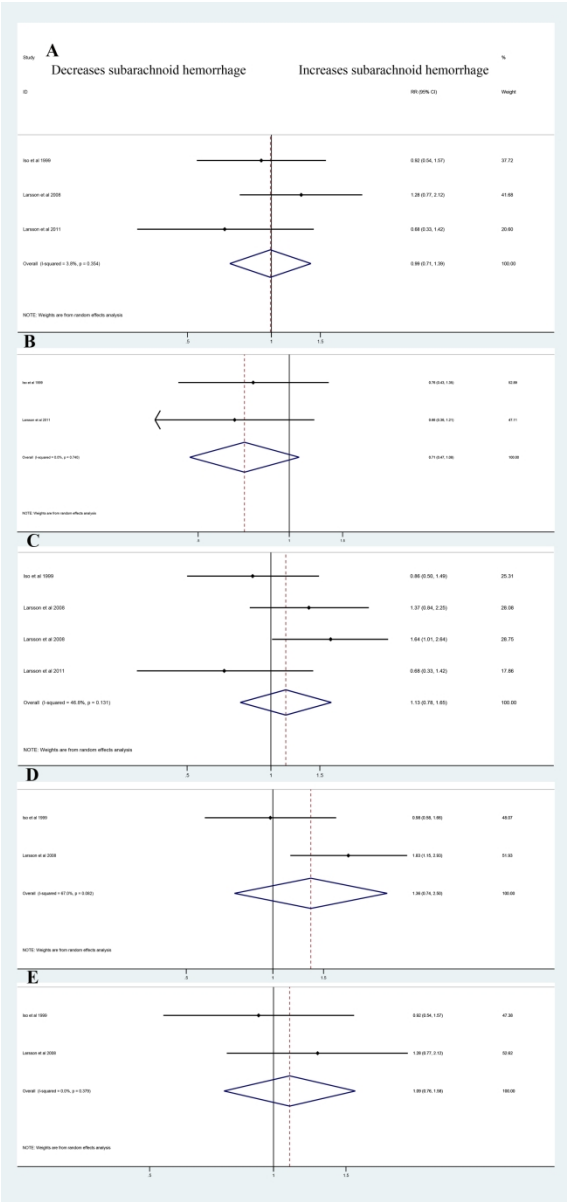
2013	Hata et al,[39]	*	*	*	*	**	*	*	*	9
2013	Lin et al,[40]	*	*	*	*	**	*	*	*	9
2013	Oba et al,[41]	*	*	*	*	**	*	*	*	9
2013	Sluijs et al,[42]	*	*	*	*	**		*	*	8
2014	Hruby et al,[43]	*	*	*	*	**	*	*	*	9
2014	Sluijs et al,[44]	*	*	*	*	**	*	*	*	9
2015	Adebamowo et al,[45]	*	*	*	*	**	*	*	*	9
2015	Adebamowo et al (2),[46]	*	*	*	*	**	*	*	*	9
2015	Bain et al,[47]	*	*	*	*	**	*	*	*	9
2015	Huang et al,[48]	*	*	*		**	*	*	*	8
2017	Hruby et al,[49]	*	*	*	*	**	*	*	*	9
2017	Kokubo et al,[50]	*	*	*	*	**	*	*	*	9
2017	Konishi et al,[51]	*	*	*	*	*	*	*	*	9

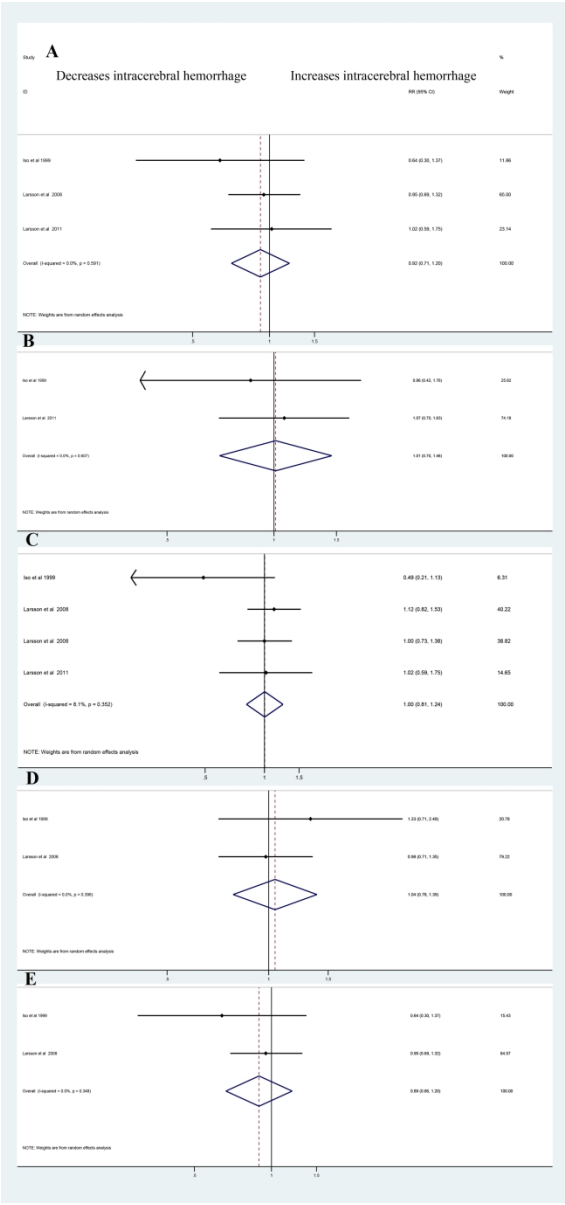

A
funnel plot with pseudo 95% confidence limits
B
C


A
Decreases total stroke
Increases total stroke
B
C
D
E

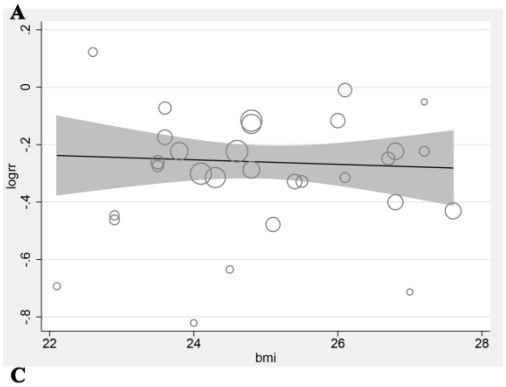

A
Decreases ischemic stroke
Increases ischemic stroke
B
C
D
E


A
Decreases hemorrhagic stroke
Increases hemorrhagic stroke
B
C
D
E


A
Decreases subarachnoid hemorrhage
Increases subarachnoid hemorrhage
B
C
D
E


A
Decreases intracerebral hemorrhage
Increases intracerebral hemorrhage
B
C
D
E

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	10	28.57	28.57
female	17	48.57	77.14
male	8	22.86	100.00
Total	35	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      35
REML estimate of between-study variance         tau2           = .004692
% residual variation due to heterogeneity       I-squared_res  =  36.58%
Proportion of between-study variance explained  Adj R-squared  = -26.08%
Joint test for all covariates                   Model F(2,32)  =    1.31
With Knapp-Hartung modification                 Prob > F       =  0.2841
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.1314075	.0857784	-1.53	0.135	-.3061323	.0433174
sexnew2	-.0630804	.0541113	-1.17	0.252	-.1733016	.0471407
_cons	-.1956565	.0461514	-4.24	0.000	-.2896637	-.1016492

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	13	37.14	37.14
Multiple nations	5	14.29	51.43
North America	17	48.57	100.00
Total	35	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      35
REML estimate of between-study variance         tau2           = .004868
% residual variation due to heterogeneity       I-squared_res  =  39.22%
Proportion of between-study variance explained  Adj R-squared  = -30.89%
Joint test for all covariates                   Model F(2,32)  =    0.16
With Knapp-Hartung modification                 Prob > F       =  0.9047
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew2	.0027567	.0731865	0.04	0.970	-.1463193	.1518327
participantsregionnew3	-.0201457	.0599158	-0.34	0.739	-.1422102	.1018788
_cons	-.2392399	.0510872	-4.68	0.000	-.3433012	-.1351786

D

```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

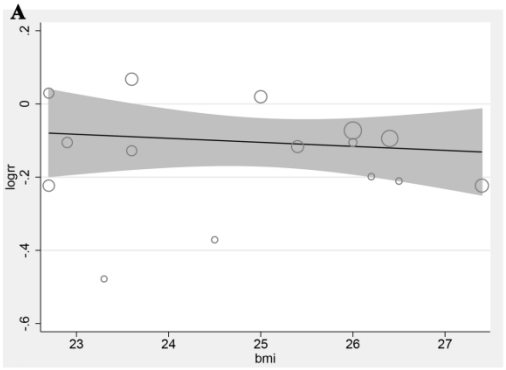
dietaryassessment	Freq.	Percent	Cum.
24h dietary recall and SFFQ	1	2.86	2.86
FFQ	4	11.43	14.29
SFFQ	1	2.86	17.14
validated DHQ	1	2.86	20.00
validated FFQ	17	48.57	68.57
validated SFFQ	11	31.43	100.00
Total	35	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4 dietaryassessmentnew5 dietary
> assessmentnew6, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew4 dropped because of collinearity

Meta-regression                                 Number of obs  =      35
REML estimate of between-study variance         tau2           = .004258
% residual variation due to heterogeneity       I-squared_res  =  38.44%
Proportion of between-study variance explained  Adj R-squared  = -14.42%
Joint test for all covariates                   Model F(5,29)  =    0.86
With Knapp-Hartung modification                 Prob > F       =  0.5210
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew1	.1072455	.5318922	0.20	0.841	-.97894	1.193431
dietaryassessmentnew2	.4672073	.294568	1.58	0.126	-.1393423	1.073757
dietaryassessmentnew3	.5183445	.311752	1.66	0.107	-.1192599	1.155949
dietaryassessmentnew5	.3650754	.2813784	1.30	0.205	-.2104981	.9405589
dietaryassessmentnew6	.3944872	.2812621	1.40	0.171	-.1807583	.9697328
_cons	-.6348783	.279223	-2.27	0.031	-1.205958	-.0637991

A



B

```
. tabulate sex, generate (sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	3	20.00	20.00
female	7	46.67	66.67
male	5	33.33	100.00
Total	15	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   0.00%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    2.64
With Knapp-Hartung modification                 Prob > F       =  0.1120
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew2	.1870375	.0983982	1.90	0.082	-.0273537	.4014286
sexnew3	.2312472	.1011998	2.29	0.041	.0107518	.4517427
_cons	-.2844281	.0870478	-3.27	0.007	-.4740889	-.0947673

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	6	33.33	33.33
Europe	6	33.33	66.67
North America	6	33.33	100.00
Total	18	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml random
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      18
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   1.81%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,15)  =    0.32
With Knapp-Hartung modification                 Prob > F       =  0.7332
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	.0566278	.0763754	0.74	0.470	-.1061625	.2194181
participantsregionnew2	.0028959	.0725841	0.04	0.969	-.1518136	.1576053
_cons	-.1370955	.0474962	-2.87	0.012	-.2387575	-.0354336

D

```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

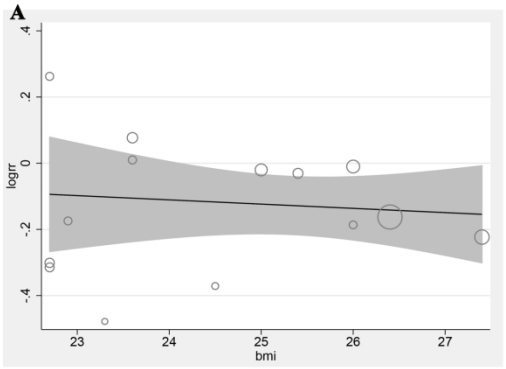
dietaryassessment	Freq.	Percent	Cum.
7-day diary recall	2	11.11	11.11
FFQ	6	33.33	44.44
validated FFQ	9	50.00	94.44
validated SFFQ	1	5.56	100.00
Total	18	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4, wsse (selogrr) knapphartung
> reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      18
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   8.20%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(3,14)  =    0.21
With Knapp-Hartung modification                 Prob > F       =  0.8911
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0596066	.167476	0.36	0.727	-.2995937	.418807
dietaryassessmentnew3	.0984932	.1614344	0.61	0.552	-.2481701	.4651645
dietaryassessmentnew4	.1211665	.291519	0.42	0.684	-.5044595	.7464325
_cons	-.2045601	.1567379	-1.31	0.213	-.5407374	.1316013

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	4	26.67	26.67
female	7	46.67	73.33
male	4	26.67	100.00
Total	15	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .004782
% residual variation due to heterogeneity       I-squared_res  =   1.79%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    2.39
With Knapp-Hartung modification                 Prob > F       =  0.1339
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.2383161	.109578	-2.17	0.050	-.4770662	.0004339
sexnew2	-.0739192	.0940187	-0.79	0.447	-.2787683	.1309299
_cons	-.048002	.0681983	-0.70	0.495	-.1965933	.1005894

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	6	40.00	40.00
Europe	3	20.00	60.00
North America	6	40.00	100.00
Total	15	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .00114
% residual variation due to heterogeneity       I-squared_res  = 21.76%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    0.56
With Knapp-Hartung modification                 Prob > F       =  0.5842
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	.1089103	.1083661	1.01	0.335	-.1271992	.3450197
participantsregionnew2	.0117202	.0911749	0.13	0.900	-.1869328	.2103732
_cons	-.1629514	.0653255	-2.49	0.028	-.3052835	-.0206192

D

```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

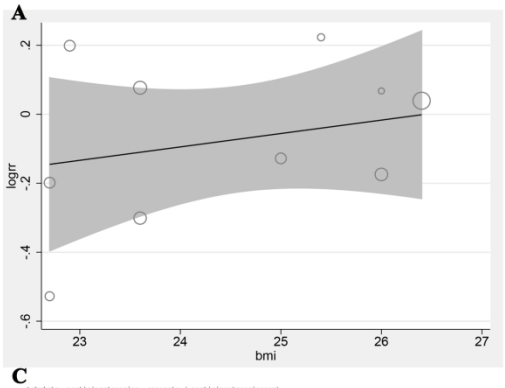
dietaryassessment	Freq.	Percent	Cum.
FFQ	6	40.00	40.00
validated FFQ	9	60.00	100.00
Total	15	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .001922
% residual variation due to heterogeneity       I-squared_res  = 21.79%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0410573	.0897444	0.46	0.655	-.1528236	.2349382
_cons	-.162938	.0753946	-2.16	0.050	-.3258182	-.0000578

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
female	6	60.00	60.00
male	4	40.00	100.00
Total	10	100.00	

```
. metareg logrr  sexnew1 sexnew2, wsse (selogrr) knapphartung reml
note: sexnew2 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   0.42%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.1120692	.1333867	-0.84	0.425	-.4196595	.1955211
_cons	-.0110753	.0978042	-0.11	0.913	-.2366123	.2144617

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	4	40.00	40.00
Europe	2	20.00	60.00
North America	4	40.00	100.00
Total	10	100.00	

```
. metareg logrr participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           = .008835
% residual variation due to heterogeneity       I-squared_res  =  15.78%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,7)   =    0.14
With Knapp-Hartung modification                 Prob > F       =  0.8726
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	-.0106555	.1797495	-0.06	0.954	-.4356955	.4143845
participantsregionnew2	.0796745	.1944402	0.41	0.694	-.3801034	.5394524
_cons	-.0943118	.1371063	-0.69	0.514	-.4185166	.229893

D

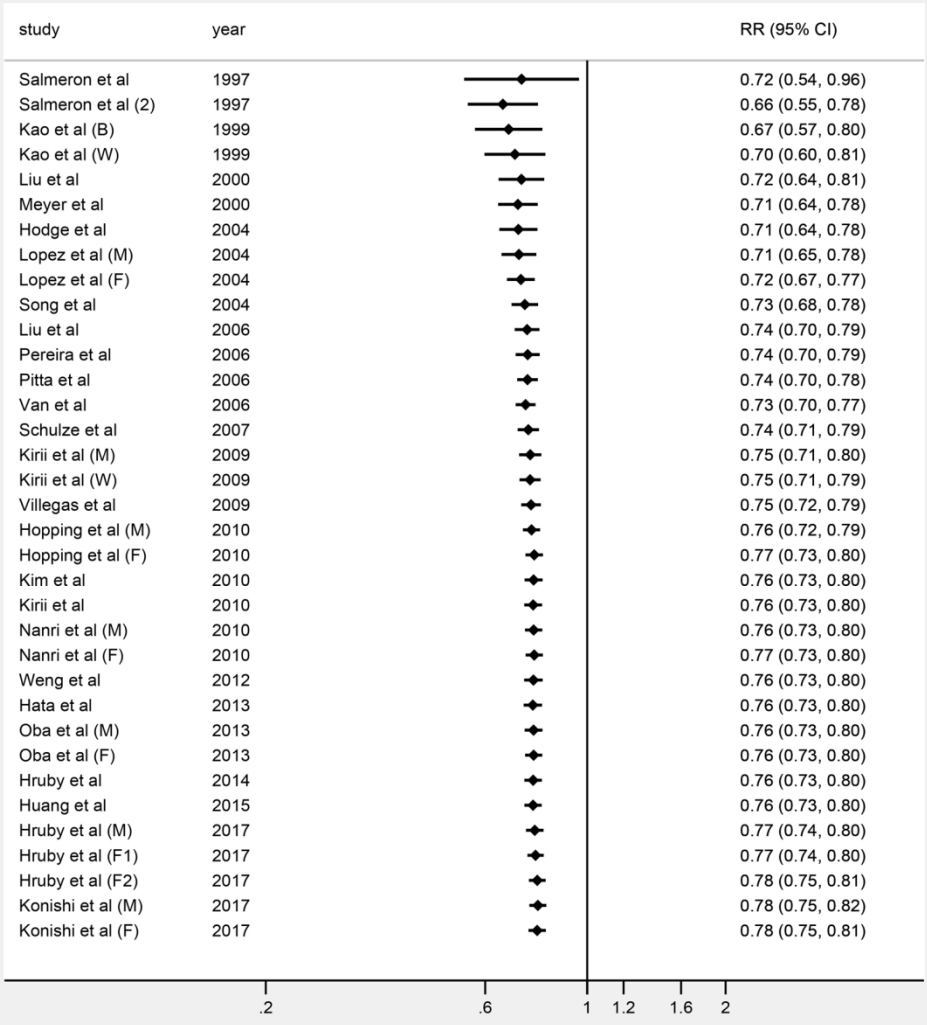
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

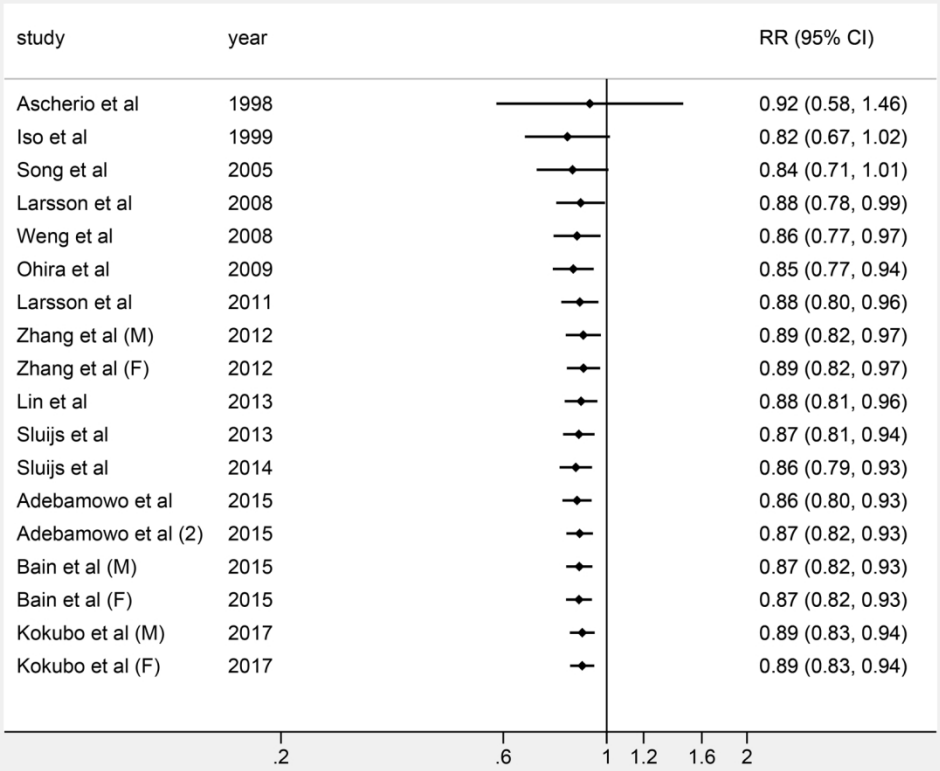
dietaryassessment	Freq.	Percent	Cum.
FFQ	4	40.00	40.00
validated FFQ	6	60.00	100.00
Total	10	100.00	

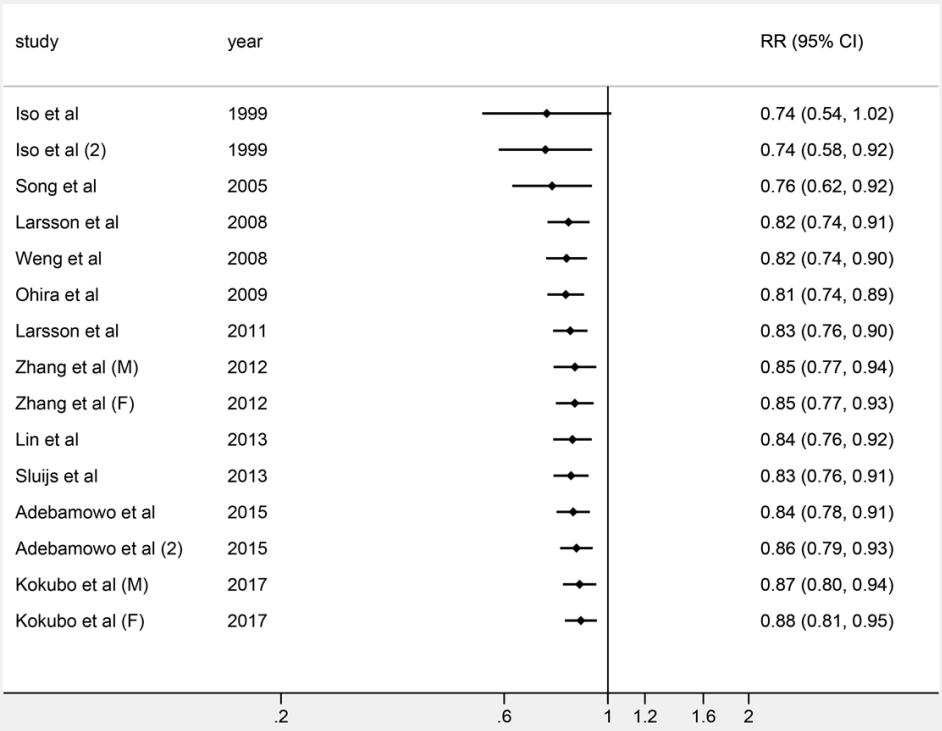
```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           = .001097
% residual variation due to heterogeneity       I-squared_res  =   6.09%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0642559	.1426454	0.45	0.664	-.2646851	.3931968
_cons	-.112665	.1133825	-0.99	0.349	-.3741255	.1487955


study
year
RR (95% CI)
Salmeron et al 1997 0.72 (0.54, 0.96)
Salmeron et al (2) 1997 0.66 (0.55, 0.78)
Kao et al (B) 1999 0.67 (0.57, 0.80)
Kao et al (W) 1999 0.70 (0.60, 0.81)
Liu et al 2000 0.72 (0.64, 0.81)
Meyer et al 2000 0.71 (0.64, 0.78)
Hodge et al 2004 0.71 (0.64, 0.78)
Lopez et al (M) 2004 0.71 (0.65, 0.78)
Lopez et al (F) 2004 0.72 (0.67, 0.77)
Song et al 2004 0.73 (0.68, 0.78)
Liu et al 2006 0.74 (0.70, 0.79)
Pereira et al 2006 0.74 (0.70, 0.79)
Pitta et al 2006 0.74 (0.70, 0.78)
Van et al 2006 0.73 (0.70, 0.77)
Schulze et al 2007 0.74 (0.71, 0.79)
Kirii et al (M) 2009 0.75 (0.71, 0.80)
Kirii et al (W) 2009 0.75 (0.71, 0.79)
Villegas et al 2009 0.75 (0.72, 0.79)
Hopping et al (M) 2010 0.76 (0.72, 0.79)
Hopping et al (F) 2010 0.77 (0.73, 0.80)
Kim et al 2010 0.76 (0.73, 0.80)
Kirii et al 2010 0.76 (0.73, 0.80)
Nanri et al (M) 2010 0.76 (0.73, 0.80)
Nanri et al (F) 2010 0.77 (0.73, 0.80)
Weng et al 2012 0.76 (0.73, 0.80)
Hata et al 2013 0.76 (0.73, 0.80)
Oba et al (M) 2013 0.76 (0.73, 0.80)
Oba et al (F) 2013 0.76 (0.73, 0.80)
Hruby et al 2014 0.76 (0.73, 0.80)
Huang et al 2015 0.76 (0.73, 0.80)
Hruby et al (M) 2017 0.77 (0.74, 0.80)
Hruby et al (F1) 2017 0.77 (0.74, 0.80)
Hruby et al (F2) 2017 0.78 (0.75, 0.81)
Konishi et al (M) 2017 0.78 (0.75, 0.82)
Konishi et al (F) 2017 0.78 (0.75, 0.81)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Ascherio et al 1998 0.92 (0.58, 1.46)
Iso et al 1999 0.82 (0.67, 1.02)
Song et al 2005 0.84 (0.71, 1.01)
Larsson et al 2008 0.88 (0.78, 0.99)
Weng et al 2008 0.86 (0.77, 0.97)
Ohira et al 2009 0.85 (0.77, 0.94)
Larsson et al 2011 0.88 (0.80, 0.96)
Zhang et al (M) 2012 0.89 (0.82, 0.97)
Zhang et al (F) 2012 0.89 (0.82, 0.97)
Lin et al 2013 0.88 (0.81, 0.96)
Sluijs et al 2013 0.87 (0.81, 0.94)
Sluijs et al 2014 0.86 (0.79, 0.93)
Adebamowo et al 2015 0.86 (0.80, 0.93)
Adebamowo et al (2) 2015 0.87 (0.82, 0.93)
Bain et al (M) 2015 0.87 (0.82, 0.93)
Bain et al (F) 2015 0.87 (0.82, 0.93)
Kokubo et al (M) 2017 0.89 (0.83, 0.94)
Kokubo et al (F) 2017 0.89 (0.83, 0.94)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Iso et al 1999 0.74 (0.54, 1.02)
Iso et al (2) 1999 0.74 (0.58, 0.92)
Song et al 2005 0.76 (0.62, 0.92)
Larsson et al 2008 0.82 (0.74, 0.91)
Weng et al 2008 0.82 (0.74, 0.90)
Ohira et al 2009 0.81 (0.74, 0.89)
Larsson et al 2011 0.83 (0.76, 0.90)
Zhang et al (M) 2012 0.85 (0.77, 0.94)
Zhang et al (F) 2012 0.85 (0.77, 0.93)
Lin et al 2013 0.84 (0.76, 0.92)
Sluijs et al 2013 0.83 (0.76, 0.91)
Adebamowo et al 2015 0.84 (0.78, 0.91)
Adebamowo et al (2) 2015 0.86 (0.79, 0.93)
Kokubo et al (M) 2017 0.87 (0.80, 0.94)
Kokubo et al (F) 2017 0.88 (0.81, 0.95)
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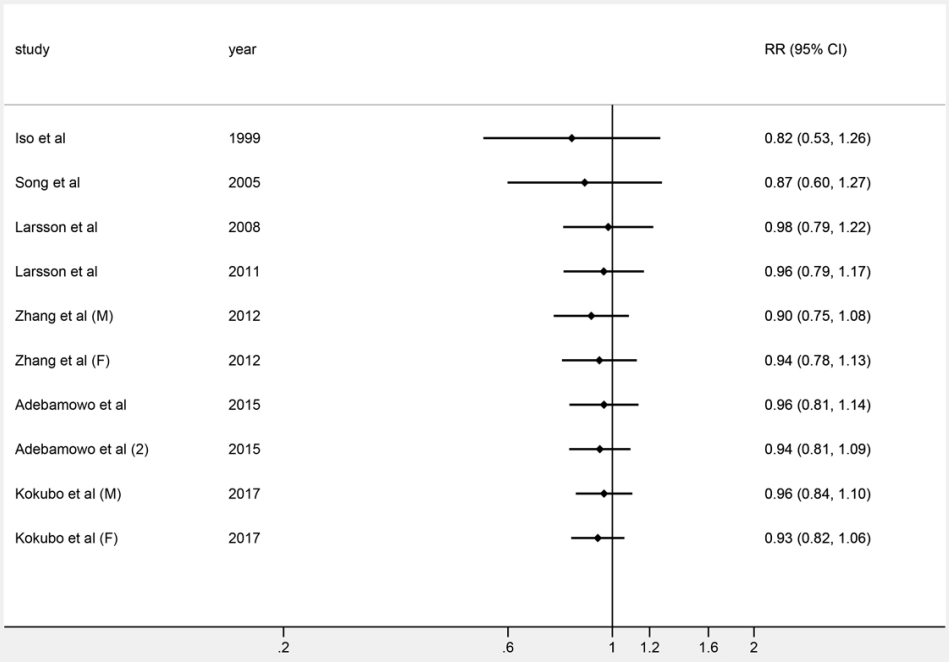
1
1.2
1.6
2


study
year
RR (95% CI)
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1999
0.82 (0.53, 1.26)
Song et al
2005
0.87 (0.60, 1.27)
Larsson et al
2008
0.98 (0.79, 1.22)
Larsson et al
2011
0.96 (0.79, 1.17)
Zhang et al (M)
2012
0.90 (0.75, 1.08)
Zhang et al (F)
2012
0.94 (0.78, 1.13)
Adebamowo et al
2015
0.96 (0.81, 1.14)
Adebamowo et al (2)
2015
0.94 (0.81, 1.09)
Kokubo et al (M)
2017
0.96 (0.84, 1.10)
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2017
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1.6
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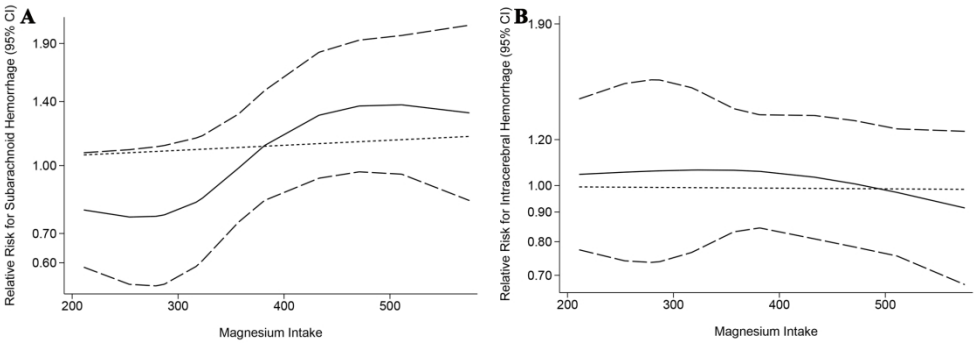
A
Relative Risk for Subarachnoid Hemorrhage (95% CI)
1.90
1.40
1.00
0.70
0.60
200
300
400
500
Magnesium Intake
B
Relative Risk for Intracerebral Hemorrhage (95% CI)
1.90
1.20
1.00
0.90
0.80
0.70
200
300
400
500
Magnesium Intake

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			2-3
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			4-5
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			5-9
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-8

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			9-16
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-16
DISCUSSION			16-22
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			23
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Magnesium intake has inverse association with type 2 diabetes and total stroke: an updated systematic review and meta-analysis

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Keywords:	Magnesium Intake, Type 2 Diabetes, Stroke < NEUROLOGY, Meta-Analysis

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Magnesium intake has inverse association with type 2 diabetes and total stroke: an updated systematic review and meta-analysis

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Short running head: Magnesium Intake Reduces Diabetes and Total Stroke.

Word count: 4971.

Abstract

Objective: The detailed associations between type 2 diabetes (T2D) and total stroke and magnesium intake as well as the dose-response manner should be timely updated.

Design: Systematic review search, methodology and meta-analyses.

Data sources: PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were rigorously searched from the inception to March 15, 2019.

Eligibility criteria: Prospective cohort studies about the two diseases

Data synthesis: Relative risk (RR) and 95% confidence intervals (95% CI) in random-effects models as well as absolute risk (AR) were pooled to calculate risk on T2D and stroke. Methodological quality was assessed by the Newcastle-Ottawa Scale.

Results: Forty-one studies involving 53 cohorts were included. The magnitude of the risk was significantly reduced by 22% for T2D (RR, 0.78 [95% CI, 0.75-0.81]; $P<$ 0.001; AR reduction, 0.120%), 11%for total stroke (RR, 0.89 [95% CI, 0.83-0.94]; $P<$ 0.001; AR reduction, 0.281%), and 12% for ischemic stroke (RR, 0.88 [95% CI, 0.81-0.95]; P = 0.001; AR reduction, 0.246%) comparing the highest magnesium intake to the lowest. The inverse association still existed when studies on T2D were adjusted for cereal fiber (RR, 0.79 [95% CI, 0.73-0.85]; $P<$ 0.001) and those on total stroke were adjusted for calcium (RR, 0.89 [95% CI, 0.80-0.99]; P = 0.040). Subgroup analyses suggested risk for total and ischemic stroke was significantly decreased in females, participants with ≥ 25 mg/m^2 body mass index, and those with ≥ 12y follow-up, the reduced risk in Asia was not so conspicuous as in North America and Europe.

Conclusions: Magnesium intake has significantly inverse associations with T2D and total stroke in a dose-dependent manner. Feasible magnesium–rich dietary pattern may highly benefit specific populations, and can be highlighted in the primary prevention of T2D and total stroke by the public.

PROSPERO registration number CRD42018092690

Strengths and limitations of this study

1. An inverse association between magnesium intake and T2D and stroke is established.
2. Magnesium-rich food consumption may be recommended for high-risk individuals in dietary guidelines.
3. Considerable evidence assists with innovation of the global dietary pattern.
4. Event ascertainments are limited by FFQ or self-reports.
5. More individual-level studies are required for reducing potential bias.

Keywords: Magnesium Intake; Type 2 Diabetes; Stroke; Meta-Analysis.

Introduction

Diabetes is a global burden with an alarming increasing rate throughout the world[1,2]. Stroke is an independent disorder and a typical macrovascular complication of type 2 diabetes (T2D) treated as the second leading cause of death after ischemic heart disease[3,4]. These pandemic health problems require more primary prevention strategies.

Magnesium, common cellular ion, acts as critical cofactor for hundreds of enzymes involved in glucose metabolism, protein production, and nucleic acid synthesis[5,6]. Low levels of magnesium have been associated with many chronic and inflammatory diseases, such as Alzheimer's disease, asthma, attention deficit hyperactivity disorder, insulin resistance, T2D, hypertension, cardiovascular disease (e.g., stroke), migraine headaches, osteoporosis and cancer[1,5,7,8].

Actually, many adults in developed countries do not successfully meet the recommended daily consumption of magnesium-rich foods such as whole grains, nuts, and green leafy vegetables, and magnesium is less mentioned in dietary guidelines and in studies about T2D or stroke prevention[9,10]. With this regard, we chose T2D and stroke as our outcome of interest (cardiovascular disease (CVD) was not elaborated because there are so many items relating to CVD and the definitions about CVD varied a lot among searched studies, which would enhance heterogeneity in the pooled process and impair our interpretation of the final conclusion). And, emerging studies[11-51] on this topic are limited, and the results still remain mixed, for example, most of the studies support magnesium intake has inverse association with T2D or

total stroke incidence, however, several studies reveal there is an inverse trend but not significant association, which possibly due to the limitations of small simple sizes and differences in intervention duration, study design, characteristics of participants. Moreover, consecutive meta-analyses[52,53] have used less rigorous inclusion, the results were incomprehensive, and they did not completely address the influence of other confounders (i.e., body mass index (BMI), cereal fiber, calcium, potassium) on the relationship. Accordingly, we performed a meta-analysis to (1) establish a comprehensive estimate and update the epidemiological evidence for clinical practice; (2) discuss the results of stroke subtype and the impact of several statistical and epidemiology confounders on the investigated association; and (3) highlight a detailed dose-response pattern for the participants in the studies analyzed.

Methods

This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines Checklist (**Table S2**) (Registration information: PROSPERO CRD42018092690).

Search Strategy

PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were systematically reviewed through inception to March 15, 2019 for studies about magnesium intake and T2D or stroke without language restrictions. The following key

words were used: “Magnesium”, “Type 2 Diabetes Mellitus”, “Type 2 Diabetes”, “Stroke”, “Cerebrovascular Stroke”, “Cohort Studies”, and “Prospective Studies”. We also manually searched the reference lists of the retrieved literature (including meta-analyses and brief reports), bibliographies and gray literature (including presentations and unpublished literature) for further eligible articles. The search strategy could be found in **Table S3**.

Selection Criteria

(1) Eligible populations must be composed of individuals with plausible dietary/energy intake, who had no history of diabetes and/or insulin treatment for T2D analysis and no current stroke for stroke analysis. (2) Their apparent life expectancy was long enough for proper follow-up. (3) We only included prospective cohort studies that reported magnesium intake and T2D and/or various types of stroke. (4) Follow-up duration of eligible studies should not be less than one year if they provided the follow-up data. Notably, magnesium intake contained dietary magnesium intake and total magnesium intake (dietary and supplementary magnesium).

Only studies containing the most comprehensive information on the population or endpoints were included to avoid duplication. We excluded reviews, basic studies, meta-analyses, studies on gestational diabetes mellitus (GDM) or studies only focusing on magnesium supplementation.

Data Extraction and Quality Assessments

Two researchers independently extracted the following information: the first author, publication year, period of cohort studies, duration of persistent exposure, basic characteristics of the enrolled participants (weight, age, region, BMI, drinking and smoking habits (previous plus current), etc.), median magnesium intake for each quantile (tertile, quartile, or quintile), diabetes and total stroke cases, subtypes of total stroke, dietary and case assessments, adjusted confounding covariates. Importantly, total stroke is classified as clinical ischemic stroke (87%), hemorrhagic stroke (13%) and undetermined stroke[54]. Hemorrhagic stroke is classified as subarachnoid hemorrhage and intracerebral hemorrhage according to anatomical site or presumed etiology[55].In cases of continuing disagreement, a final decision was reached after discussion with a third member of the panel.

Methodological quality was described by the Newcastle-Ottawa Scale (NOS), which was validated for assessment of the quality of nonrandomized controlled trials in meta-analyses[56]. As for 0-10 scale, each study was categorized as low (0-5), medium (6-7), of high (8-10) quality.

Statistical Analysis

Articles providing data separately for men and women or black and white or different types of disease within an article were treated as independent studies. Multivariate relative risk (RR) and corresponding 95% confidence intervals (CI) as well as absolute risk (AR) for measuring the quantitative associations between exposure and

T2D, total stroke and other wanted outcomes, particularly for the highest vs. the lowest categories of magnesium intake were estimated by DerSimonian-Laird random effects model because the assumptions involved account for the presence of within-study and between-study variability. Statistical heterogeneity was determined with the Cochran Q chi-square test and the I^2. An I^2> 50% or a P value for the Q test < 0.1 was considered to indicate significant heterogeneity[57]. We performed sensitivity analyses to test the robustness and post-subgroup analyses to detect source of heterogeneity. In addition, a random-effects meta-regression analysis on BMI, sex, participants region, and dietary assessments with RR for each trial was performed to obtain an understanding of the reasons for heterogeneity. RR and 95% CI might begin to significantly change as publication years increased in T2D and total stroke etc., which would be validated by cumulative meta-analyses.

The dose-response analyses for all outcomes were proposed by Greenland and Longnecker[58] and Orsini[59] et al. The categories of magnesium intake, distributions of cases and person-year, RR and 95 CI were extracted. Once the number of cases and/or person-years was not available, variance-weighted least squares regression was used to pool the risk estimate. For most studies, the median intake for each quantile (tertile, quartile or quintile) of magnesium intake was assigned as the representative dose. For continuous intake reported as category data with a range in some studies, we assigned the mid-point category of the lower and upper bound to the RR in these studies; when the highest category was open ended, we assumed the length of the open ended interval to be 1.5 times as the adjacent interval; when the lowest category was open,

we assigned the adjacent interval of the category to be 1.5 times as the length of the open ended interval. We determined generalized least squares regression models to calculate study-specific RR estimates per 50 mg/day, 100 mg/day, and 150 mg/day of magnesium intake increment if there was evidence for linear relationships. In addition, the non-linear relationships between magnesium intake and all outcomes were evaluated using restricted cubic splines with four knots located at the 5th, 35th, 65th, and 95th percentiles of the distribution. The P value for curve linearity or non-linearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. All results were presented using two-stage dose-response model plots (including linear and nonlinear relationships).Some results were demonstrated in forest plots for < 50 mg/day, ≥ 50 and < 100 mg/day, ≥ 100 and < 150 mg/day, ≥ 150 mg/day increments.

Publication bias was assessed graphically by Begg's adjusted rank correlation funnel plots[60] and Egger's linear regression tests[61]. All analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA); two-sided $P < 0.05$ was considered statistically significant except where otherwise specified.

Patient and Public Involvement

No patients were involved in setting the research question or the outcome measures, and no patients were involved in developing plans for design or implementation of the study. Furthermore, no patients were asked to advice on interpretation or writing up of results. Since this study used aggregated data from previous publications, it is not easy

to disseminate the results of the research to study participants directly.

Results

Study Characteristics and Quality Assessment

Of the total 8713 studies, 107 studies were considered for eligibility after screening of titles and abstracts (**Figure 1**). And a total of 41[11-51] prospective cohort studies involving 53 cohorts, 1 912 634 participants and 76 678 cases were eligible for current systematic review and meta-analysis (**Table S4**). Hodge et al[18] only recorded 500 mg/day increment of magnesium for further pooled analyses; 2 studies[33,51] failed to clearly distinguish the diabetes type, but the great majority of cases had T2D. We computed the subtype data in three studies[14,27,36] after the extraction of total stroke, and we considered ischemic stroke in three other studies[28,30,42] as total stroke given ischemic stroke accounting for nearly 87% of total stroke. Participants were predominately middle-age at baseline, with mean magnesium intake for the highest category of 370 mg/day, mean for the lowest category of 232 mg/day. The mean duration of all eligible studies was 10.7 years. Nineteen studies were conducted in North America (America); 5 studies were in Europe (Sweden, the Netherlands and Britain); 13 studies in Asia (China and Japan and Taipei); 4 studies enrolled individuals in multiple nations. Most of the studies included used food frequency questionnaires (FFQs) or semi-quantitative FFQs (SFFQs) to assess individual dietary intake. Eighteen studies used dietary magnesium intake, and 21 studies recorded total magnesium intake (dietary and supplementary magnesium intake). Of note,

supplementary magnesium intake was assessed from the use of magnesium or multivitamin supplements; nevertheless, dietary magnesium accounted for the majority of magnesium intake. Adjusted confounders were mostly similar; however, adjusted dietary confounders such as cereal fiber, potassium, and calcium still varied across individual studies. It was unclear whether included studies had adjusted for sodium because they did not provide the information. All these studies were written in English.

After the quality assessments of the studies according to NOS, the average score was 8.85 (**Table S5**) and all studies were of high quality (NOS score 8-10).

Magnesium Intake and T2D Incidence

Thirty-five cohorts from 26 publications[11,12,15,20,22-26,29,31-35,37,39,41,43,48,49,51](1 219 636 participants and 56 540 T2D cases) reported the magnitude of the risk of T2D was reduced by 22% (RR, 0.78 [95% CI, 0.75-0.81]; $P < 0.001$; AR reduction, 0.120%) comparing the highest category of magnesium intake to the lowest with a little evidence of heterogeneity (I^2 = 35.6%; P = 0.021). The dose category-specific analysis suggested that for < 50 mg/day magnesium increment, the risk of T2D was reduced by 10% (RR, 0.90 [95% CI, 0.88-0.93]; $P< 0.001$); for ≥ 50 and < 100 mg/day, the risk was decreased by 16% (RR, 0.84 [95% CI, 0.82-0.87]; $P < 0.001$); for ≥ 100 and < 150 mg/day, the risk was reduced by 22% (RR, 0.78 [95% CI, 0.74-0.83]; $P < 0.001$); and for ≥ 150 mg/day, the risk was reduced by 21% (RR, 0.79 [95% CI, 0.74-0.84]; $P < 0.001$) (**Figure 2**). Little evidence of publication bias was

found (Egger's test: $P = 0.088$) (**Figure S1A**).

Magnesium Intake and Stroke Incidence

Eighteen cohorts from 15 publications[13,14,21,27,28,30,36,38,40,42,44-47,50] (692 998 participants and 20 138 total stroke cases) reported the magnitude of the risk of total stroke was decreased by 11% (RR, 0.89 [95% CI, 0.83-0.94]; $P < 0.001$; AR reduction, 0.281%) with no heterogeneity ($I^2 = 0\%$; $P = 0.529$) in the highest category of magnesium intake VS. the lowest. Dose category-specific analysis identified no significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and < 150 mg/day of increments. For the ≥ 150 mg/day increment, the risk of total stroke was decreased by 15% (RR, 0.85 [95% CI, 0.79-0.91]; $P< 0.001$) (**Figure S2)**. Publication bias was evaluated for stroke subtypes respectively.

Fifteen cohorts from 12 publications[14,21,27,28,30,36,38,40,42,45,46,50] reported ischemic stroke. The magnitude of the risk of ischemic stroke was reduced by 12% (RR, 0.88 [95% CI, 0.81-0.95]; $P = 0.001$; AR reduction, 0.246%) with no significant heterogeneity ($I^2 = 16.9\%$; $P = 0.265$). Dose category-specific analysis identified no significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and < 150 mg/day increments. A trend to decrease existed but remained insignificant. The original risk was reduced by 16%in the analysis of the ≥ 150 mg/day increment (RR, 0.84 [95% CI, 0.78-0.91]; $P< 0.001$) (**Figure S3)**. No publication bias was observed in terms of ischemic stroke (Egger's test: $P = 0.937$) (**Figure S1B**).

Ten cohorts from 8 studies[14,21,27,36,38,45,46,50] reported that hemorrhagic stroke was

not significantly associated with magnesium intake (RR, 0.93 [95% CI, 0.82-1.06]; P = 0.282). Dose category-specific analysis identified no significant association (**Figure S4)**. No significant heterogeneity or publication bias were identified with regard to hemorrhagic stroke (Egger's test: P = 0.809) (**Figure S1C**).

Three publications involving 3 cohorts[14,27,36] showed that high magnesium intake had no significant efficacy in reducing subarachnoid hemorrhage risk (RR, 0.99 [95% CI, 0.71-1.39]; P = 0.963). Dose category-specific analysis identified no significant association (**Figure S5)**.

With respect to intracerebral hemorrhage, the pooled results from 3 cohorts[14,27,36] in 3 publications revealed no significant advantages of intracerebral hemorrhage (RR, 0.92 [95% CI, 0.71-1.20]; P = 0.540). Dose category-specific analysis identified no significant association (**Figure S6)**.

Meta-Regression and Cumulative Meta-Analysis

Meta-regression identified no evidence of BMI, sex, participant region and dietary assessment for each individual trial bias in T2D (**Figure S7**), total stroke (**Figure S8**), ischemic stroke (**Figure S9**) and hemorrhagic stroke events (**Figure S10**). The male subgroup (P = 0.041) in the sex category might cast little heterogeneity on total stroke; however, the sex category (P = 0.112) had no association with total stroke incidence.

Analyses on T2D (**Figure S11)**, total stroke (**Figure S12)** and ischemic stroke demonstrated that the RRs of the final results became robust within a narrow range and remained significant as publication years increased and as recent high quality

studies were included. After inclusion of the Iso et al[14] study, the RR and 95% CI for ischemic stroke decreased to less than 1 and became stable (**Figure S13).** Although there was no significantly reduced risk in hemorrhagic stroke, clear evidence showed that the confidence interval was becoming narrow, which had a trend toward significance (**Figure S14**). Thus, risk for hemorrhagic stroke might be reduced, and further studies are still needed.

Sensitivity Analysis

When three[24-26] studies were excluded in T2D analysis, the summary RR changed from 0.78 ([95% CI, 0.75-0.81]) to 0.78 ([95% CI, 0.75-0.82]) with the heterogeneity declining from (I^2 = 35.6%; P = 0.021) to (I^2 = 24.0%; P = 0.112). Among T2D analysis, eight studies[19,22,23,26,33,39,48,49] adjusted for cereal fiber intake yield an RR of 0.79 ([95% CI, 0.73-0.85]; P< 0.001) and two studies[15,35] for calcium yielded an RR of 0.87 ([95% CI, 0.73-1.04]; P = 0.128). While among total stroke analysis, the summary RR was 0.92 ([95% CI, 0.82-1.02]; P = 0.097) in five studies[13,44-46,50] adjusted for potassium intake and was 0.89 ([95% CI, 0.80-0.99]; P = 0.040) in five studies[14,44-46,50] adjusted for calcium. Only one study[15] adjusted for potassium intake in T2D, one study[36] for cereal fiber in total stroke.

Subgroup Analysis

Stratified analyses by characteristics of the population and study design were conducted on T2D (**Table 1**), total stroke, ischemic stroke and hemorrhagic stroke

(**Table 2**). The inverse association with T2D remained robust across all subgroups with little evidence of heterogeneity. As for stroke incidence, a decreased risk of total stroke and ischemic stroke was found in female participants (RR, 0.91 [95% CI, 0.83-0.99] for total stroke; 0.89 [95% CI, 0.79-1.00] for ischemic stroke) and individuals with ≥ 25 kg/m^2 mean BMI (RR, 0.89 [95% CI, 0.82-0.96] for total stroke; 0.88 [95% CI, 0.81-0.96] for ischemic stroke). When restricted to a ≥ 12 y follow-up, the risk of total stroke and ischemic stroke could be significantly reduced (RR, 0.89 [95% CI, 0.83-0.95] for total stroke; 0.88 [95% CI, 0.81-0.95] for ischemic stroke). These risks were more reduced in North American and European individuals than Asians. Cardiovascular events (CV events, coronary heart disease, heart failure, atrial fibrillation, and self-reported heart disease etc. other than stroke), hypercholesterolemia and diabetes would blunt the effect of magnesium on total and ischemic stroke. However, magnesium intake could still, or at least, demonstrate the trend to decrease total and ischemic stroke in individuals even with those risk factors. Similarly, CV events, hypercholesterolemia and family diabetes history had no substantial impact on the inverse association between T2D incidence and magnesium intake. We did not find significantly reduced risk in hemorrhagic stroke across the subgroup analyses.

Dose-Response Analysis

In this part, both linear and nonlinear relationships were found in T2D (**Figure 3A)**, in total stroke (**Figure 3B)**, and in ischemic stroke (**Figure 3C).** However, no linear or

non-linear dose-response relationship was observed in hemorrhagic stroke (**Figure 3D)** along with the subtypes including subarachnoid hemorrhage and intracerebral hemorrhage (**Figure S15)**.

Specifically, we calculated RR for the magnesium increments if there was linear relationship found. The calculated RR was 0.94 ([95% CI, 0.93-0.95]) for the 100 mg/day increment for T2D. For total stroke, the summary RR was 0.98 ([95% CI, 0.97-0.99]) related to 100 mg/day increment in magnesium intake, RR for ischemic stroke was 0.98 ([95% CI, 0.97-0.99]) related to 100 mg/day increment in magnesium intake. There was no RR cut-off point at which the decreasing trend reversed, but the RR decreased a bit rapidly with any slightly decreases at approximately 260 mg/day for T2D and 350 mg/day for total/ischemic stroke. But there was substantial uncertainty in the lower range of this distribution (**Figure 3A, 3B, 3C)**.

Discussion

Main findings

This paper used a general and up-to-date search strategy to identify some additional studies that were missed in prior meta-analyses under real-world conditions. Our results support a significant inverse association between magnesium consumption and T2D, total stroke and ischemic stroke at the highest level vs. the lowest. No significant association for hemorrhagic stroke, subarachnoid hemorrhage and intracerebral hemorrhage was detected. Female obese participants (mean BMI ≥ 25 kg/m^2) with longer follow-up period (≥ 12 y) might obtain a greater benefit from

magnesium intake with a lower risk of total and ischemic stroke incidence. In subgroup analyses, RR of stroke risk was highly decreased among North American and European individuals. Significant risk reduced by 6%, 2%, and 2% for T2D, total stroke and ischemic stroke respectively at per 100 mg/day increment in magnesium intake level. Overall, our study supports the guidelines to address the role of magnesium intake for T2D and stroke early prevention. Even though, we still require more randomized controlled trials (RCTs) in the future to validate the causality.

Clinical implications

Dietary nutrients are hot topics for current clinical medicine, folic acid, vitamin D, and ω-3 fatty acids have been specifically recommended to pregnant women, infants and children, and the elderly[62,63], however, magnesium has been less extensively discussed. This is a noteworthy study for the following reasons. First, current study reinforces the possible role of magnesium in the prevention and management of two chronic illnesses and causes new considerations on the avoidance of other chronic disease with potential diet strategy. Second, this comprehensive study with nearly two million individuals and abundant statistical power provides confirming evidence for medical practitioners, health educators and policy makers. Third, until this study, no related paper has discussed such detailed stratified analyses, which helps physicians to amplify the dietary benefits through individualized strategies. Interestingly, we detected North American and European participants seemed to receive more benefits from magnesium intake than Asians. Fourth, to our knowledge, this is the first study

in which cumulative meta-analysis was performed to forecast the changing tendency of main risk estimates. Based on past and current cutting edge evidence about nutrition and T2D prevention, the US Diabetes Prevention Program (DPP) conducted a study that demonstrated that proper lifestyle modification (exercise and Mediterranean diet) significantly reduced T2D risks irrespective of population baselines, and the benefit expanded with increased follow-up[64]. The UK national health service (UK NHS) will launch an intervention program including weight loss, nutrition, monitoring and peer support targeting up to 10 000 people prone to develop T2D[65].

2018 American Diabetes Association (ADA) guidelines[66] recommend to enhance intake of nuts, berries, yogurt, coffee and tea in individuals who are at high risk of diabetes. The latest guidelines by the American Heart Association (AHA)/American Stroke Association (ASA)[9] also validate considerable status of early management of stroke (ischemic stroke). In fact, magnesium is a cofactor of enzyme systems that regulate diversity biomedical reactions including protein synthesis, muscle and nerve transmission, neuromuscular conduction, signal transduction blood glucose control and blood pressure management[67]. Magnesium played a role in transporting calcium and potassium ions across cell membrane, also is crucial for structural function of proteins, nucleic acids or mitochondria[68]. In diabetes, magnesium achieves glucose and insulin metabolism through tyrosine kinase activity of the insulin receptor, intake of magnesium also influences phosphorylase B kinase activity by releasing glucose-1-phophate from glycogen. Magnesium regulates glucose translocation into

the cell[69]. In stroke higher magnesium level deregulates glutamate and calcium cation influx by reducing NMDA receptor activity, and blocks voltage-gated calcium channel eliminating calcium cation cytotoxicity. Additionally, magnesium has vasodilatory effect which may do benefit to ischemic stroke patients[70]. In deed, a poor outcome on hemorrhagic stroke was observed in a RCT, however, high serum magnesium might be better for intracerebral hemorrhage prognosis[71].

Most specific nutrients especially macronutrients are correlated with total energy intake. In included free-living human studies, variation of total energy intake is originated from physical activity, differences in body size, and differences in energy efficiency[72]. Thus total energy intake can weaken the investigated association with considerable nutrients intake if this covariable is not properly removed. Epidemiologists should assess reproducibility and validity of energy-adjusted nutrients as well as absolute nutrients intake. Though micronutrient as magnesium is, inverse association could be still found in T2D, total stroke and ischemic stroke outcomes after total energy intake adjustment. As for other nutrients, potassium intake is proposed to lower blood pressure (BP) and improve vascular outcomes (including stroke); dietary potassium may also be influential in glucose control and limiting the risk of diabetes[73]. Vitamin D and calcium may negatively influence glycemia, but the evidence is limited for mostly being based on cross-sectional observational studies[74]. Calcium may be inversely associated with stroke in populations with low to moderate calcium intakes, but no significant association was found between calcium and CVD[75]. All things considered, magnesium-rich food such as nuts (151-567 mg/100g edibles),

fruits (132-448 mg/100g edibles), vegetables (132-1257 mg/100g edibles), legumes (138-243 mg/100g edibles), fish (143-303 mg/100g edibles) and total grain (134-306 mg/100g edibles) should be recommended to populations with insufficient magnesium intake.

Compared with other similar studies

This seminar has several differences with previous studies. Dong et al[52] found magnesium intake had an inverse association with T2D incidence (RR, 0.78 [95% CI, 0.73-0.84]), and with an intake of 100 mg/day magnesium, the risk was reduced by 14%. In fact, they failed to include adequate studies, and standard quality assessments of eligible studies were absent. Individuals from multiple nations in some studies[18,25,26,32] were incorrectly assigned to Asia or the U.S. in the subgroups, and minor imperfections existed in the selection criteria because it was unclear whether they excluded participants with subclinical diabetes. BMI was not a potential modifier for T2D in our study due to the inclusion of more evidence which had longer follow-up period. Fang et al[76] revealed dietary magnesium was significantly associated with reduced risk of T2D (RR, 0.74 [95% CI, 0.69-0.80]) and stroke (RR, 0.88 [95% CI, 0.82-0.95]). The results were comparable, but they just focused on dietary magnesium intake rather than overall magnesium intake (total or dietary), and subtypes of total stroke were missed. To our overall knowledge, BMI, follow-up, family diabetes history, etc. were crucial confounders for evaluating the association, which were not addressed in their study. Moreover, researchers had better investigate

the likelihood of linear association in the dose-response pattern (using methods by Greenland and Orsini et al). Fang et al[77] found that the 100 mg/day intake of dietary magnesium was associated with an 8-13% reduction in T2D risk, and while a nonlinear relationship did not exist, a minor publication bias was present. Twenty-five studies were eligible; however, some of them focused not on dietary but on total magnesium intake. Moreover, there were two included studies focusing on red meat intake instead of magnesium intake. After excluding actual ineligible studies, we found no evidence of publication bias. Additionally, both linear and nonlinear relationships existed for T2D, because the RRs of the highest category of magnesium intake VS. the lowest in our pooled study were still used. A study by Larsson et al[53]including 7 studies supported a modest but statistically significant inverse association between dietary magnesium intake and stroke. The sample size was quite small, and there was no useful information for stroke subtypes (e.g., ischemic stroke, hemorrhagic stroke) in the main analysis. In our opinion, a well-designed subgroup analysis is a compulsory undertaking, and a pooled stroke result restricted by potassium and calcium adjustment is recommended. The current study found magnesium intake was strongly inversely associated with total stroke and ischemic stroke, which still existed in the dose-response pattern.

Directions for further research

Future studies still have something to be addressed. At first, no significant association was found in hemorrhagic stroke, however, the beneficial trend was observed in the

cumulative meta-analysis, which addresses needs for more updated prospective studies and RCTs. Second, there is a key question regarding the optimal time to start prevention and methods to screen severe complications. Cardiovascular events occur in more than 50% and diabetic kidney disease occurs in 20-40% of patients with diabetes. Actually, cardiovascular events increase the risk of death three to four times compared with patients without such complications. A sustained period of intensive glucose control early in T2D has been confirmed to reduce complication rates[78]. Most importantly, to the public, educators and guideline makers, boosting magnesium-rich food consumption relates to considerable benefits to T2D and total stroke prevention, especially in high-risk populations.

Limitations

Several limitations deserve further discussion. First, this group-level meta-analysis is insufficient. Although strong inverse associations for T2D and total stroke were reported, individual-level studies having more detection power are required. Second, several variations cannot be totally understood, for example, we cannot exclude the possibility that other nutrients and/or dietary components correlated with dietary magnesium may have been responsible, either partially or entirely, for the observed associations. Based on eligible studies, we could not quantify the impact of supplementary magnesium (not combined with dietary intake) on T2D and stroke incidence. The real effect of some dietary supplements on T2D or cardiovascular disease seems very interesting to a number of medical experts, clinicians and nutrition

educators. Third, FFQs/validated FFQs mostly used in primary studies could not characterize all the nutrients, which misclarified plausible associations. It was suggested that magnesium specific food questionnaire and/or food records should be reasonably used for accurate magnesium intake estimation. Finally, we still required further RCTs, because observational studies might only reach the same conclusion (i.e., magnesium intake is inversely associated with T2D incidence) but could not prove causality.

Conclusion

Magnesium intake has a substantial inverse association with T2D and total stroke. Among these populations, magnesium consumption can be recommended as an optimization for T2D, total stroke and ischemic stroke primary prevention or early management. In particular, the greater the magnesium intake, the more reduced risk is observed. As patients, physicians, policy makers and legislators debate on these issues, such a cost-effective alternative is needed to inform policy decisions and assist reform in global dietary health care.

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Competing interests

None declared

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All data relevant to the study are included in the article or uploaded as supplementary information.

Patient consent for publication

Not required.

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Table 1 Subgroup Analysis relating to Magnesium Intake and Type 2Diabetes (T2D)

Group	T2D					
	No. of studies	RR (95% CI)	P_{ES}	$P_{heterogeneity}$	I^2 (%)	$P_{interaction}$
Total	26	0.78 (0.75-0.81)	< 0.001	0.021	35.6	NA
Participants region	26					0.905
North America	13	0.77 (0.73-0.82)	< 0.001	0.048	39.5	
Europe	0	NA	NA	NA	NA	
Asia	9	0.78 (0.71-0.87)	< 0.001	0.165	21.7	
Multiple nations	4	0.79 (0.71-0.88)	< 0.001	0.048	58.3	
Sex[a]	34					0.284
Male	9	0.81(0.76-0.87)	< 0.001	0.337	11.7	
Female	17	0.77 (0.73-0.81)	< 0.001	0.055	37.5	
Both[b]	8	0.70 (0.57-0.85)	< 0.001	0.067	45.3	
BMI (kg/m^2)	26					0.716
≥ 25	12	0.75 (0.69-0.81)	< 0.001	0.135	31	
< 25	11	0.78 (0.74-0.83)	< 0.001	0.022	45.4	
Unknown	3	0.81 (0.76-0.86)	< 0.001	0.586	0	
Follow-up duration (y)	26					0.150
≥ 10	12	0.80 (0.76-0.84)	< 0.001	0.047	38.8	
< 10	14	0.74 (0.68-0.80)	< 0.001	0.164	25.2	
Dietary assessment	26					0.281
FFQ/validated FFQ	15	0.77 (0.73-0.82)	< 0.001	0.159	23.7	
SFFQ/validated SFFQ	9	0.79 (0.74-0.84)	< 0.001	0.017	52.5	
Other	2	0.55 (0.36-0.83)	0.005	0.826	0	
Magnesium intake type[c]	28					0.335
Total magnesium intake[d]	15	0.79 (0.75-0.84)	< 0.001	0.035	39.8	
Dietary magnesium intake	13	0.77 (0.72-0.82)	< 0.001	0.166	25.0	
Total energy adjustment	26					0.396
Yes	17	0.79 (0.74-0.84)	< 0.001	0.027	40.4	
No	9	0.76 (0.72-0.81)	< 0.001	0.225	21.6	
Difference between top and bottom intake (mg/day)[e]	27					0.671
≥ 140	13	0.78 (0.74-0.83)	< 0.001	0.020	45.3	
< 140	14	0.77 (0.72-0.82)	< 0.001	0.209	21.0	
Current CV events status[f]	26					0.536
Yes	13	0.79 (0.74-0.83)	< 0.001	0.049	37.9	
Unknown	13	0.77 (0.71-0.82)	< 0.001	0.082	35.1	
Hypercholesterolemia status[g]	26					0.625
Yes	5	0.79 (0.73-0.85)	< 0.001	0.021	57.5	
Unknown	21	0.77 (0.73-0.82)	< 0.001	0.096	27.3	
Family diabetes history	26					0.168
Yes	17	0.76 (0.72-0.80)	< 0.001	0.021	41.8	
Unknown	9	0.81 (0.76-0.87)	< 0.001	0.258	14.3	

Abbreviation: T2D, type 2 diabetes; BMI, body mass index; FFQ, food frequencyquestionnaire; SFFQ, semi-quantitative food frequent questionnaire; RR, relative risk; ES, effect size; CV events, cardiovascular events.

[a], Male and female of T2D outcome were treated as independent cohorts within eight studies;

[b], Male and female participants were in independent cohorts;

[c], Two studies reported total magnesium and dietary magnesium intake outcome;

[d], Total magnesium intake (milligrams per day) included the total amount of magnesium from both food (diet) and supplement;

[e], Subtract the lowest category intake from the highest. Oba el al (M) was in < 140 group, while Oba el al (F) was in ≥ 140 group;

[f], Grouped by whether participants with or without CV events. CV events in this part include coronary heart disease, heart failure, stroke, atrial fibrillation, and self-reported heart disease etc;

[g], Grouped by whether participants with or without hypercholesterolemia. Hypercholesterolemia in this part means cholesterol concentration ≥ 240 mg/dL.

Table 2. Subgroup Analyses Relating to Magnesium Intake and Total Stroke, Ischemic Stroke, Hemorrhagic stroke.

Group	Total Stroke				Ischemic Stroke				Hemorrhagic stroke			
	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$
Total	15	0.89 (0.83-0.94)	0.00	NA	12	0.88 (0.81-0.95)	16.90	NA	8	0.93 (0.82-1.06)	0.461	NA
Participants region	15			0.733	12			0.584	8			0.873
North America	6	0.87 (0.79-0.96)	0.00		5	0.85 (0.76-0.95)	0.00		4	0.90 (0.71-1.15)	0.00	
Europe	5	0.87 (0.77-0.98)	14.80		3	0.86 (0.78-0.95)	0.00		2	0.99 (0.79-1.25)	0.00	
Asia	4	0.90 (0.78-1.05)	32.80		4	0.93 (0.75-1.14)	45.50		2	0.89 (0.66-1.21)	53.40	
Multiple nations	0	NA	NA		0	NA	NA		0	NA	NA	
Sex[a]	18			0.031	14			0.134	10			0.425
Male	6	0.95(0.86-1.05)	0.00		4	0.99 (0.82-1.19)	52.80		4	0.97 (0.75-1.26)	35.50	
Female	7	0.91 (0.83-0.99)	0.00		6	0.89 (0.79-1.00)	0.00		6	0.88 (0.74-1.06)	0.00	
Both[b]	5	0.74 (0.64-0.85)	0.00		4	0.76 (0.65-0.88)	0.00		0	NA	NA	
Mean BMI (kg/m^2)	15			0.606	12			0.631	8			0.418
≥ 25	8	0.89 (0.82-0.96)	0.00		6	0.88 (0.81-0.96)	0.00		5	0.97 (0.81-1.17)	0.00	
< 25	5	0.89 (0.78-1.01)	30.00		5	0.87 (0.73-1.03)	44.00		3	0.88 (0.69-1.12)	39.30	
Unknown	2	0.80 (0.63-1.02)	0.00		1	0.76 (0.57-1.07)	NA		0	NA	NA	
Follow-up duration (y)	15			0.798	12			0.811	8			0.808
≥ 12	11	0.88 (0.82-0.94)	5.30		10	0.87 (0.80-0.95)	19.10		7	0.93 (0.81-1.08)	7.70	
< 12	4	0.90 (0.77-1.05)	0.00		2	0.86 (0.62-1.20)	48.40		1	0.88 (0.57-1.36)	NA	
Dietary assessment	15			0.578	12			NA	8			NA
FFQ/validated FFQ	14	0.89 (0.83-0.95)	3.80		12	0.88 (0.81-0.95)	16.90		8	0.93 (0.82-1.06)	0.00	
SFFQ/validated SFFQ	0	NA	NA		0	NA	NA		0	NA	NA	
Other	1	0.81 (0.61-1.09)	0.00		0	NA	NA		0	NA	NA	
Magnesium intake type	15			0.865	12			0.831	8			0.831
Total magnesium intake[c]	8	0.89 (0.82-0.96)	0.00		6	0.87 (0.80-0.94)	0.00		5	0.94 (0.79-1.12)	0.00	
Dietary magnesium		0.88	0.44			0.89	35.40			0.91 (0.70-1.18)	39.40	

intake	7	(0.81-0.96)			6	(0.77-1.03)			3		
Total energy adjustment	15			0.888	12			0.689	8		0.538
Yes	5	0.87 (0.77-0.99)	27.00		2	0.86 (0.78-0.94)	0.00		2	0.93 (0.82-1.06)	0.00
No	10	0.89 (0.83-0.96)	0.00		10	0.88 (0.79-0.99)	26.60		6	0.90 （0.76-1.07）	11.40
Difference between top and bottom intake (mg/day)[d]	15			0.107	12			0.180	8		0..244
≥ 180	7	0.83 (0.76-0.91)	0.00		5	0.83 (0.76-0.91)	0.00		6	1.07 (0.83-1.37)	0.00
< 180	8	0.93 (0.86-1.00)	0.00		7	0.92 (0.81-1.03)	26.20		2	0.89 (0.76-1.03)	0.00
Current CV events status[e]	15			0.074	12			0.393	8		NA
Yes	12	0.90 (0.85-0.96)	0.00		11	0.88 (0.81-0.96)	18.20		8	0.93 (0.82-1.06)	0.00
Unknown	3	0.75 (0.63-0.90)	0.00		1	0.76 (0.57-1.01)	NA		0	NA	NA
Hypercholesterolemia status[f]	15			0.480	12			0.565	8		0.651
Yes	7	0.91 (0.83-0.99)	0.00		6	0.90 (0.80-1.01)	6.90		5	0.90 (0.76-1.08)	0.00
Unknown	8	0.86 (0.79-0.95)	13.10		6	0.86 (0.77-0.97)	32.40		3	0.94 (0.72-1.22)	40.30
Current diabetes status[g]	15			0.039	12			0.159	8		NA
Yes	10	0.91 (0.82-0.97)	0.00		10	0.89 (0.82-0.97)	13.50		8	0.93 (0.82-1.06)	0.00	0.00
Unknown	5	0.75 (0.64-0.88)	0.00		2	0.72 (0.56-0.92)	0.00		0	NA	NA	NA

Abbreviation: BMI, body mass index; FFQ, food frequency questionnaire; SFFQ, semi-quantitative food frequency questionnaire; CV events, cardiovascular events; RR, relative risk; NA, not available.

[a], several studies reported stroke outcome of male and female participants in different cohorts;

[b], male and female participants were in the same cohort;

c, total magnesium intake (milligrams per day) included the total amount of magnesium from both food (diet) and supplements;

[d], subtract the lowest category intake from the highest;

[e], grouped by whether participants with or without CV events. CV events in this part include coronary heart disease, heart failure, atrial fibrillation, and self-reported heart disease etc., stroke is not included;

[f], grouped by whether participants with or without hypercholesterolemia. Hypercholesterolemia in this part means cholesterol concentration ≥ 240 mg/dL;

[g], grouped by whether participants with or without diabetes.

Figure Legends

Figure 1. Flow Chart for Literature Search and Screening Process

Figure 2. Forest Plots for Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure 3. Two-Stage Dose-Response Effect on the Relationships betweenMagnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).

Supplementary material online:

Table S1. PRISMA 2009 Checklist

Table S2. MOOSE Checklist

Table S3. The complete search terms for Pubmed

Table S4. Summary of Baseline Characteristics of Included Studies

Table S5. Methodological Quality Assessments Of Studies Included With Newcastle-Ottawa Scales

Figure S1. Funnel Plots for Magnesium Intake and Type 2 Diabetes (A), Ischemic Stroke (B) and Hemorrhagic Stroke (C).

Figure S2. Forest Plots for Risk of Total Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure S3. Forest Plots for Risk of Ischemic Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure S4. Forest Plots for Risk of Hemorrhagic Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

Figure S5. Forest Plots for Risk of Subarachnoid Hemorrhage for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E)

Figure S6. Forest Plots for Risk of Intracerebral Hemorrhage for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E)

Figure S7. Meta-Regression of Relative Risk for Type 2 Diabetes According to Body

Mass Index (A, $P = 0.716$), Sex (B, $P = 0.284$), Participant Region (C, $P = 0.904$) and Dietary Assessment (D, $P = 0.521$).

Figure S8. Meta-Regression of Relative Risk for Total Stroke According to Body Mass Index (A, $P = 0.606$), Sex (B, $P = 0.112$), Participant region (C, $P = 0.891$) and Dietary Assessment (D, $P = 0.891$).

Figure S9. Meta-Regression of Relative Risk for Ischemic Stroke According to Body Mass Index (A, $P = 0.631$), Sex (B, $P = 0.134$), Participant Region (C, $P = 0.584$) and Dietary Assessment (D, no regression *P*-value due to limited data).

Figure S10. Meta-Regression of Relative Risk for Hemorrhagic Stroke According to Body Mass Index (A, $P = 0.418$), Sex (B, $P = 0.872$), Participant Region (C, $P = 0.872$) and Dietary Assessment (D, no regression P-value due to limited data).

Figure S11. Cumulative Meta-Analysis Related to Magnesium Intake and Type 2 Diabetes (T2D)

Figure S12. Cumulative Meta-Analysis Related to Magnesium Intake and Total Stroke

Figure S13. Cumulative Meta-Analysis Related to Magnesium Intake and Ischemic Stroke

Figure S14. Cumulative Meta-Analysis Related to Magnesium Intake and Hemorrhagic Stroke

Figure S15. Dose-Response Effect on the Relationships between Magnesium Intake and Subarachnoid Hemorrhage (A) and Intracerebral Hemorrhage (B).

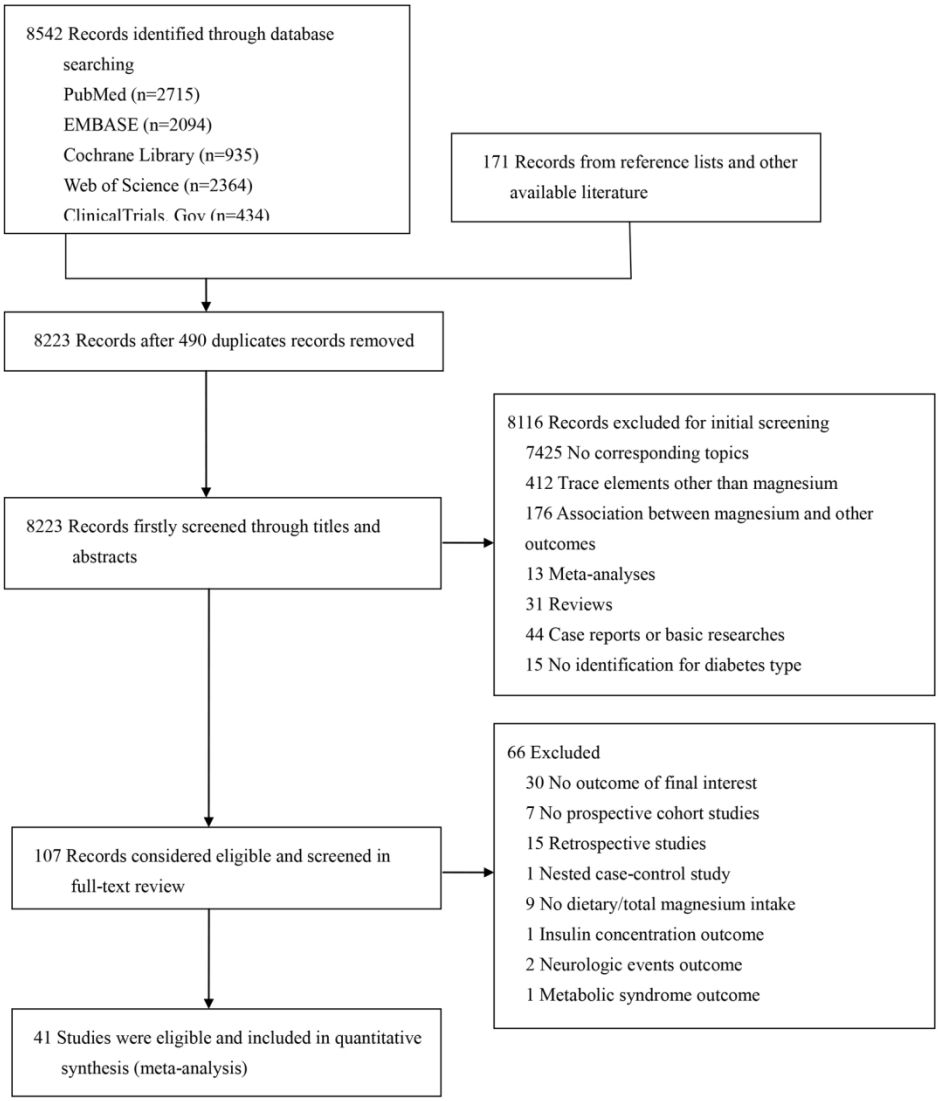


Figure 1. Flow Chart for Literature Search and Screening Process

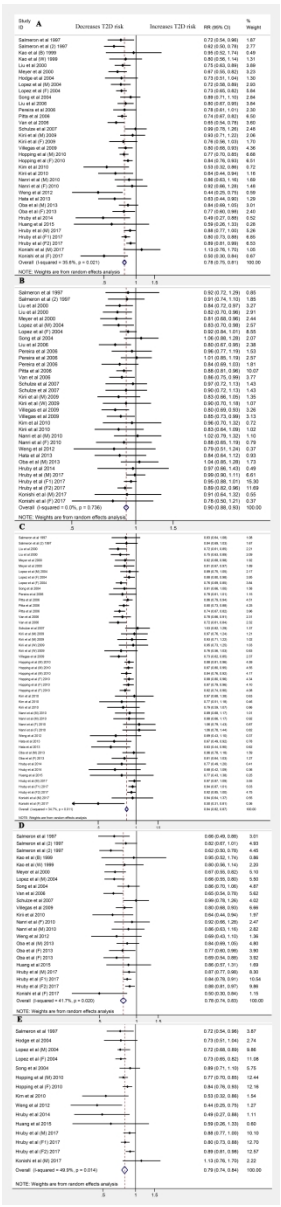


Figure 2. Forest Plots for Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

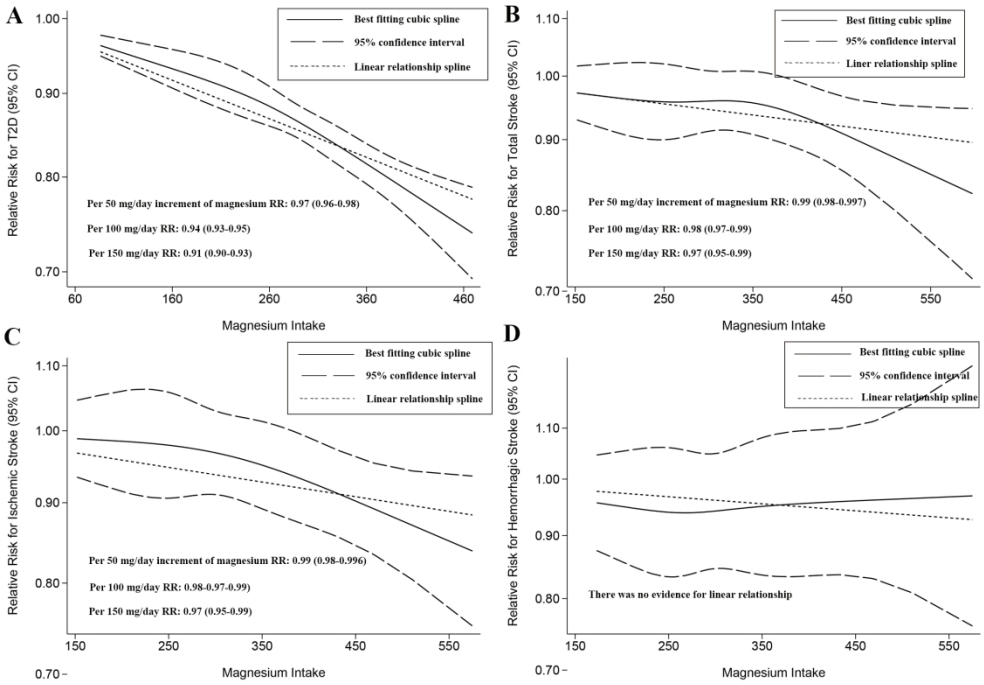


Figure 3. Two-Stage Dose-Response Effect on the Relationships betweenMagnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			2-3
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			4-5
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			5-9
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-10

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			9-16
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-16
DISCUSSION			16-22
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			23
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S2. MOOSE Checklist

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	4-5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6-7
8	Search strategy, including time period included in the synthesis and key words	5-6
9	Effort to include all available studies, including contact with authors	5-6
10	Databases and registries searched	5-6
11	Search software used, name and version, including special features used (eg, explosion)	5-6
12	Use of hand searching (eg, reference lists of obtained articles)	5-6
13	List of citations located and those excluded, including justification	6
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-9
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-9
22	Assessment of heterogeneity	7-9
23	Description of statistical methods (eg, complete description of fixed	7-9

	or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	9
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	10-14
26	Table giving descriptive information for each study included	10-11, Table S4
27	Results of sensitivity testing (eg, subgroup analysis)	14
28	Indication of statistical uncertainty of findings	16

Item No	**Recommendation**	**Reported on Page No**
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11-14
30	Justification for exclusion (eg, exclusion of non-English language citations)	10
31	Assessment of quality of included studies	11, Table S5
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	16-22
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 23
34	Guidelines for future research	17-20, 22
35	Disclosure of funding source	None

Table S3. The complete search terms for Pubmed

A search example for Pubmed

The combined text and medical subject heading (MeSH) terms used were: “Magnesium” and “Magnesium Supplementation” “Diabetes Mellitus, Type 2”, “Stroke”, “Cerebrovascular Stroke”, and “Cohort Studies”. The complete search terms for PubMed included: (Magnesium [MeSH terms]) AND (Magnesium Supplementation [MeSH terms]) AND (Diabetes Mellitus, Type 2 [MeSH term] OR Diabetes Mellitus, Noninsulin-Dependent [Text Word] OR Diabetes Mellitus, Ketosis-Resistant [Text Word] OR Diabetes Mellitus, Non-Insulin-Dependent [Text Word] OR Non-Insulin-Dependent Diabetes Mellitus [Text Word] OR Diabetes Mellitus, Stable [Text Word] OR NIDDM [Text Word] OR Maturity-Onset Diabetes Mellitus [Text Word] OR Diabetes Mellitus, Slow-Onset [Text Word] OR Type 2 Diabetes [Text Word] OR Diabetes Mellitus, Adult-Onset [Text Word]) AND (Stroke [MeSH terms] OR Cerebrovascular Stroke [Text Word] OR Cerebrovascular Accident [Text Word] OR CVA (Cerebrovascular Accident) [Text Word] OR Vascular Accident, Brain [Text Word] OR Cerebrovascular Apoplexy [Text Word] OR Cerebral Stroke [Text Word] OR Stroke, Acute [Text Word] OR Cerebrovascular Accident, Acute [Text Word] OR Acute Cerebrovascular Accident [Text Word] OR Apoplexy, Cerebrovascular [Text Word]) AND (Cohort Studies [MeSH term] OR Cohort Study [Text Word] OR Studies, Cohort [Text Word] OR Study, Cohort [Text Word] OR Concurrent Studies [Text Word] OR Studies, Concurrent [Text Word] OR Closed Cohort Studies [Text Word] OR Closed Cohort Study [Text Word] OR Study, Closed Cohort [Text Word] OR Cohort Analysis [Text Word] OR Cohort Analysis [Text Word] OR Prospective Studies [Text Word] OR Prospective Study [Text Word] OR Studies, Prospective [Text Word])

Table S4 Summary of Baseline Characteristics of Included Studies

Source	Nation	Period	Population	BMI	Dietary Assessment	Case Ascertainment	Case (Cohort size)	Magnesium intake (mg/day) highest VS. the lowest [Adjusted RR (95% CI)]
Salmeron 1997[11]	USA	1986-1992	M; 40-75 y	25.5	validated SFFQ	self-reported questionnaire	523 T2D (42759)	461 VS. 262 (0.72 (0.54-0.96))
Salmeron 1997(2)[12]	USA	1986-1992	F; 40-65 y	25.1	validated SFFQ	self-reported questionnaire	915 T2D (65173)	338 VS. 222 (0.62 (0.50-0.78))
Ascherio 1998[13]	USA	1986-1994	M; 40-75 y	NA	validated FFQ	self-reported questionnaire	328 stroke (43738)	425 VS. 243 (0.92 (0.58-1.46))
Iso 1999[14]	USA	1980-1994	F; 34-59 y	22.7	FFQ	self-reported questionnaire	690 stroke (85764)	381 VS. 211 (0.80 (0.63-1.01))
Kao 1999[15]	USA	NA	M/F; 45-64 y	27.2	FFQ	self-reported questionnaire	black: 367 T2D (2622) white: 739 T2D (9506)	374 VS. 264 (0.95 (0.52-1.74)) 418 VS. 308 (0.80 (0.56-1.14))
Liu 2000[16]	USA	1976-1984	F; 38-63 y	24.8	validated FFQ	self-reported questionnaire	1879 T2D (75521)	342 VS. 248 (0.75 (0.63-0.89))
Meyer 2000[17]	USA	1986-1992	F; 55-69 y	26.8	validated FFQ	self-reported questionnaire	1141 T2D (35998)	362 VS. 220 (0,67 (0.55-0.82))
Hodge 2004[18a]	multiple	1990-1994	M/F; 45-64 y	26.1	validated FFQ	self-reported questionnaire	365 T2D (31641)	500 increment per day
Lopez 2004[19]	USA	M: 1986-1998 W: 1980-1998	M; 40-75 y F; 30-35 y	25.4 24.3	validated SFFQ	self-reported questionnaire	1333 T2D (42872) 4085 T2D (85060)	457 VS. 314 (0.72 (0.58-0.89)) 373 VS. 222 (0.73 (0.65-0.82))
Song 2004[20]	USA	1993-2001	F; ⩾45 y[c]	26	SFFQ	self-reported questionnaire	918 T2D (38025)	433 VS. 255 (0.89 (0.71-1.10))
Song 2005[21]	USA	1993-2003	F; 39-89 y	26	FFQ	follow-up examination	368 stroke (39876)	433 VS. 255 (0.90 (0.65-1.26))
Liu 2006[22]	USA	1996-2006	F; 47-63 y	25.8	validated SFFQ	self-reported questionnaire	1603 T2D (37183)	340 VS. 307 (0.80 (0.67-0.95))
Pereira 2006[23]	USA	1986-1997	F; 56-66 y	26.7	validated FFQ	self-reported questionnaire	1418 T2D (28812)	334 VS. 281 (0.78(0.61-1.01))
Pittas 2006[24]	USA	1980-2000	F; 30-55 y	24.1	validated SFFQ	self-reported questionnaire	4843 T2D (83779)	352 VS. 258 (0.74 (0.67-0.82))
Van 2006[25]	multiple	1995-2003	F; 21-69 y	27.6	validated FFQ	self-reported questionnaire	1964 T2D (41186)	244 VS. 115 (0.65 (0.54-0.78))
Schulze2007[26]	multiple	1994-2005	M/F; 35-65 y	26.1	validated SFFQ	self-reported questionnaire	844 T2D (25067)	377 VS. 268 (0.99 (0.78-1.26))
Larsson 2008[27]	Sweden	1985-2004	M; 50-69 y	26.4	validated FFQ	follow-up examination	3370 stroke (26556)	575 VS. 382 (0.91 (0.77-1.07))
Weng 2008[28]	Taipei	1989-2002	M/F; ≥40 y	24.5	validated FFQ	Self-reported and cross-checked questionnaire	132 ischemic stroke (1772)	423 VS. 162 (0.69 (0.45-1.06))
Kirii 2009[29]	Japan	1993-1998	M; 40-69 y F; 40-69 y	23.6 23.5	FFQ	self-reported questionnaire	634 T2D (25876) 480 T2D (33919)	331 VS. 245 (0.93 (0.71-1.22)) 314 VS. 248 (0.76 (0.56-1.03))
Ohira 2009[30]	USA	1987-2004	M/F; 45-64 y	27.4	validated FFQ	follow-up examination	577 ischemic stroke (14221)	362 VS. 152 (0.80 (0.75-1.13))
Villegas 2009[31]	China	2000-2006	F; 40-70 y	23.8	validated FFQ	follow-up examination	2273 T2D (64191)	318 VS. 214 (0.80 (0.68-0.93))
Hopping 2010[32]	multiple	1993-2007	M; 45-75 y F; 45-75 y	NA	validated FFQ	self-reported questionnaire	4555 T2D (36256) 4032 T2D (39256)	278 VS. 86 (0.77 (0.70-0.85)) 300 VS. 93 (0.84 (0.76-0.93))
Kim 2010[33]	USA	1985-2005	M/F; 18-30 y	24.5	validated DHQ	self-reported questionnaire	330 T2D (4497)	302 VS. 182 (0.53 (0.32-0.86))
Kirii 2010[34]	Japan	NA	M/F; 40-65 y	22.9	validated FFQ	self-reported questionnaire	459 T2D (17592)	303 VS. 158 (0.64 (0.44-0.94))

Nanri 2010[35]	Japan	1990-1995	M; 40-65 y F; 40-65 y	NA	validated FFQ	self-reported questionnaire	634 T2D (25872) 480 T2D (33919)	348 VS. 213 (0.86 (0.63-1.16)) 333 VS. 213 (0.92 (0.66-1.28))
Larsson 2011[36]	Sweden	1998-2008	F; 49-83 y	25	validated FFQ	follow-up examination	1680 stroke (34670)	373 VS. 297 (1.02 (0.82-1.27))
Weng 2012[37]	Taipei	1993-2002	M/F; ≥30 y	24	validated FFQ	follow-up examination or self-reported questionnaire	141 T2D (1604)	406 VS. 212 (0.44 (0.25-0.75))
Zhang 2012[38]	Japan	1988-2006/	M; 40-79 y F; 40-79 y	22.7 22.9	validated FFQ	follow-up examination	634 stroke (23083) 620 stroke (35533)	294 VS. 173 (1.03 (0.79-1.35)) 274 VS. 175 (0.90 (0.69-1.16))
Hata 2013[39]	Japan	1988-2009	M/F; 40-79 y	22.9	validated SFFQ	self-reported questionnaire	417 T2D (1999)	215 VS. 133 (0.63 (0.44-0.90))
Lin 2013[40]	Taipei	1989-2002	M/F; ≥ 18 y	23.3	validated FFQ	follow-up examination and self-reported questionnaire	123 stroke (2061)	378 VS. 210 (0.62 (0.40-0.97))
Oba 2013[41]	Japan	1990-2000	M; 40-69 y F; 40-69 y	23.6 23.5	validated FFQ	self-reported questionnaire	690 T2D (27769) 500 T2D (36864)	349 VS. 232 (0.84 (0.69-1.05)) 356 VS. 211 (0.69 (0.54-0.88))
Sluijs 2013[42]	Netherland	NA	M/F; 21-70 y	NA	FFQ	NA	361 ischemic stroke (36359)	435 VS. 253 (0.76 (0.57-1.01))
Hruby 2014[43]	USA	1995-2001	M/F; 26-81 y	27	validated FFQ	self-reported questionnaire	179 T2D (2582)	395 VS. 235 (0.49 (0.27-0.88))
Sluijs 2014[44]	Netherland	NA	M/F; 21-70 y	NA	FFQ	follow-up examination	631 stroke (36094)	597 VS. 190 (0.64 (0.44-0.94))
Adebamowo 2015[45]	USA	1986-2010	M; 40-75 y	25.4	validated FFQ	self-reported questionnaire	1547 stroke (42669)	467 VS. 267 (0.89 (0.71-1.11))
Adebamowo 2015(2)[46]	USA	1976-2006 1989-2011	F; 30-55 y F; 25-42 y	26.4 25.7	validated FFQ	self-reported questionnaire	3237 stroke (86149) 543 stroke (94715)	411 VS. 233 (0.93 (0.79-1.08))
Bain 2015[47]	Britain	2002-2008	M; 40-75 y F; 40-75 y	26.5 26.2	7-day diary recall	follow-up examination	364 stroke (2000) 511 stroke (2445)	456 VS. 266 (0.81 (0.53-1.22)) 374 VS. 456 (0.82 (0.54-1.24))
Huang 2015[48]	Taipei	2000-2008	M/F; ≥65 y	NA	24 h dietary recall and SFFQ	follow-up examination	231 T2D (1400)	398 VS. 103 (0.59 (0.26-1.33))
Hruby 2017[49]	USA	1984-2012 1991-2013 1986-2012	F; 30-55 y F; 25-42 y M; mean 53.5 y	24.8 24.6 24.8	validated SFFQ	self-reported questionnaire	7620 T2D (69176) 6080 T2D (91471) 3430 T2D (42096)	390 VS. 229 (0.80 (0.73-0.88)) 424 VS. 249 (0.89 (0.81-0.99)) 469 VS. 280 (0.88 (0.77-1.00))
Kokubo 2017[50b]	Japan	1990-2009 1993-2010	M; 40-69 y F; 40-69 y	23.6 23.6	FFQ	follow-up examination	2576 stroke (39505) 1846 stroke (45788)	348 VS. 213 (1.07 (0.86-1.33)) 333 VS. 213 (0.88 (0.67-1.14))
Konishi 2017[51]	Japan	1992-2002	M; ≥35 y F; ≥35 y	22.6 22.1	validated FFQ	self-reported questionnaire	266 T2D (5885) 172 T2D (7640)	469 VS. 310 (1.13 (0.76-1.70)) 432 VS. 285 (0.50 (0.30-0.84))

Abbreviations: FFQ, food-frequency questionnaire; SFFQ, semi-quantitative food-frequency questionnaire; BMI, body mass index; T2D, type 2 diabetes; NA, not available.

[a], different ethnicities of participants are in multiple nations cohort;

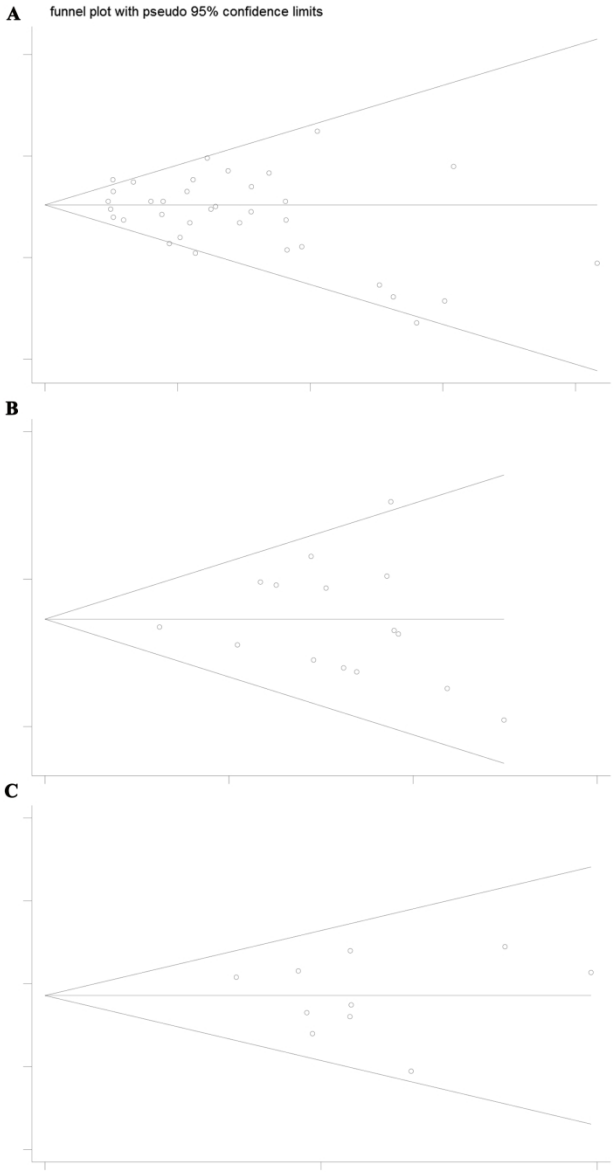
[b], the dose of magnesium intake which is not available in this study is retrieved from the same cohort reported in former publication;

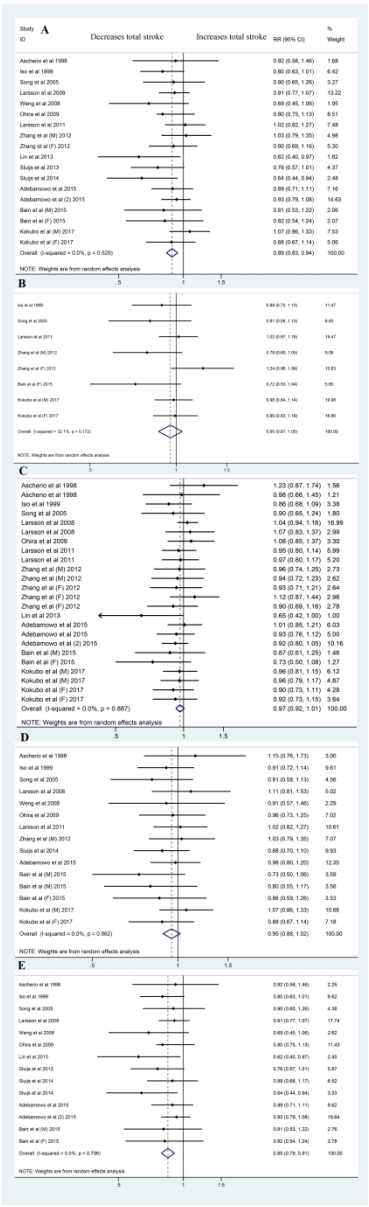
[c] the range of enrolled participants age is not mentioned.

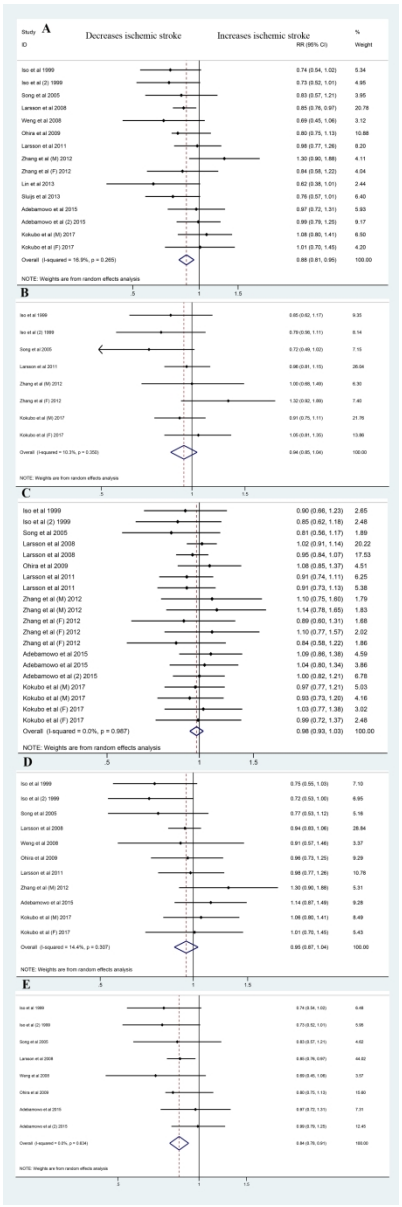
Table S5 Methodological Quality Assessments Of Included Studies With Newcastle-Ottwa Scales

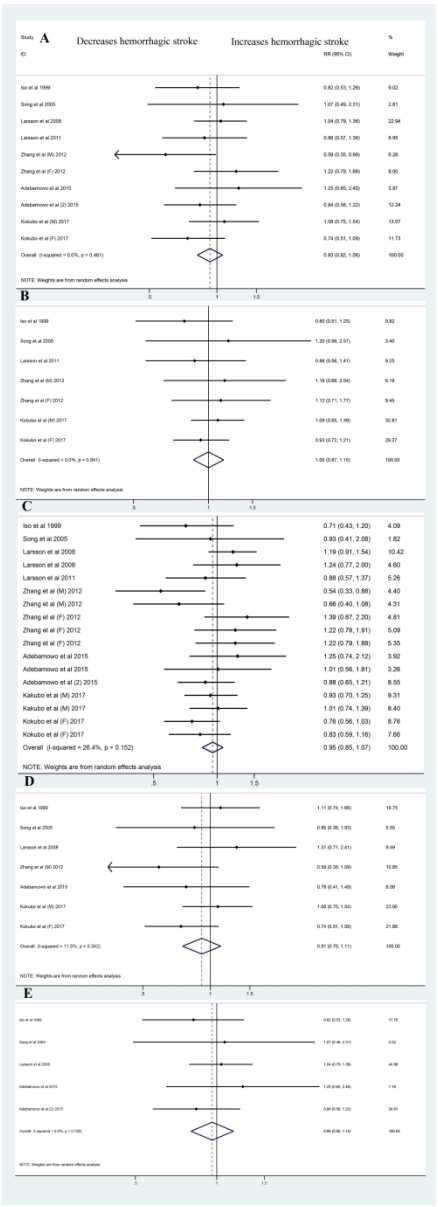
	Study	Selection				Comparability	Outcome			Total score
		Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
1997	Salmeron et al,[11]	*	*	*	*	**	*	*		9
1997	Salmeron et al (2),[12]	*	*	*	*	**	*	*	*	9
1998	Ascherio et al,[13]	*	*	*	*	**	*	*	*	9
1999	Iso et al,[14]	*	*	*	*	**	*	*	*	9
1999	Kao et al,[15]	*	*	*	*	**	*	*	*	9
2000	Liu et al,[16]	*	*	*	*	**	*	*	*	9
2000	Meyer et al,[17]	*	*	*	*	**	*	*	*	9
2004	Hodge et al,[18]	*	*	*	*	*	*	*		7
2004	Lopez et al,[19]	*	*	*	*	**	*	*	*	9
2004	Song et al,[20]	*	*	*	*	**	*	*	*	9
2005	Song et al,[21]	*	*	*	*	**	*	*	*	9
2006	Liu et al,[22]	*	*	*	*	**	*	*	*	9
2006	Pereira et al,[23]	*	*	*	*	**	*	*	*	9
2006	Pittas et al,[24]	*	*	*	*	**	*	*	*	9
2006	Van et al,[25]	*	*	*	*	**	*	*	*	9
2007	Schulze et al,[26]	*	*	*	*	**	*	*	*	9
2008	Larsson et al,[27]	*	*	*	*	**	*	*	*	9
2008	Weng et al,[28]	*	*	*	*	**	*	*	*	9
2009	Kirii et al,[29]	*	*	*	*	**	*	*	*	9
2009	Ohira et al,[30]	*	*	*	*	**	*	*	*	9
2009	Villegas et al,[31]	*	*	*	*	**	*	*	*	9
2010	Hopping et al,[32]	*	*	*	*	**	*	*	*	9
2010	Kim et al,[33]	*	*	*		**	*	*	*	8
2010	Kirii et al,[34]	*	*	*	*	**	*	*	*	9
2010	Nanri et al,[35]	*	*	*	*	**	*	*	*	9
2011	Larsson et al,[36]	*	*	*	*	**	*	*	*	9
2012	Weng et al,[37]	*	*	*	*	**	*	*		8
2012	Zhang et al,[38]	*	*	*	*	**	*	*	*	9

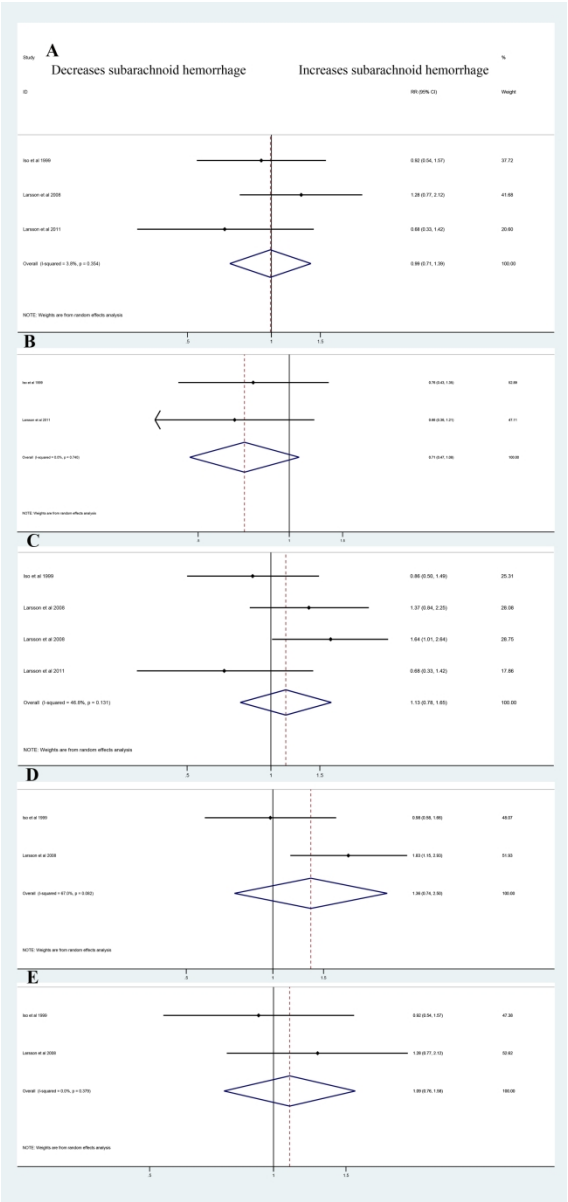
2013	Hata et al,[39]	*	*	*	*	**	*	*	*	9
2013	Lin et al,[40]	*	*	*	*	**	*	*	*	9
2013	Oba et al,[41]	*	*	*	*	**	*	*	*	9
2013	Sluijs et al,[42]	*	*	*	*	**		*	*	8
2014	Hruby et al,[43]	*	*	*	*	**	*	*	*	9
2014	Sluijs et al,[44]	*	*	*	*	**	*	*	*	9
2015	Adebamowo et al,[45]	*	*	*	*	**	*	*	*	9
2015	Adebamowo et al (2),[46]	*	*	*	*	**	*	*	*	9
2015	Bain et al,[47]	*	*	*	*	**	*	*	*	9
2015	Huang et al,[48]	*	*	*		**	*	*	*	8
2017	Hruby et al,[49]	*	*	*	*	**	*	*	*	9
2017	Kokubo et al,[50]	*	*	*	*	**	*	*	*	9
2017	Konishi et al,[51]	*	*	*	*	*	*	*	*	9

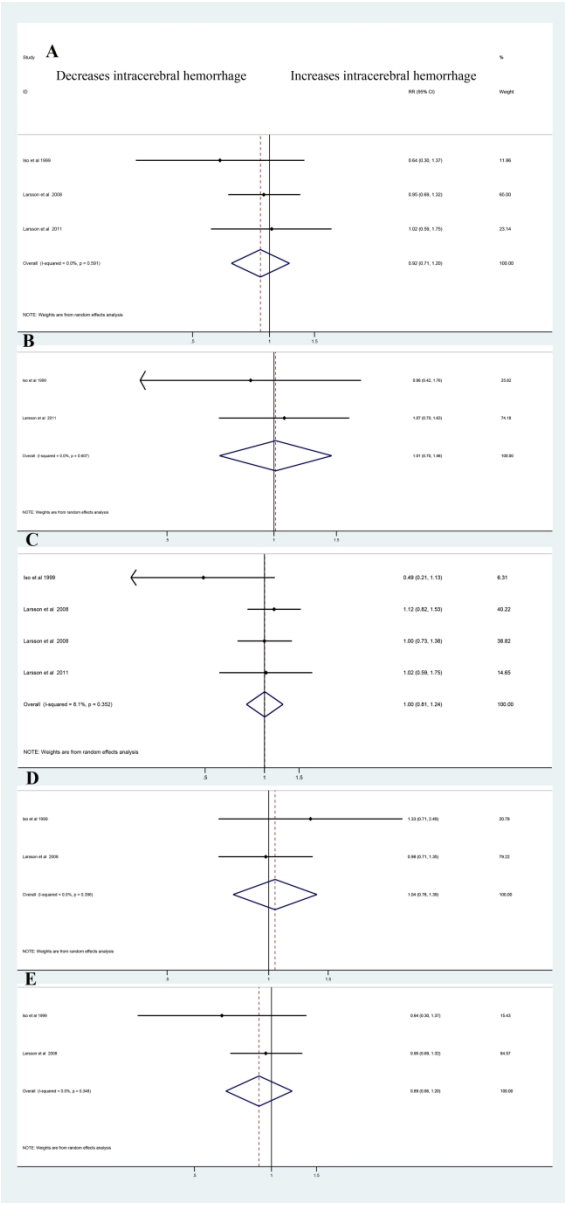

A
funnel plot with pseudo 95% confidence limits
B
C


A
Decreases total stroke
Increases total stroke
B
C
D
E

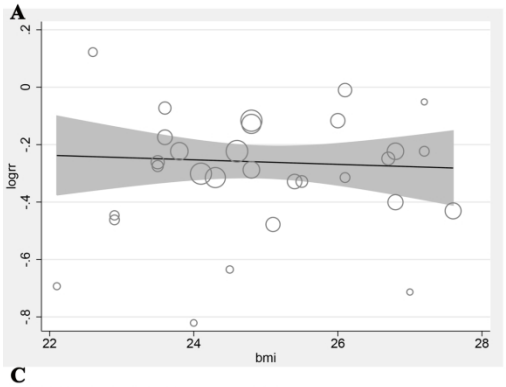

A
Decreases ischemic stroke
Increases ischemic stroke
B
C
D
E


A
Decreases hemorrhagic stroke
Increases hemorrhagic stroke
B
C
D
E


A
Decreases subarachnoid hemorrhage
Increases subarachnoid hemorrhage
B
C
D
E


A
Decreases intracerebral hemorrhage
Increases intracerebral hemorrhage
B
C
D
E

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	10	28.57	28.57
female	17	48.57	77.14
male	8	22.86	100.00
Total	35	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =       35
REML estimate of between-study variance         tau2           = .004692
% residual variation due to heterogeneity       I-squared_res  =  36.58%
Proportion of between-study variance explained  Adj R-squared  = -26.08%
Joint test for all covariates                   Model F(2,32)  =    1.31
With Knapp-Hartung modification                 Prob > F       =  0.2841
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.1314075	.0857784	-1.53	0.135	-.3061323	.0433174
sexnew2	-.0630804	.0541113	-1.17	0.252	-.1733016	.0471407
_cons	-.1956565	.0461514	-4.24	0.000	-.2896637	-.1016492

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	13	37.14	37.14
Multiple nations	5	14.29	51.43
North America	17	48.57	100.00
Total	35	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =       35
REML estimate of between-study variance         tau2           = .004868
% residual variation due to heterogeneity       I-squared_res  =  39.22%
Proportion of between-study variance explained  Adj R-squared  = -30.89%
Joint test for all covariates                   Model F(2,32)  =    0.10
With Knapp-Hartung modification                 Prob > F       =  0.9047
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew2	.0027567	.0731865	0.04	0.970	-.1463193	.1518327
participantsregionnew3	-.0201457	.0599158	-0.34	0.739	-.1422102	.1018788
_cons	-.2392399	.0510872	-4.68	0.000	-.3433012	-.1351786

D

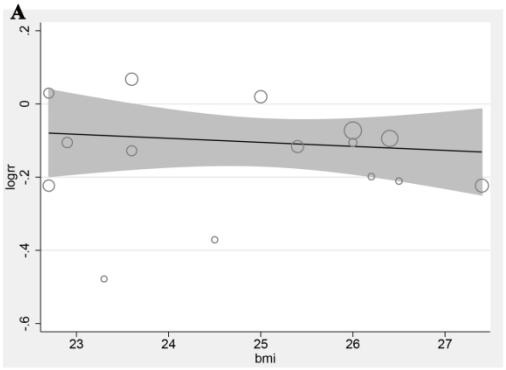
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

dietaryassessment	Freq.	Percent	Cum.
24h dietary recall and SFFQ	1	2.86	2.86
FFQ	4	11.43	14.29
SFFQ	1	2.86	17.14
validated DHQ	1	2.86	20.00
validated FFQ	17	48.57	68.57
validated SFFQ	11	31.43	100.00
Total	35	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4 dietaryassessmentnew5 dietary
> assessmentnew6, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew4 dropped because of collinearity

Meta-regression                                 Number of obs  =       35
REML estimate of between-study variance         tau2           = .004258
% residual variation due to heterogeneity       I-squared_res  =  38.44%
Proportion of between-study variance explained  Adj R-squared  = -14.42%
Joint test for all covariates                   Model F(5,29)  =    0.86
With Knapp-Hartung modification                 Prob > F       =  0.5210
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew1	.1072455	.5318922	0.20	0.841	-.97894	1.193431
dietaryassessmentnew2	.4672073	.294568	1.58	0.126	-.1393423	1.073757
dietaryassessmentnew3	.5183445	.311752	1.66	0.107	-.1192599	1.155949
dietaryassessmentnew5	.3650754	.2813784	1.30	0.205	-.2104981	.9405589
dietaryassessmentnew6	.3944872	.2812621	1.40	0.171	-.1807583	.9697328
_cons	-.6368783	.279223	-2.27	0.031	-1.205958	-.0677991

A



B

```
. tabulate sex, generate (sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	3	20.00	20.00
female	7	46.67	66.67
male	5	33.33	100.00
Total	15	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   0.00%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    2.64
With Knapp-Hartung modification                 Prob > F       =  0.1120
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew2	.1870375	.0983982	1.90	0.082	-.0273537	.4014286
sexnew3	.2312472	.1011998	2.29	0.041	.0107518	.4517427
_cons	-.2844281	.0870478	-3.27	0.007	-.4740889	-.0947673

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	6	33.33	33.33
Europe	6	33.33	66.67
North America	6	33.33	100.00
Total	18	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml random
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      18
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   1.81%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,15)  =    0.32
With Knapp-Hartung modification                 Prob > F       =  0.7332
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	.0566278	.0763754	0.74	0.470	-.1061625	.2194181
participantsregionnew2	.0028959	.0725841	0.04	0.969	-.1518136	.1576053
_cons	-.1370955	.0474962	-2.87	0.012	-.2387575	-.0354336

D

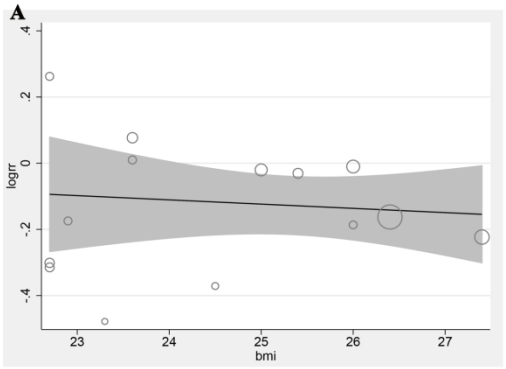
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

dietaryassessment	Freq.	Percent	Cum.
7-day diary recall	2	11.11	11.11
FFQ	6	33.33	44.44
validated FFQ	9	50.00	94.44
validated SFFQ	1	5.56	100.00
Total	18	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4, wsse (selogrr) knapphartung
> reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      18
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   8.20%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(3,14)  =    0.21
With Knapp-Hartung modification                 Prob > F       =  0.8911
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0596066	.167476	0.36	0.727	-.2995937	.418807
dietaryassessmentnew3	.0984932	.1614344	0.61	0.552	-.2481701	.4651645
dietaryassessmentnew4	.1211665	.291519	0.42	0.684	-.5044595	.7464325
_cons	-.2045601	.1567379	-1.31	0.213	-.5407374	.1316013

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	4	26.67	26.67
female	7	46.67	73.33
male	4	26.67	100.00
Total	15	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .004782
% residual variation due to heterogeneity       I-squared_res  =   1.79%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    2.39
With Knapp-Hartung modification                 Prob > F       =  0.1339
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.2383161	.109578	-2.17	0.050	-.4770662	.0004339
sexnew2	-.0739192	.0940187	-0.79	0.447	-.2787683	.1309299
_cons	-.048002	.0681983	-0.70	0.495	-.1965933	.1005894

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	6	40.00	40.00
Europe	3	20.00	60.00
North America	6	40.00	100.00
Total	15	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .00114
% residual variation due to heterogeneity       I-squared_res  =  21.76%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    0.56
With Knapp-Hartung modification                 Prob > F       =  0.5842
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	.1089103	.1083661	1.01	0.335	-.1271992	.3450197
participantsregionnew2	.0117202	.0911749	0.13	0.900	-.1869328	.2103732
_cons	-.1629514	.0653255	-2.49	0.028	-.3052835	-.0206192

D

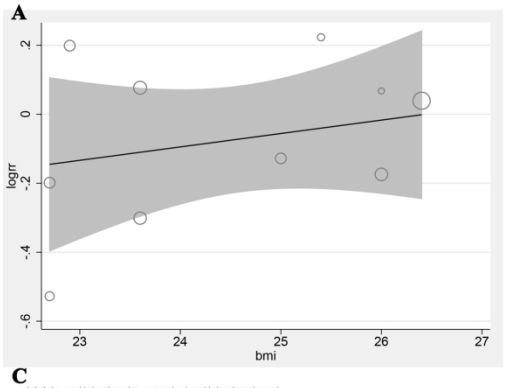
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

dietaryassessment	Freq.	Percent	Cum.
FFQ	6	40.00	40.00
validated FFQ	9	60.00	100.00
Total	15	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .001922
% residual variation due to heterogeneity       I-squared_res  =  21.79%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0410573	.0897444	0.46	0.655	-.1528236	.2349382
_cons	-.162938	.0753946	-2.16	0.050	-.3258182	-.0000578

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
female	6	60.00	60.00
male	4	40.00	100.00
Total	10	100.00	

```
. metareg logrr  sexnew1 sexnew2, wsse (selogrr) knapphartung reml
note: sexnew2 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   0.42%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.1120692	.1333867	-0.84	0.425	-.4196595	.1955211
_cons	-.0110753	.0978042	-0.11	0.913	-.2366123	.2144617

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	4	40.00	40.00
Europe	2	20.00	60.00
North America	4	40.00	100.00
Total	10	100.00	

```
. metareg logrr participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           = .008835
% residual variation due to heterogeneity       I-squared_res  =  15.78%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,7)   =    0.14
With Knapp-Hartung modification                 Prob > F       =  0.8726
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	-.0106555	.1797495	-0.06	0.954	-.4356955	.4143845
participantsregionnew2	.0796745	.1944402	0.41	0.694	-.3801034	.5394524
_cons	-.0943118	.1371063	-0.69	0.514	-.4185166	.229893

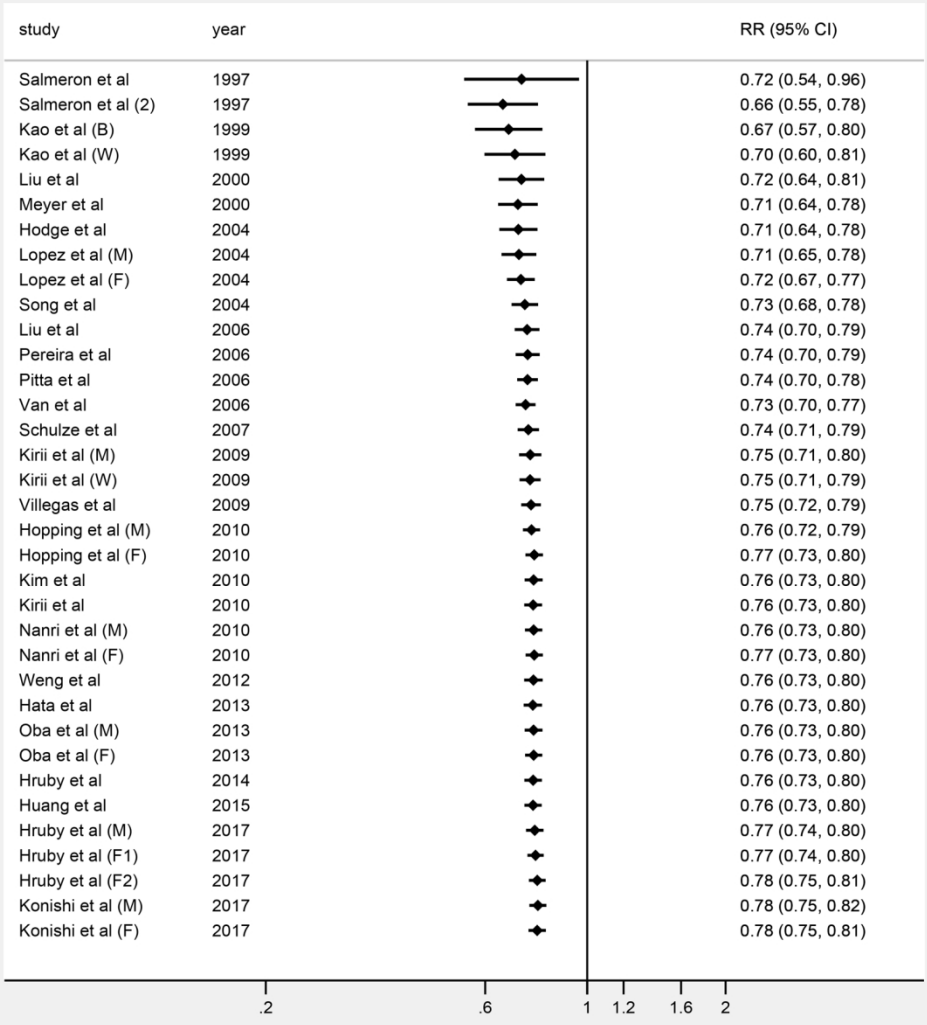
D

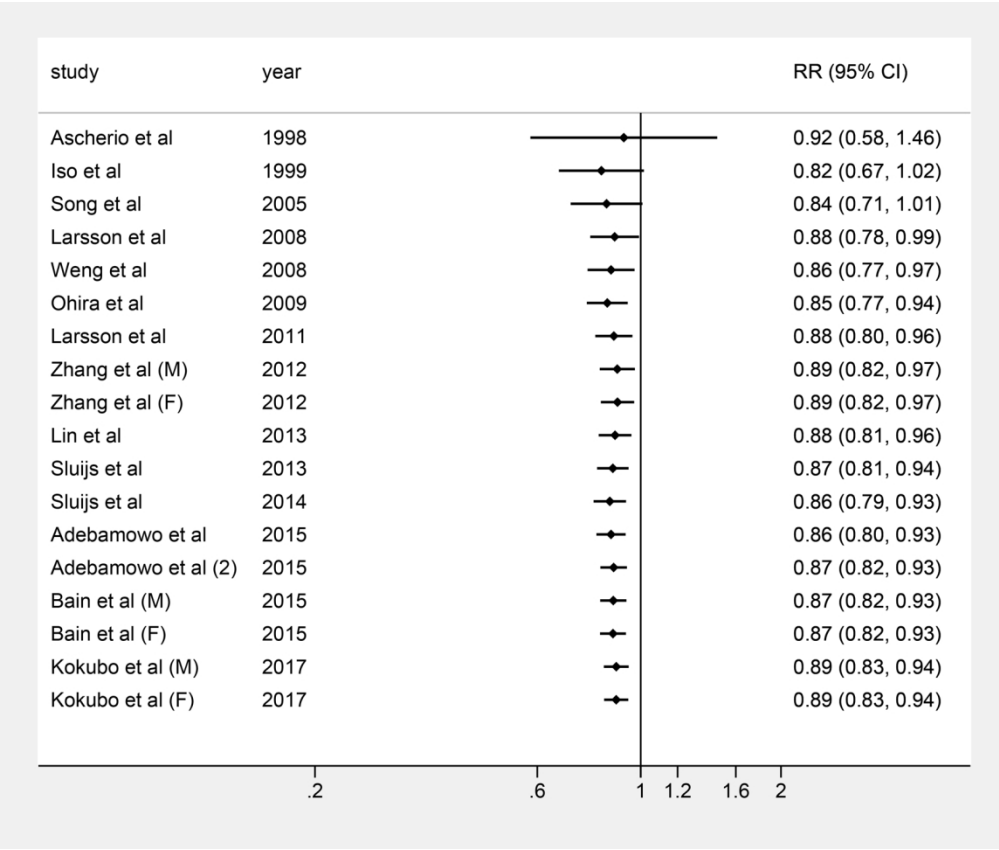
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

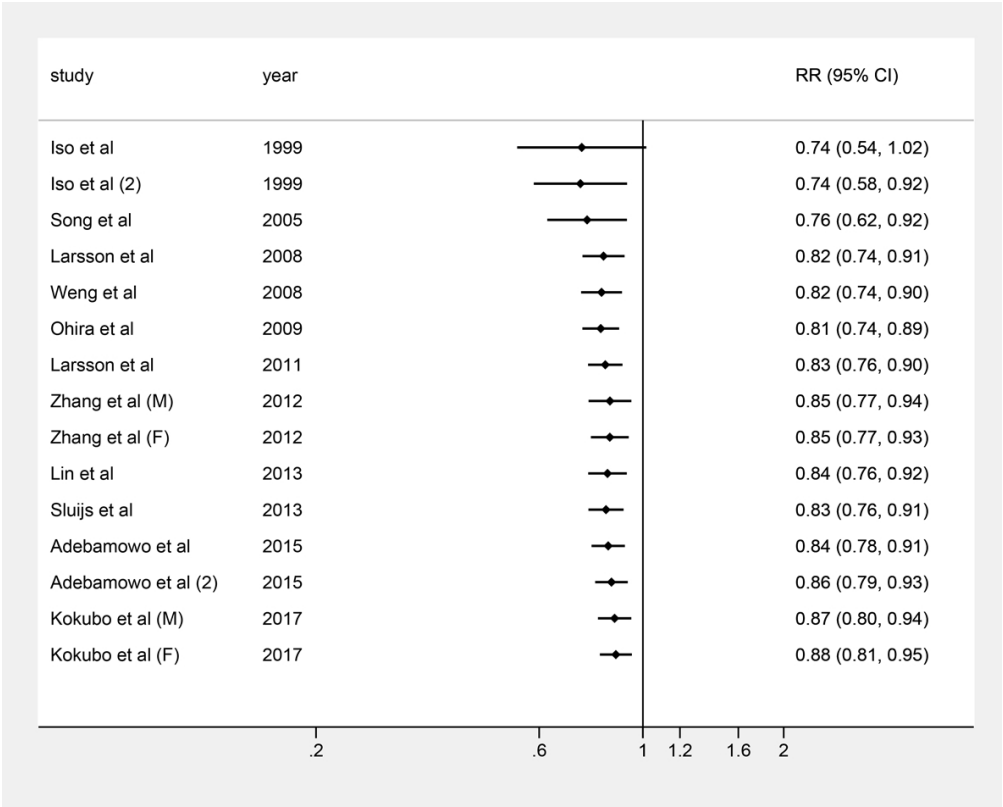
dietaryassessment	Freq.	Percent	Cum.
FFQ	4	40.00	40.00
validated FFQ	6	60.00	100.00
Total	10	100.00	

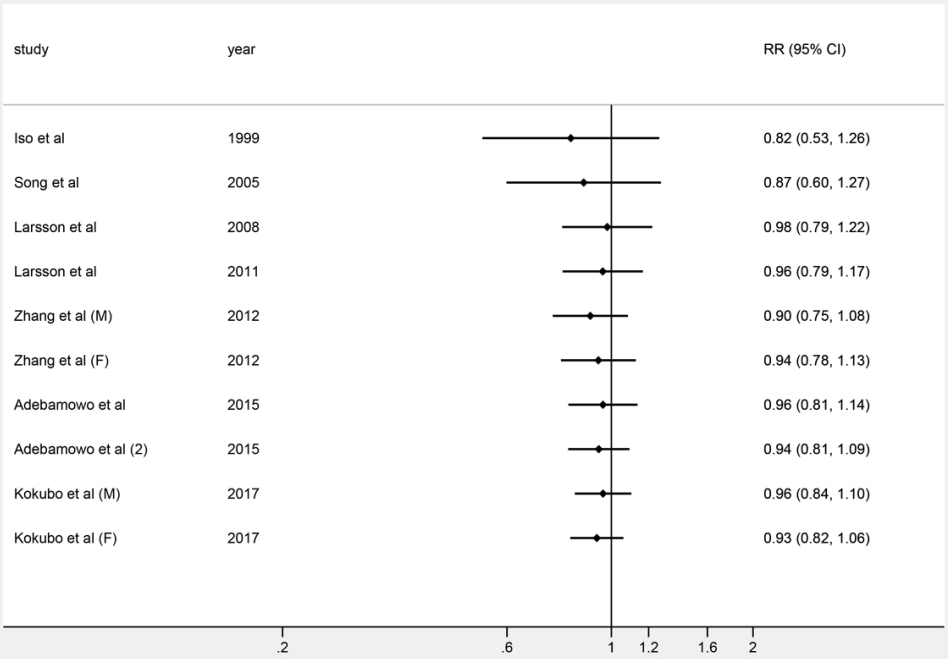
```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           = .001097
% residual variation due to heterogeneity       I-squared_res  =   6.09%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0642559	.1426454	0.45	0.664	-.2646851	.3931968
_cons	-.112665	.1133825	-0.99	0.349	-.3741255	.1487955


study
year
RR (95% CI)
Salmeron et al 1997 0.72 (0.54, 0.96)
Salmeron et al (2) 1997 0.66 (0.55, 0.78)
Kao et al (B) 1999 0.67 (0.57, 0.80)
Kao et al (W) 1999 0.70 (0.60, 0.81)
Liu et al 2000 0.72 (0.64, 0.81)
Meyer et al 2000 0.71 (0.64, 0.78)
Hodge et al 2004 0.71 (0.64, 0.78)
Lopez et al (M) 2004 0.71 (0.65, 0.78)
Lopez et al (F) 2004 0.72 (0.67, 0.77)
Song et al 2004 0.73 (0.68, 0.78)
Liu et al 2006 0.74 (0.70, 0.79)
Pereira et al 2006 0.74 (0.70, 0.79)
Pitta et al 2006 0.74 (0.70, 0.78)
Van et al 2006 0.73 (0.70, 0.77)
Schulze et al 2007 0.74 (0.71, 0.79)
Kirii et al (M) 2009 0.75 (0.71, 0.80)
Kirii et al (W) 2009 0.75 (0.71, 0.79)
Villegas et al 2009 0.75 (0.72, 0.79)
Hopping et al (M) 2010 0.76 (0.72, 0.79)
Hopping et al (F) 2010 0.77 (0.73, 0.80)
Kim et al 2010 0.76 (0.73, 0.80)
Kirii et al 2010 0.76 (0.73, 0.80)
Nanri et al (M) 2010 0.76 (0.73, 0.80)
Nanri et al (F) 2010 0.77 (0.73, 0.80)
Weng et al 2012 0.76 (0.73, 0.80)
Hata et al 2013 0.76 (0.73, 0.80)
Oba et al (M) 2013 0.76 (0.73, 0.80)
Oba et al (F) 2013 0.76 (0.73, 0.80)
Hruby et al 2014 0.76 (0.73, 0.80)
Huang et al 2015 0.76 (0.73, 0.80)
Hruby et al (M) 2017 0.77 (0.74, 0.80)
Hruby et al (F1) 2017 0.77 (0.74, 0.80)
Hruby et al (F2) 2017 0.78 (0.75, 0.81)
Konishi et al (M) 2017 0.78 (0.75, 0.82)
Konishi et al (F) 2017 0.78 (0.75, 0.81)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Ascherio et al 1998 0.92 (0.58, 1.46)
Iso et al 1999 0.82 (0.67, 1.02)
Song et al 2005 0.84 (0.71, 1.01)
Larsson et al 2008 0.88 (0.78, 0.99)
Weng et al 2008 0.86 (0.77, 0.97)
Ohira et al 2009 0.85 (0.77, 0.94)
Larsson et al 2011 0.88 (0.80, 0.96)
Zhang et al (M) 2012 0.89 (0.82, 0.97)
Zhang et al (F) 2012 0.89 (0.82, 0.97)
Lin et al 2013 0.88 (0.81, 0.96)
Sluijs et al 2013 0.87 (0.81, 0.94)
Sluijs et al 2014 0.86 (0.79, 0.93)
Adebamowo et al 2015 0.86 (0.80, 0.93)
Adebamowo et al (2) 2015 0.87 (0.82, 0.93)
Bain et al (M) 2015 0.87 (0.82, 0.93)
Bain et al (F) 2015 0.87 (0.82, 0.93)
Kokubo et al (M) 2017 0.89 (0.83, 0.94)
Kokubo et al (F) 2017 0.89 (0.83, 0.94)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Iso et al 1999 0.74 (0.54, 1.02)
Iso et al (2) 1999 0.74 (0.58, 0.92)
Song et al 2005 0.76 (0.62, 0.92)
Larsson et al 2008 0.82 (0.74, 0.91)
Weng et al 2008 0.82 (0.74, 0.90)
Ohira et al 2009 0.81 (0.74, 0.89)
Larsson et al 2011 0.83 (0.76, 0.90)
Zhang et al (M) 2012 0.85 (0.77, 0.94)
Zhang et al (F) 2012 0.85 (0.77, 0.93)
Lin et al 2013 0.84 (0.76, 0.92)
Sluijs et al 2013 0.83 (0.76, 0.91)
Adebamowo et al 2015 0.84 (0.78, 0.91)
Adebamowo et al (2) 2015 0.86 (0.79, 0.93)
Kokubo et al (M) 2017 0.87 (0.80, 0.94)
Kokubo et al (F) 2017 0.88 (0.81, 0.95)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Iso et al
1999
0.82 (0.53, 1.26)
Song et al
2005
0.87 (0.60, 1.27)
Larsson et al
2008
0.98 (0.79, 1.22)
Larsson et al
2011
0.96 (0.79, 1.17)
Zhang et al (M)
2012
0.90 (0.75, 1.08)
Zhang et al (F)
2012
0.94 (0.78, 1.13)
Adebamowo et al
2015
0.96 (0.81, 1.14)
Adebamowo et al (2)
2015
0.94 (0.81, 1.09)
Kokubo et al (M)
2017
0.96 (0.84, 1.10)
Kokubo et al (F)
2017
0.93 (0.82, 1.06)
.2
.6
1
1.2
1.6
2

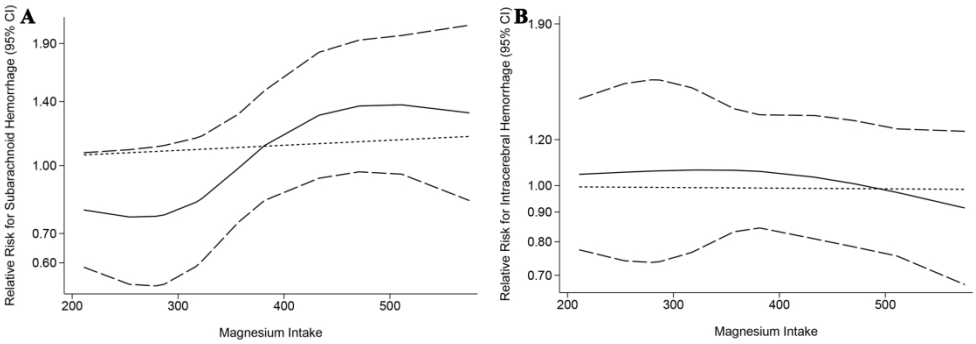

A
Relative Risk for Subarachnoid Hemorrhage (95% CI)
1.90
1.40
1.00
0.70
0.60
200
300
400
500
Magnesium Intake
B
Relative Risk for Intracerebral Hemorrhage (95% CI)
1.90
1.20
1.00
0.90
0.80
0.70
200
300
400
500
Magnesium Intake

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			2-3
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			4-5
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			5-9
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-8

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			9-16
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-16
DISCUSSION			16-22
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			23
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	4-5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6-7
8	Search strategy, including time period included in the synthesis and key words	5-6
9	Effort to include all available studies, including contact with authors	5-6
10	Databases and registries searched	5-6
11	Search software used, name and version, including special features used (eg, explosion)	5-6
12	Use of hand searching (eg, reference lists of obtained articles)	5-6
13	List of citations located and those excluded, including justification	6
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-9
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-9
22	Assessment of heterogeneity	7-9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or	7-9

	cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	9
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	10-14
26	Table giving descriptive information for each study included	10-11, Table S4
27	Results of sensitivity testing (eg, subgroup analysis)	14
28	Indication of statistical uncertainty of findings	16

Item No	**Recommendation**	**Reported on Page No**
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11-14
30	Justification for exclusion (eg, exclusion of non-English language citations)	10
31	Assessment of quality of included studies	11, Table S5
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	16-22
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 23
34	Guidelines for future research	17-20, 22
35	Disclosure of funding source	None

BMJ Open

The association of magnesium intake with type 2 diabetes and total stroke: an updated systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2019-032240.R2
Article Type:	Original research
Date Submitted by the Author:	09-Feb-2020
Complete List of Authors:	Zhao, Binghao; The Second Affiliated Hospital of Nanchang University, Department of Cardio-Thoracic Surgery Zeng, Lianli; The second affiliated hospital of Nanchang University, Department of Cardiovascular Medicine Zhao, Jiani; The second affiliated hospital of Nanchang University, Department of Cardiovascular Medicine Wu, Qian; The second affiliated hospital of Nanchang University, Department of Cardiovascular Medicine Dong, Yifei; The second affiliated hospital of Nanchang University, Department of Cardiovascular Medicine Zou, Fang; The second affiliated hospital of Nanchang University, Department of Endocrinology Gan, Li; The second affiliated hospital of Nanchang University, Department of Neurology Wei, Yiping; The Second Affiliated Hospital of Nanchang University, Department of Cardio-Thoracic Surgery Zhang, Wenxiong; The Second Affiliated Hospital of Nanchang University, Department of Cardio-Thoracic Surgery
Primary Subject Heading:	Nutrition and metabolism
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Keywords:	Magnesium Intake, Type 2 Diabetes, Stroke < NEUROLOGY, Meta-Analysis

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The association of magnesium intake with type 2 diabetes and total stroke: an updated systematic review and meta-analysis

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Abstract

Objective: The detailed associations between type 2 diabetes (T2D) and total stroke and magnesium intake as well as the dose-response trend should be updated in a timely manner.

Design: Systematic review and meta-analyses.

Data sources: PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were rigorously searched from inception to March 15, 2019.

Eligibility criteria: Prospective cohort studies investigating these two diseases were included.

Data synthesis: Relative risk (RR) and 95% confidence intervals (95% CI) in random effects models as well as absolute risk (AR) were pooled to calculate the risk of T2D and stroke. Methodological quality was assessed by the Newcastle-Ottawa Scale.

Results: Forty-one studies involving 53 cohorts were included. The magnitude of the risk was significantly reduced by 22% for T2D (RR, 0.78 [95% CI, 0.75-0.81]; $P<$ 0.001; AR reduction, 0.120%), 11% for total stroke (RR, 0.89 [95% CI, 0.83-0.94]; $P<$ 0.001; AR reduction, 0.281%), and 12% for ischemic stroke (RR, 0.88 [95% CI, 0.81-0.95]; P = 0.001; AR reduction, 0.246%) when comparing the highest magnesium intake to the lowest. The inverse association still existed when studies on T2D were adjusted for cereal fiber (RR, 0.79; $P<$ 0.001) and those on total stroke were adjusted for calcium (RR, 0.89; P = 0.040). Subgroup analyses suggested that the risk for total and ischemic stroke was significantly decreased in females, participants with ≥ 25 mg/m^2 body mass index, and those with ≥ 12 y follow-up; the

reduced risk in Asians was not as notable as that in North American and European populations.

Conclusions: Magnesium intake has significantly inverse associations with T2D and total stroke in a dose-dependent manner. Feasible magnesium-rich dietary patterns may be highly beneficial for specific populations and could be highlighted in the primary T2D and total stroke prevention strategies disseminated to the public.

PROSPERO registration number CRD42018092690

Strengths and limitations of this study

1. In this study, we performed an updated comprehensive quantitative analysis focusing on the dietary effect of magnesium intake.
2. The study identified an inverse association between magnesium intake and T2D and stroke.
3. A quite number of prospective cohort studies were employed to guarantee the robust evidence.
4. There was imperfect of not including randomized controlled trails to prove the causality.
5. Cases ascertainments are limited by FFQ or self-reports.

Keywords: Magnesium Intake; Type 2 Diabetes; Stroke; Meta-Analysis.

Introduction

Diabetes is a global burden with an alarming increasing rate throughout the world[1,2]. Stroke is an independent disorder and a typical macrovascular complication of type 2 diabetes (T2D), and it is regarded as the second leading cause of death after ischemic heart disease[3,4]. These pandemic health problems necessitate better primary prevention strategies.

Magnesium, a common cellular ion, acts as a critical cofactor for hundreds of enzymes involved in glucose metabolism, protein production, and nucleic acid synthesis[5,6]. Low levels of magnesium have been associated with many chronic and inflammatory diseases, such as Alzheimer's disease, asthma, attention deficit hyperactivity disorder, insulin resistance, T2D, hypertension, cardiovascular disease (e.g., stroke), migraine headaches, osteoporosis and cancer[1,5,7,8].

Notably, many adults in developed countries do not consume the recommended daily amount of magnesium-rich foods such as whole grains, nuts, and green leafy vegetables, and magnesium is less mentioned in dietary guidelines and in studies on T2D or stroke prevention[9,10]. Thus, we chose T2D and stroke as our outcome of interest (cardiovascular disease (CVD) was not evaluated because there is already a wealth of research relating to CVD, and the definitions of CVD vary greatly among studies, which would increase the heterogeneity in the pooled process and impair our interpretation of the final conclusions). Emerging studies[11-51] on this topic are limited, and the results remain mixed. For example, most studies have indicated that magnesium intake has an inverse association with T2D or total stroke incidence;

however, several others have revealed that there is an inverse trend but not a significant association, which is possibly due to limitations related to small sample sizes and differences in the intervention duration, study design, and participant characteristics. Moreover, consecutive meta-analyses[52,53] have used less rigorous inclusion; the results were not comprehensive, and they did not completely address the influence of other confounders (i.e., body mass index (BMI), cereal fiber, calcium, potassium) on the relationship. Accordingly, we performed a meta-analysis to (1) establish a comprehensive estimate and update the epidemiological evidence for clinical practice; (2) discuss the results of stroke subtype and the impact of several statistical and epidemiology confounders on the investigated association; and (3) highlight the details of the dose-response pattern observed among the participants analyzed in the studies.

Methods

This study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**) and the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Guidelines Checklist (**Table S2**) (Registration information: PROSPERO CRD42018092690).

Search Strategy

PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were systematically reviewed through inception to March 15, 2019, for studies on

magnesium intake and T2D or stroke without language restrictions. The following key words were used: “Magnesium”, “Type 2 Diabetes Mellitus”, “Type 2 Diabetes”, “Stroke”, “Cerebrovascular Stroke”, “Cohort Studies”, and “Prospective Studies”. We also manually searched the reference lists of the retrieved literature (including meta-analyses and brief reports), bibliographies and gray literature (including presentations and unpublished literature) for further eligible articles. The search strategy can be found in **Table S3**.

Selection Criteria

(1) Eligible populations must be composed of individuals with plausible dietary/energy intake who had no history of diabetes and/or insulin treatment for T2D analysis and no current stroke for stroke analysis. (2) Their apparent life expectancy was long enough for proper follow-up. (3) We included only prospective cohort studies that reported magnesium intake and T2D and/or various types of stroke. (4) The follow-up duration of eligible studies was at least one year if they provided follow-up data. Notably, magnesium intake consisted of both dietary magnesium intake and total magnesium intake (dietary and supplementary magnesium).

Only studies containing the most comprehensive information on the population or endpoints were included to avoid duplication. We excluded reviews, basic science studies, meta-analyses, studies on gestational diabetes mellitus (GDM) and studies that focused only on magnesium supplementation.

Data Extraction and Quality Assessments

Two researchers independently extracted the following information: the first author, publication year, period of cohort studies, duration of persistent exposure, basic characteristics of the enrolled participants (weight, age, region, BMI, drinking and smoking habits (previous plus current), etc.), median magnesium intake for each quantile (tertile, quartile, or quintile), diabetes and total stroke cases, subtypes of total stroke, dietary and case assessments, adjusted confounding covariates. Importantly, total stroke is classified as clinical ischemic stroke (87%), hemorrhagic stroke (13%) and undetermined stroke[54]. Hemorrhagic stroke is classified as subarachnoid hemorrhage and intracerebral hemorrhage according to anatomical site or presumed etiology[55]. In cases of continuing disagreement, a final decision was reached after discussion with a third member of the panel.

Methodological quality was described by the Newcastle-Ottawa Scale (NOS), which was validated for assessment of the quality of nonrandomized controlled trials in meta-analyses[56]. For the 0-10 scale, each study was categorized as low (0-5), medium (6-7), or high (8-10) quality.

Statistical Analysis

Articles providing data separately for men and women or black and white or different types of disease within an article were treated as independent studies. Multivariate relative risk (RR) and corresponding 95% confidence intervals (CI) as well as absolute risk (AR) for measuring the quantitative associations between exposure and

T2D, total stroke and other wanted outcomes, particularly for the highest vs. the lowest categories of magnesium intake, were estimated by the DerSimonian-Laird random effects model because the assumptions involved account for the presence of within-study and between-study variability. Statistical heterogeneity was determined with the Cochran Q chi-square test and the I^2. An I^2> 50% or a *P*-value for the Q test < 0.1 was considered to indicate significant heterogeneity[57]. We performed sensitivity analyses to test the robustness and post-subgroup analyses to detect the source of heterogeneity. In addition, a random effects meta-regression analysis on BMI, sex, participant region, and dietary assessments with RR for each trial was performed to obtain an understanding of the reasons for heterogeneity. RR and 95% CI might begin to significantly change as publication years increased in T2D and total stroke, etc., which would be validated by cumulative meta-analyses.

The dose-response analyses for all outcomes were proposed by Greenland and Longnecker[58] and Orsini[59] et al. The categories of magnesium intake, distributions of cases and person-year, RR and 95 CI were extracted. If the number of cases and/or person-years was not available, variance-weighted least squares regression was used to pool the risk estimate. For most studies, the median intake for each quantile (tertile, quartile or quintile) of magnesium intake was assigned as the representative dose. For continuous intake, which was reported as categorical data (range) in some studies, we assigned the midpoint category of the lower and upper bounds to the RR in these studies; when the highest category was open ended, we assumed the length of the open-ended interval to be 1.5 times the adjacent interval; when the lowest category

was open, we assigned the adjacent interval of the category to be 1.5 times the length of the open-ended interval. We employed generalized least squares regression models to calculate study-specific RR estimates per 50 mg/day, 100 mg/day, and 150 mg/day magnesium intake increment if there was evidence of a linear relationship. Nonlinear relationships between magnesium intake and all outcomes were evaluated using restricted cubic splines with four knots located at the 5th, 35th, 65th, and 95th percentiles of the distribution. The *P-value* for curve linearity or nonlinearity was calculated by testing the null hypothesis that the coefficient of the second spline is equal to zero. All results were presented using two-stage dose-response model plots (including linear and nonlinear relationships). Some results were demonstrated as forest plots for intake increments of < 50 mg/day, ≥ 50 and < 100 mg/day, ≥ 100 and < 150 mg/day, and ≥ 150 mg/day.

Publication bias was assessed graphically by Begg's adjusted rank correlation funnel plots[60] and Egger's linear regression tests[61]. All analyses were performed using Stata version 14.0 (StataCorp, College Station, TX, USA); two-sided $P < 0.05$ was considered statistically significant except where otherwise specified.

Patient and Public Involvement

No patients were involved in developing the research question or the outcome measures, and no patients were involved in planning the design or implementation of the study. Furthermore, no patients were asked to advise on the interpretation or writeup of the results. Since this study used aggregated data from previous

publications, it is not easy to disseminate the results of the research to study participants directly.

Results

Study Characteristics and Quality Assessment

Of the 8713 studies, 107 studies were considered for eligibility after screening the titles and abstracts (**Figure 1**). A total of 41[11-51] prospective cohort studies comprising 53 cohorts, 1 912 634 participants and 76 678 cases were eligible for inclusion in the systematic review and meta-analysis (**Table S4**). Hodge et al[18] recorded only 500 mg/day increments of magnesium for further pooled analyses; 2 studies[33,51] failed to clearly distinguish the diabetes type, but the vast majority of cases had T2D. We computed the subtype data in three studies[14,27,36] after the extraction of total stroke, and we regarded ischemic stroke in three other studies[28,30,42] as total stroke given that ischemic stroke accounted for nearly 87% of total stroke. Participants were predominately middle-aged at baseline, with a mean magnesium intake of 370 mg/day for the highest category and 232 mg/day for the lowest category. The mean duration of all eligible studies was 10.7 years. Nineteen studies were conducted in North America (America); 5 studies were conducted in Europe (Sweden, the Netherlands and Britain); 13 studies were conducted in Asia (China and Japan and Taipei); and 4 studies enrolled individuals in multiple nations. Most of the included studies used food frequency questionnaires (FFQs) or semiquantitative FFQs (SFFQs) to assess individual dietary intake. Eighteen studies used dietary magnesium intake, and 21

studies recorded total magnesium intake (dietary and supplementary magnesium intake). Of note, supplementary magnesium intake was assessed by the use of magnesium or multivitamin supplements; nevertheless, dietary magnesium accounted for the majority of magnesium intake. Adjusted confounders were mostly similar; however, adjusted dietary confounders such as cereal fiber, potassium, and calcium still varied across individual studies. It was unclear whether the included studies had adjusted for sodium because they did not provide this information. All the studies were written in English.

After the quality assessments of the studies according to NOS, the average score was 8.85 (**Table S5**), and all studies were of high quality (NOS score 8-10).

Magnesium Intake and T2D Incidence

Thirty-five cohorts from 26 publications[11,12,15,20,22-26,29,31-35,37,39,41,43,48,49,51] (1 219 636 participants and 56 540 T2D cases) reported that the magnitude of T2D risk was reduced by 22% (RR, 0.78 [95% CI, 0.75-0.81]; $P < 0.001$; AR reduction, 0.120%), comparing the highest category of magnesium intake to the lowest, with little evidence of heterogeneity ($I^2 = 35.6\%$; $P = 0.021$). The dose category-specific analysis suggested that for the < 50 mg/day magnesium increment, the risk of T2D was reduced by 10% (RR, 0.90 [95% CI, 0.88-0.93]; $P< 0.001$); for the ≥ 50 and < 100 mg/day increments, the risk was decreased by 16% (RR, 0.84 [95% CI, 0.82-0.87]; $P < 0.001$); for ≥ 100 and < 150 mg/day increments, the risk was reduced by 22% (RR, 0.78 [95% CI, 0.74-0.83]; $P < 0.001$); and for the ≥ 150 mg/day

increment, the risk was reduced by 21% (RR, 0.79 [95% CI, 0.74-0.84]; $P < 0.001$) (**Figure 2**). Little evidence of publication bias was found (Egger's test: $P = 0.088$) (**Figure S1A**).

Magnesium Intake and Stroke Incidence

Eighteen cohorts from 15 publications[13,14,21,27,28,30,36,38,40,42,44-47,50] (692 998 participants and 20 138 total stroke cases) reported that the magnitude of the risk of total stroke was decreased by 11% (RR, 0.89 [95% CI, 0.83-0.94]; $P < 0.001$; AR reduction, 0.281%), comparing the highest category of magnesium intake with the lowest, with no heterogeneity ($I^2 = 0\%$; $P = 0.529$). The dose category-specific analysis revealed no significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day increments or the ≥ 100 and < 150 mg/day increments. For the ≥ 150 mg/day increment, the risk of total stroke was decreased by 15% (RR, 0.85 [95% CI, 0.79-0.91]; $P< 0.001$) (**Figure S2**). Publication bias was evaluated for stroke subtypes.

Fifteen cohorts from 12 publications[14,21,27,28,30,36,38,40,42,45,46,50] reported ischemic stroke. The magnitude of the risk of ischemic stroke was reduced by 12% (RR, 0.88 [95% CI, 0.81-0.95]; $P = 0.001$; AR reduction, 0.246%) with no significant heterogeneity ($I^2 = 16.9\%$; $P = 0.265$). The dose category-specific analysis identified no significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and < 150 mg/day increments. A decreasing trend existed but remained nonsignificant. The original risk was reduced by 16% in the analysis of the ≥ 150 mg/day increment

(RR, 0.84 [95% CI, 0.78-0.91]; $P< 0.001$) (**Figure S3**). No publication bias was observed in terms of ischemic stroke (Egger's test: $P = 0.937$) (**Figure S1B**).

Ten cohorts from 8 studies[14,21,27,36,38,45,46,50] reported that hemorrhagic stroke was not significantly associated with magnesium intake (RR, 0.93 [95% CI, 0.82-1.06]; $P = 0.282$). The dose category-specific analysis identified no significant association (**Figure S4**). No significant heterogeneity or publication bias was observed in terms of hemorrhagic stroke (Egger's test: $P = 0.809$) (**Figure S1C**).

Three publications involving 3 cohorts[14,27,36] showed that high magnesium intake had no significant effect on reducing the risk of subarachnoid hemorrhage (RR, 0.99 [95% CI, 0.71-1.39]; $P = 0.963$). The dose category-specific analysis revealed no significant association (**Figure S5**).

With respect to intracerebral hemorrhage, the pooled results from 3 cohorts[14,27,36] in 3 publications revealed no significant advantages of intracerebral hemorrhage (RR, 0.92 [95% CI, 0.71-1.20]; $P = 0.540$). The dose category-specific analysis revealed no significant association (**Figure S6**).

Meta-Regression and Cumulative Meta-Analysis

According to the meta-regression results, there was no evidence of BMI, sex, participant region or dietary assessment for each individual trial bias in terms of T2D (**Figure S7**), total stroke (**Figure S8**), ischemic stroke (**Figure S9**) and hemorrhagic stroke events (**Figure S10**). The male subgroup ($P = 0.041$) in the sex category might lead to slight heterogeneity in terms of total stroke; however, sex ($P = 0.112$) showed

no association with total stroke incidence.

Analyses of T2D (**Figure S11**), total stroke (**Figure S12**) and ischemic stroke demonstrated that the RRs of the final results became robust within a narrow range and remained significant as publication years increased and more recent high-quality studies were included. After inclusion of the Iso et al[14] study, the RR and 95% CI for ischemic stroke decreased to less than 1 and then became stable (**Figure S13**)**.** Although there was no significant reduction in the risk of hemorrhagic stroke, the evidence clearly showed that the confidence interval was becoming narrow, which trended toward significance (**Figure S14**). Thus, the risk for hemorrhagic stroke might be reduced; additional studies are warranted.

Sensitivity Analysis

When three[24-26] studies were excluded from the T2D analysis, the summary RR changed from 0.78 ([95% CI, 0.75-0.81]) to 0.78 ([95% CI, 0.75-0.82]), with the heterogeneity declining from (I^2 = 35.6%; P = 0.021) to (I^2 = 24.0%; P = 0.112). Among T2D analyses, eight studies[19,22,23,26,33,39,48,49] adjusted for cereal fiber intake yielded an RR of 0.79 ([95% CI, 0.73-0.85]; P< 0.001), and two studies[15,35] adjusted for calcium yielded an RR of 0.87 ([95% CI, 0.73-1.04]; P = 0.128). Among the total stroke analysis, the summary RR was 0.92 ([95% CI, 0.82-1.02]; P = 0.097) in five studies[13,44-46,50] adjusted for potassium intake and was 0.89 ([95% CI, 0.80-0.99]; P = 0.040) in five studies[14,44-46,50] adjusted for calcium. Only one study[15] adjusted for potassium intake in T2D, and one study[36] adjusted for cereal fiber in total stroke.

Subgroup Analysis

Stratified analyses by characteristics of the population and study design were conducted on T2D (**Table 1**), total stroke, ischemic stroke and hemorrhagic stroke (**Table 2**). The inverse association with T2D remained robust across all subgroups with little evidence of heterogeneity. For stroke incidence, a decreased risk of total stroke and ischemic stroke was found in female participants (RR, 0.91 [95% CI, 0.83-0.99] for total stroke; 0.89 [95% CI, 0.79-1.00] for ischemic stroke) and individuals with ≥ 25 kg/m^2 mean BMI (RR, 0.89 [95% CI, 0.82-0.96] for total stroke; 0.88 [95% CI, 0.81-0.96] for ischemic stroke). When restricted to a ≥ 12 y follow-up, the risk of total stroke and ischemic stroke was significantly reduced (RR, 0.89 [95% CI, 0.83-0.95] for total stroke; 0.88 [95% CI, 0.81-0.95] for ischemic stroke). These risks were more reduced in North American and European individuals than in Asians. Cardiovascular events (CV events, coronary heart disease, heart failure, atrial fibrillation, self-reported heart disease, etc. other than stroke), hypercholesterolemia and diabetes would blunt the effect of magnesium on total and ischemic stroke. However, magnesium intake could still, or at least, demonstrate the trend to decrease total and ischemic stroke in individuals even with those risk factors. Similarly, CV events, hypercholesterolemia and family diabetes history had no substantial impact on the inverse association between T2D incidence and magnesium intake. We did not find a significantly reduced risk of hemorrhagic stroke in the subgroup analyses.

Dose-Response Analysis

In this part, both linear and nonlinear relationships were found in T2D (**Figure 3A**), in total stroke (**Figure 3B**), and in ischemic stroke (**Figure 3C**). However, no linear or nonlinear dose-response relationship was observed in hemorrhagic stroke (**Figure 3D**) along with the subtypes including subarachnoid hemorrhage and intracerebral hemorrhage (**Figure S15**).

Specifically, we calculated the RR for the magnesium increments if a linear relationship was found. The calculated RR was 0.94 ([95% CI, 0.93-0.95]) for the 100 mg/day increment for T2D. For total stroke, the summary RR was 0.98 ([95% CI, 0.97-0.99]) related to a 100 mg/day increment in magnesium intake, and the RR for ischemic stroke was 0.98 ([95% CI, 0.97-0.99]) related to a 100 mg/day increment in magnesium intake. There was no RR cut-off point at which the decreasing trend reversed, but the RR decreased slightly rapidly with any slight decreases at approximately 260 mg/day for T2D and 350 mg/day for total/ischemic stroke. However, there was substantial uncertainty in the lower range of this distribution (**Figure 3A, 3B, 3C**).

Discussion

Main findings

This paper used a general and up-to-date search strategy to identify additional studies that were missed in prior meta-analyses under real-world conditions. Our results support a significant inverse association between magnesium consumption and T2D,

total stroke and ischemic stroke at the highest level vs. the lowest. No significant association for hemorrhagic stroke, subarachnoid hemorrhage or intracerebral hemorrhage was detected. Female obese participants (mean BMI ≥ 25 kg/m^2) with a longer follow-up period (≥ 12 y) might obtain greater benefit from magnesium intake with a lower risk of total and ischemic stroke incidence. In subgroup analyses, the RR of stroke risk was highly decreased among North American and European individuals. Significant risk was reduced by 6%, 2%, and 2% for T2D, total stroke and ischemic stroke, respectively, per 100 mg/day increment in magnesium intake level. Overall, our study supports the guidelines to address the role of magnesium intake in early prevention strategies to combat T2D and stroke. However, additional randomized controlled trials (RCTs) are needed in the future to validate the causality.

Clinical implications

Dietary nutrients are popular topics for current clinical medicine; folic acid, vitamin D, and ω-3 fatty acids have been specifically recommended to pregnant women, infants and children, and the elderly[62,63]. However, magnesium has been less extensively discussed. This is a noteworthy study for the following reasons. First, the current study reinforces the possible role of magnesium in the prevention and management of two chronic illnesses and invites new considerations regarding the potential avoidance of other chronic diseases through dietary strategies. Second, this comprehensive study including nearly two million individuals and possessing abundant statistical power provides confirmatory evidence for medical practitioners,

health educators and policymakers. Third, to date, no related paper has discussed such detailed stratified analyses; thus, this work helps physicians amplify dietary benefits through individualized strategies. Interestingly, North American and European participants seemed to receive more benefits from magnesium intake than Asians. Fourth, to the best of our knowledge, this is the first study in which a cumulative meta-analysis was performed to predict changes in the tendency of main risk estimates. Based on past and current cutting edge evidence about nutrition and T2D prevention, the US Diabetes Prevention Program (DPP) conducted a study and demonstrated that proper lifestyle modification (exercise and Mediterranean diet) significantly reduced T2D risk irrespective of population baselines, and this benefit was enhanced with increased follow-up[64]. The UK National Health Service (UK NHS) will launch an intervention program including weight loss, nutrition, monitoring and peer support targeting up to 10 000 people prone to develop T2D[65].

The 2018 American Diabetes Association (ADA) guidelines[66] recommend that the intake of nuts, berries, yogurt, coffee and tea be increased in individuals who are at high risk of diabetes. The latest guidelines by the American Heart Association (AHA)/American Stroke Association (ASA)[9] also validate the considerable status of early management of stroke (ischemic stroke). In fact, magnesium is a cofactor in enzyme systems that regulate diverse biomedical reactions, including protein synthesis, muscle and nerve transmission, neuromuscular conduction, signal transduction blood glucose control and blood pressure management[67]. Magnesium also plays a role in transporting calcium and potassium ions across the cell membrane

and is crucial for the structural function of proteins, nucleic acids or mitochondria[68]. In diabetes, magnesium is involved in glucose and insulin metabolism by regulating the tyrosine kinase activity of the insulin receptor. Magnesium also influences phosphorylase B kinase activity by releasing glucose-1-phosphate from glycogen and regulates glucose translocation into the cell[69]. In stroke, higher magnesium levels lead to the deregulation of glutamate and calcium cation influx by reducing NMDA receptor activity and blocking voltage-gated calcium channels, eliminating calcium cation cytotoxicity. Additionally, the vasodilatory effects of magnesium may benefit ischemic stroke patients[70]. Indeed, a poor outcome of hemorrhagic stroke was observed in an RCT; however, high serum magnesium might be better for the prognosis of intracerebral hemorrhage[71].

Most specific nutrients, especially macronutrients, are correlated with total energy intake. In the included free-living human studies, the variation in total energy intake originated from differences in physical activity levels, body size, and energy efficiency[72]. Thus, total energy intake can weaken the investigated association with considerable nutrient intake if this covariable is not properly removed. Epidemiologists should assess the reproducibility and validity of energy-adjusted nutrients as well as absolute nutrient intake. For micronutrients such as magnesium, an inverse association with T2D, total stroke and ischemic stroke outcomes could be still found after total energy intake adjustment. In terms of other nutrients, potassium intake is proposed to lower blood pressure (BP) and improve vascular outcomes (including stroke); dietary potassium may also be influential in glucose control and

limiting the risk of diabetes[73]. Vitamin D and calcium may negatively influence glycemia, but the evidence is limited and mostly based on cross-sectional observational studies[74]. Calcium may be inversely associated with stroke in populations with low to moderate calcium intakes, but no significant association was found between calcium and CVD[75]. Altogether, the results indicate that magnesium-rich food such as nuts (151-567 mg/100 g edibles), fruits (132-448 mg/100 g edibles), vegetables (132-1257 mg/100 g edibles), legumes (138-243 mg/100 g edibles), fish (143-303 mg/100 g edibles) and total grain (134-306 mg/100 g edibles) should be recommended to populations with insufficient magnesium intake.

Comparisons with other similar studies

This analysis has several differences from previous studies. Dong et al[52] found that magnesium intake had an inverse association with T2D incidence (RR, 0.78 [95% CI, 0.73-0.84]), and with an intake of 100 mg/day magnesium, the risk was reduced by 14%. However, they failed to include adequate studies, and standard quality assessments of eligible studies were absent. Individuals from multiple nations were included in some studies[18,25,26,32] but were incorrectly assigned to Asia or the U.S. in the subgroups; other minor issues also existed in the selection criteria, making it unclear whether they excluded participants with subclinical diabetes. BMI was not a potential modifier for T2D in our study due to the inclusion of more evidence with a longer follow-up period. Fang et al[76] revealed that dietary magnesium was significantly associated with a reduced risk of T2D (RR, 0.74 [95% CI, 0.69-0.80])

and stroke (RR, 0.88 [95% CI, 0.82-0.95]). The results were comparable, but they focused only on dietary magnesium intake rather than overall magnesium intake (total or dietary), and subtypes of total stroke were missing. To the best of our knowledge, BMI, follow-up, family diabetes history, etc. are crucial confounders for evaluating the association, and these factors were not addressed in their study. Moreover, other researchers have better investigated the likelihood of a linear association in the dose-response pattern (using methods by Greenland and Orsini et al.). For example, Fang et al[77] found that the 100 mg/day intake of dietary magnesium was associated with an 8-13% reduction in T2D risk, and while a nonlinear relationship did not exist, a minor publication bias was present. Twenty-five studies were eligible; however, some of them focused not on dietary intake but rather on total magnesium intake. Moreover, there were two included studies focusing on red meat intake instead of magnesium intake. After excluding ineligible studies, we found no evidence of publication bias. Additionally, both linear and nonlinear relationships existed for T2D because the RRs of the highest category of magnesium intake vs. the lowest in our pooled study were still used. A study by Larsson et al[53] including 7 studies supported a modest but statistically significant inverse association between dietary magnesium intake and stroke. However, the sample size was quite small, and there was no useful information on stroke subtypes (e.g., ischemic stroke, hemorrhagic stroke) in the main analysis. In our opinion, a well-designed subgroup analysis is compulsory, and a pooled stroke result restricted by potassium and calcium adjustment is recommended. The current study found that magnesium intake was strongly inversely associated with

total stroke and ischemic stroke, which still existed in the dose-response pattern.

Directions for future research

Future studies are needed to address some remaining questions. At first, no significant association was found for hemorrhagic stroke; however, a beneficial trend was observed in the cumulative meta-analysis, which highlights the need for more updated prospective studies and RCTs. Second, there is a key question regarding the optimal time to start prevention and methods to screen severe complications. Cardiovascular events occur in more than 50% of patients with diabetes, and diabetic kidney disease occurs in 20-40%. Additionally, cardiovascular events increase the risk of death three- to fourfold compared with patients without such complications. A sustained period of intensive glucose control early in T2D has been confirmed to reduce complication rates[78]. Most importantly, for the public, educators and policymakers, promoting magnesium-rich food consumption can translate into considerable benefit in preventing T2D and total stroke, especially for high-risk populations.

Limitations

This work has several limitations that deserve further discussion. First, this group-level meta-analysis is insufficient. Although strong inverse associations for T2D and total stroke were reported, individual-level studies having more detection power are required. Second, several variations cannot be totally understood; for example, we cannot exclude the possibility that other nutrients and/or dietary

components correlated with dietary magnesium may have been responsible, either partially or entirely, for the observed associations. Based on eligible studies, we could not quantify the impact of supplementary magnesium (not combined with dietary intake) on T2D and stroke incidence. The real effect of some dietary supplements on T2D or cardiovascular disease has proven very interesting to a number of medical experts, clinicians and nutrition educators. Third, FFQs/validated FFQs mostly used in primary studies could not characterize all the nutrients, which misclarified plausible associations. It was suggested that magnesium-specific food questionnaires and/or food records should be reasonably used for accurate magnesium intake estimation. Finally, additional RCT are needed, as observational studies might only reach one conclusion (i.e., magnesium intake is inversely associated with T2D incidence) and cannot prove causality.

Conclusion

Magnesium intake has a substantial inverse association with T2D and total stroke. Among these populations, magnesium consumption can be recommended as an optimization for T2D, total stroke and ischemic stroke primary prevention or early management. In particular, the greater the magnesium intake is, the greater the reduction in risk. As patients, physicians, policy makers and legislators debate these issues, such a cost-effective alternative is needed to inform policy decisions and aid in reforming nutritional health care worldwide.

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Competing interests

None declared

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All data relevant to the study are included in the article or uploaded as supplementary information.

Patient consent for publication

Not required.

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Table 1 Subgroup Analysis relating to Magnesium Intake and Type 2Diabetes (T2D)

Group	T2D					
	No. of studies	RR (95% CI)	P_{ES}	$P_{heterogeneity}$	I^2 (%)	$P_{interaction}$
Total	26	0.78 (0.75-0.81)	< 0.001	0.021	35.6	NA
Participants region	26					0.905
North America	13	0.77 (0.73-0.82)	< 0.001	0.048	39.5	
Europe	0	NA	NA	NA	NA	
Asia	9	0.78 (0.71-0.87)	< 0.001	0.165	21.7	
Multiple nations	4	0.79 (0.71-0.88)	< 0.001	0.048	58.3	
Sex[a]	34					0.284
Male	9	0.81(0.76-0.87)	< 0.001	0.337	11.7	
Female	17	0.77 (0.73-0.81)	< 0.001	0.055	37.5	
Both[b]	8	0.70 (0.57-0.85)	< 0.001	0.067	45.3	
BMI (kg/m^2)	26					0.716
≥ 25	12	0.75 (0.69-0.81)	< 0.001	0.135	31	
< 25	11	0.78 (0.74-0.83)	< 0.001	0.022	45.4	
Unknown	3	0.81 (0.76-0.86)	< 0.001	0.586	0	
Follow-up duration (y)	26					0.150
≥ 10	12	0.80 (0.76-0.84)	< 0.001	0.047	38.8	
< 10	14	0.74 (0.68-0.80)	< 0.001	0.164	25.2	
Dietary assessment	26					0.281
FFQ/validated FFQ	15	0.77 (0.73-0.82)	< 0.001	0.159	23.7	
SFFQ/validated SFFQ	9	0.79 (0.74-0.84)	< 0.001	0.017	52.5	
Other	2	0.55 (0.36-0.83)	0.005	0.826	0	
Magnesium intake type[c]	28					0.335
Total magnesium intake[d]	15	0.79 (0.75-0.84)	< 0.001	0.035	39.8	
Dietary magnesium intake	13	0.77 (0.72-0.82)	< 0.001	0.166	25.0	
Total energy adjustment	26					0.396
Yes	17	0.79 (0.74-0.84)	< 0.001	0.027	40.4	
No	9	0.76 (0.72-0.81)	< 0.001	0.225	21.6	
Difference between top and bottom intake (mg/day)[e]	27					0.671
≥ 140	13	0.78 (0.74-0.83)	< 0.001	0.020	45.3	
< 140	14	0.77 (0.72-0.82)	< 0.001	0.209	21.0	
Current CV events status[f]	26					0.536
Yes	13	0.79 (0.74-0.83)	< 0.001	0.049	37.9	
Unknown	13	0.77 (0.71-0.82)	< 0.001	0.082	35.1	
Hypercholesterolemia status[g]	26					0.625
Yes	5	0.79 (0.73-0.85)	< 0.001	0.021	57.5	
Unknown	21	0.77 (0.73-0.82)	< 0.001	0.096	27.3	
Family diabetes history	26					0.168
Yes	17	0.76 (0.72-0.80)	< 0.001	0.021	41.8	
Unknown	9	0.81 (0.76-0.87)	< 0.001	0.258	14.3	

Abbreviation: T2D, type 2 diabetes; BMI, body mass index; FFQ, food frequencyquestionnaire; SFFQ, semi-quantitative food frequent questionnaire; RR, relative risk; ES, effect size; CV events, cardiovascular events.

[a], Male and female of T2D outcome were treated as independent cohorts within eight studies;

[b], Male and female participants were in independent cohorts;

[c], Two studies reported total magnesium and dietary magnesium intake outcome;

[d], Total magnesium intake (milligrams per day) included the total amount of magnesium from both food (diet) and supplement;

[e], Subtract the lowest category intake from the highest. Oba el al (M) was in < 140 group, while Oba el al (F) was in ≥ 140 group;

[f], Grouped by whether participants with or without CV events. CV events in this part include coronary heart disease, heart failure, stroke, atrial fibrillation, and self-reported heart disease etc;

[g], Grouped by whether participants with or without hypercholesterolemia. Hypercholesterolemia in this part means cholesterol concentration ≥ 240 mg/dL.

Table 2. Subgroup Analyses Relating to Magnesium Intake and Total Stroke, Ischemic Stroke, Hemorrhagic stroke.

Group	Total Stroke				Ischemic Stroke				Hemorrhagic stroke			
	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$	No.of studies	RR (95% CI)	I^2 (%)	$P_{interation}$
Total	15	0.89 (0.83-0.94)	0.00	NA	12	0.88 (0.81-0.95)	16.90	NA	8	0.93 (0.82-1.06)	0.461	NA
Participants region	15			0.733	12			0.584	8			0.873
North America	6	0.87 (0.79-0.96)	0.00		5	0.85 (0.76-0.95)	0.00		4	0.90 (0.71-1.15)	0.00	
Europe	5	0.87 (0.77-0.98)	14.80		3	0.86 (0.78-0.95)	0.00		2	0.99 (0.79-1.25)	0.00	
Asia	4	0.90 (0.78-1.05)	32.80		4	0.93 (0.75-1.14)	45.50		2	0.89 (0.66-1.21)	53.40	
Multiple nations	0	NA	NA		0	NA	NA		0	NA	NA	
Sex[a]	18			0.031	14			0.134	10			0.425
Male	6	0.95(0.86-1.05)	0.00		4	0.99 (0.82-1.19)	52.80		4	0.97 (0.75-1.26)	35.50	
Female	7	0.91 (0.83-0.99)	0.00		6	0.89 (0.79-1.00)	0.00		6	0.88 (0.74-1.06)	0.00	
Both[b]	5	0.74 (0.64-0.85)	0.00		4	0.76 (0.65-0.88)	0.00		0	NA	NA	
Mean BMI (kg/m^2)	15			0.606	12			0.631	8			0.418
≥ 25	8	0.89 (0.82-0.96)	0.00		6	0.88 (0.81-0.96)	0.00		5	0.97 (0.81-1.17)	0.00	
< 25	5	0.89 (0.78-1.01)	30.00		5	0.87 (0.73-1.03)	44.00		3	0.88 (0.69-1.12)	39.30	
Unknown	2	0.80 (0.63-1.02)	0.00		1	0.76 (0.57-1.07)	NA		0	NA	NA	
Follow-up duration (y)	15			0.798	12			0.811	8			0.808
≥ 12	11	0.88 (0.82-0.94)	5.30		10	0.87 (0.80-0.95)	19.10		7	0.93 (0.81-1.08)	7.70	
< 12	4	0.90 (0.77-1.05)	0.00		2	0.86 (0.62-1.20)	48.40		1	0.88 (0.57-1.36)	NA	
Dietary assessment	15			0.578	12			NA	8			NA
FFQ/validated FFQ	14	0.89 (0.83-0.95)	3.80		12	0.88 (0.81-0.95)	16.90		8	0.93 (0.82-1.06)	0.00	
SFFQ/validated SFFQ	0	NA	NA		0	NA	NA		0	NA	NA	
Other	1	0.81 (0.61-1.09)	0.00		0	NA	NA		0	NA	NA	
Magnesium intake type	15			0.865	12			0.831	8			0.831
Total magnesium intake[c]	8	0.89 (0.82-0.96)	0.00		6	0.87 (0.80-0.94)	0.00		5	0.94 (0.79-1.12)	0.00	
Dietary magnesium		0.88	0.44			0.89	35.40			0.91 (0.70-1.18)	39.40	

intake	7	(0.81-0.96)			6	(0.77-1.03)			3			
Total energy adjustment	15			0.888	12			0.689	8			0.538
Yes	5	0.87 (0.77-0.99)	27.00		2	0.86 (0.78-0.94)	0.00		2	0.93 (0.82-1.06)	0.00	
No	10	0.89 (0.83-0.96)	0.00		10	0.88 (0.79-0.99)	26.60		6	0.90 （0.76-1.07）	11.40	
Difference between top and bottom intake (mg/day)[d]	15			0.107	12			0.180	8			0..244
≥ 180	7	0.83 (0.76-0.91)	0.00		5	0.83 (0.76-0.91)	0.00		6	1.07 (0.83-1.37)	0.00	
< 180	8	0.93 (0.86-1.00)	0.00		7	0.92 (0.81-1.03)	26.20		2	0.89 (0.76-1.03)	0.00	
Current CV events status[e]	15			0.074	12			0.393	8			NA
Yes	12	0.90 (0.85-0.96)	0.00		11	0.88 (0.81-0.96)	18.20		8	0.93 (0.82-1.06)	0.00	
Unknown	3	0.75 (0.63-0.90)	0.00		1	0.76 (0.57-1.01)	NA		0	NA	NA	
Hypercholesterolemia status[f]	15			0.480	12			0.565	8			0.651
Yes	7	0.91 (0.83-0.99)	0.00		6	0.90 (0.80-1.01)	6.90		5	0.90 (0.76-1.08)	0.00	
Unknown	8	0.86 (0.79-0.95)	13.10		6	0.86 (0.77-0.97)	32.40		3	0.94 (0.72-1.22)	40.30	
Current diabetes status[g]	15			0.039	12			0.159	8			NA
Yes	10	0.91 (0.82-0.97)	0.00		10	0.89 (0.82-0.97)	13.50		8	0.93 (0.82-1.06)	0.00	0.00
Unknown	5	0.75 (0.64-0.88)	0.00		2	0.72 (0.56-0.92)	0.00		0	NA	NA	NA

Abbreviation: BMI, body mass index; FFQ, food frequency questionnaire; SFFQ, semi-quantitative food frequency questionnaire; CV events, cardiovascular events; RR, relative risk; NA, not available.

[a], several studies reported stroke outcome of male and female participants in different cohorts;

[b], male and female participants were in the same cohort;

c, total magnesium intake (milligrams per day) included the total amount of magnesium from both food (diet) and supplements;

[d], subtract the lowest category intake from the highest;

[e], grouped by whether participants with or without CV events. CV events in this part include coronary heart disease, heart failure, atrial fibrillation, and self-reported heart disease etc., stroke is not included;

[f], grouped by whether participants with or without hypercholesterolemia. Hypercholesterolemia in this part means cholesterol concentration ≥ 240 mg/dL;

[g], grouped by whether participants with or without diabetes.

Figure Legends

Figure 1. Flow Chart for the Literature Search and Screening Process

Figure 2. Forest Plots for the Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Increments (E).

Figure 3. Two-Stage Dose-Response Effect on the Relationships between Magnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).

Supplementary material online:

Table S1. PRISMA 2009 Checklist

Table S2. MOOSE Checklist

Table S3. Complete Search Terms for PubMed

Table S4. Summary of Baseline Characteristics of the Included Studies

Table S5. Methodological Quality Assessments of the Included Studies with Newcastle-Ottawa Scales

Figure S1. Funnel Plots for Magnesium Intake and Type 2 Diabetes (A), Ischemic Stroke (B) and Hemorrhagic Stroke (C).

Figure S2. Forest Plots for the Risk of Total Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Increments (E).

Figure S3. Forest Plots for the Risk of Ischemic Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Increments (E).

Figure S4. Forest Plots for the Risk of Hemorrhagic Stroke for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Increments (E).

Figure S5. Forest Plots for the Risk of Subarachnoid Hemorrhage for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Increments (E)

Figure S6. Forest Plots for the Risk of Intracerebral Hemorrhage for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Increments (E)

Figure S7. Meta-Regression of the Relative Risk for Type 2 Diabetes According to

Body Mass Index (A, P = 0.716), Sex (B, P = 0.284), Participant Region (C, P = 0.904) and Dietary Assessment (D, P = 0.521).

Figure S8. Meta-Regression of the Relative Risk for Total Stroke According to Body Mass Index (A, P = 0.606), Sex (B, P = 0.112), Participant region (C, P = 0.891) and Dietary Assessment (D, P = 0.891).

Figure S9. Meta-Regression of the Relative Risk for Ischemic Stroke According to Body Mass Index (A, P = 0.631), Sex (B, P = 0.134), Participant Region (C, P = 0.584) and Dietary Assessment (D, no regression P-value due to limited data).

Figure S10. Meta-Regression of the Relative Risk for Hemorrhagic Stroke According to Body Mass Index (A, P = 0.418), Sex (B, P = 0.872), Participant Region (C, P = 0.872) and Dietary Assessment (D, no regression P-value due to limited data).

Figure S11. Cumulative Meta-Analysis Related to Magnesium Intake and Type 2 Diabetes (T2D)

Figure S12. Cumulative Meta-Analysis Related to Magnesium Intake and Total Stroke

Figure S13. Cumulative Meta-Analysis Related to Magnesium Intake and Ischemic Stroke

Figure S14. Cumulative Meta-Analysis Related to Magnesium Intake and Hemorrhagic Stroke

Figure S15. Dose-Response Effect on the Relationships between Magnesium Intake and Subarachnoid Hemorrhage (A) and Intracerebral Hemorrhage (B).

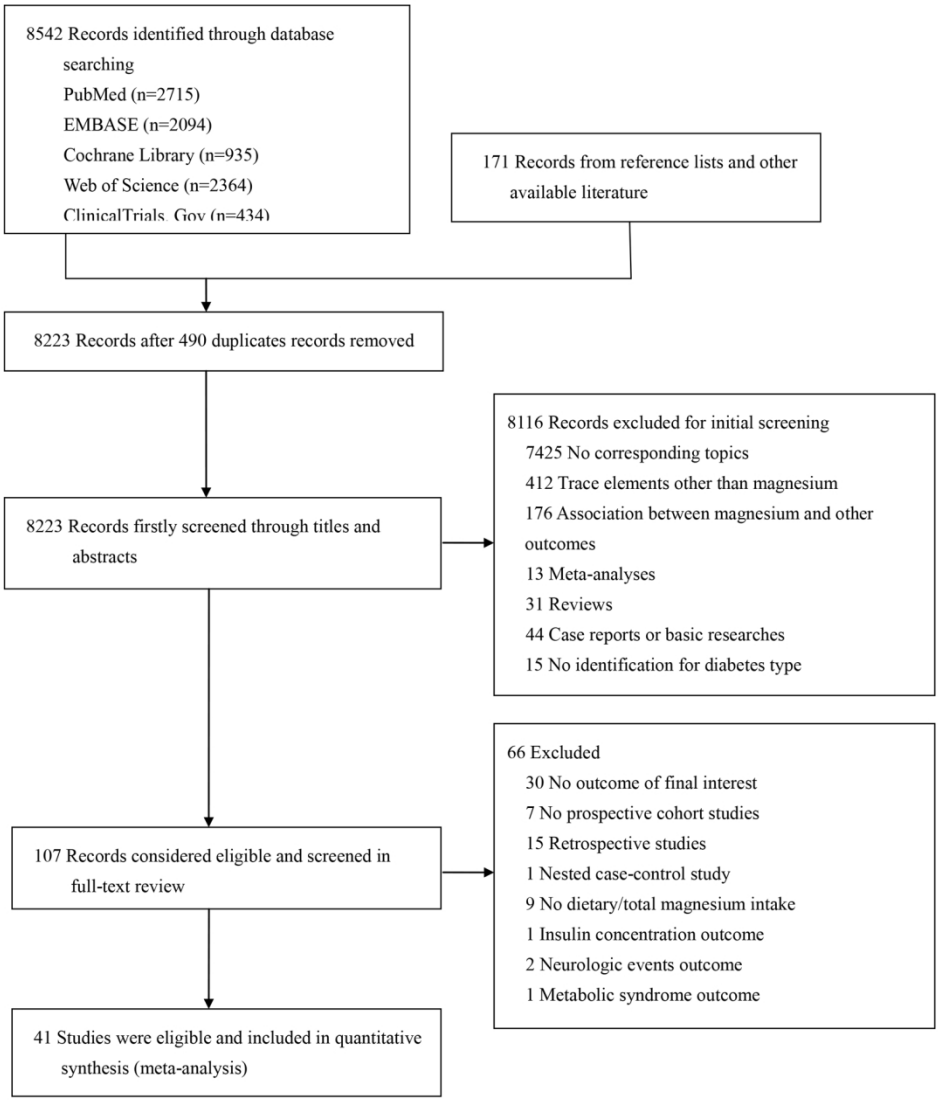


Figure 1. Flow Chart for the Literature Search and Screening Process

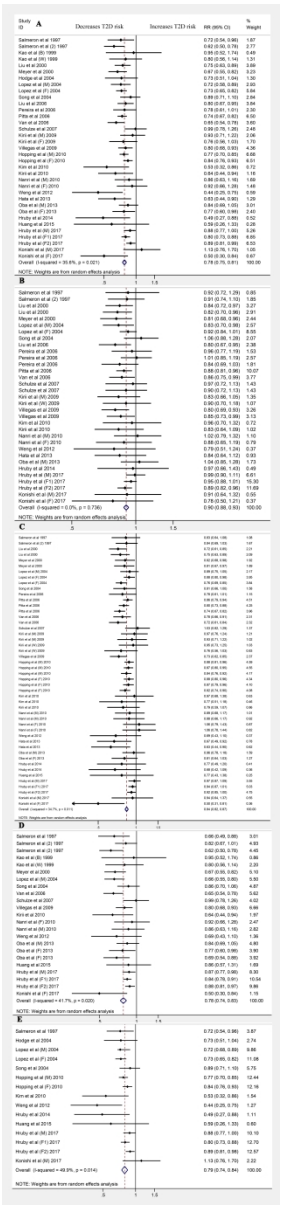


Figure 2. Forest Plots for the Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥100 and <150 mg/day (D) and ≥ 150 mg/day Increments (E).

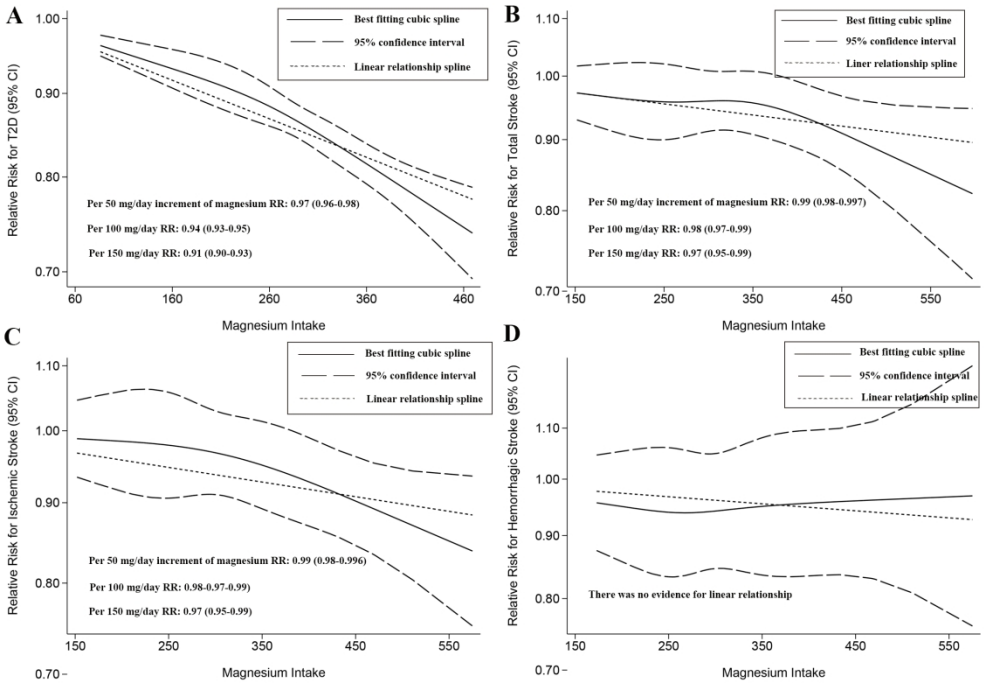


Figure 3. Two-Stage Dose-Response Effect on the Relationships between Magnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			2-3
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			4-5
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			5-9
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-10

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			9-16
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-16
DISCUSSION			16-22
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			23
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: **www.prisma-statement.org**.

Table S2. MOOSE Checklist

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	4-5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6-7
8	Search strategy, including time period included in the synthesis and key words	5-6
9	Effort to include all available studies, including contact with authors	5-6
10	Databases and registries searched	5-6
11	Search software used, name and version, including special features used (eg, explosion)	5-6
12	Use of hand searching (eg, reference lists of obtained articles)	5-6
13	List of citations located and those excluded, including justification	6
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-9
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-9
22	Assessment of heterogeneity	7-9
23	Description of statistical methods (eg, complete description of fixed	7-9

	or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	9
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	10-14
26	Table giving descriptive information for each study included	10-11, Table S4
27	Results of sensitivity testing (eg, subgroup analysis)	14
28	Indication of statistical uncertainty of findings	16

Item No	**Recommendation**	**Reported on Page No**
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11-14
30	Justification for exclusion (eg, exclusion of non-English language citations)	10
31	Assessment of quality of included studies	11, Table S5
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	16-22
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 23
34	Guidelines for future research	17-20, 22
35	Disclosure of funding source	None

Table S3. Complete Search Terms for PubMed

A search example for Pubmed

The combined text and medical subject heading (MeSH) terms used were: “Magnesium” and “Magnesium Supplementation” “Diabetes Mellitus, Type 2”, “Stroke”, “Cerebrovascular Stroke”, and “Cohort Studies”. The complete search terms for PubMed included: (Magnesium [MeSH terms]) AND (Magnesium Supplementation [MeSH terms]) AND (Diabetes Mellitus, Type 2 [MeSH term] OR Diabetes Mellitus, Noninsulin-Dependent [Text Word] OR Diabetes Mellitus, Ketosis-Resistant [Text Word] OR Diabetes Mellitus, Non-Insulin-Dependent [Text Word] OR Non-Insulin-Dependent Diabetes Mellitus [Text Word] OR Diabetes Mellitus, Stable [Text Word] OR NIDDM [Text Word] OR Maturity-Onset Diabetes Mellitus [Text Word] OR Diabetes Mellitus, Slow-Onset [Text Word] OR Type 2 Diabetes [Text Word] OR Diabetes Mellitus, Adult-Onset [Text Word]) AND (Stroke [MeSH terms] OR Cerebrovascular Stroke [Text Word] OR Cerebrovascular Accident [Text Word] OR CVA (Cerebrovascular Accident) [Text Word] OR Vascular Accident, Brain [Text Word] OR Cerebrovascular Apoplexy [Text Word] OR Cerebral Stroke [Text Word] OR Stroke, Acute [Text Word] OR Cerebrovascular Accident, Acute [Text Word] OR Acute Cerebrovascular Accident [Text Word] OR Apoplexy, Cerebrovascular [Text Word]) AND (Cohort Studies [MeSH term] OR Cohort Study [Text Word] OR Studies, Cohort [Text Word] OR Study, Cohort [Text Word] OR Concurrent Studies [Text Word] OR Studies, Concurrent [Text Word] OR Closed Cohort Studies [Text Word] OR Closed Cohort Study [Text Word] OR Study, Closed Cohort [Text Word] OR Cohort Analysis [Text Word] OR Cohort Analysis [Text Word] OR Prospective Studies [Text Word] OR Prospective Study [Text Word] OR Studies, Prospective [Text Word])

Table S4. Summary of Baseline Characteristics of the Included Studies

Source	Nation	Period	Population	BMI	Dietary Assessment	Case Ascertainment	Case (Cohort size)	Magnesium intake (mg/day) highest VS. the lowest [Adjusted RR (95% CI)]
Salmeron 1997[11]	USA	1986-1992	M; 40-75 y	25.5	validated SFFQ	self-reported questionnaire	523 T2D (42759)	461 VS. 262 (0.72 (0.54-0.96))
Salmeron 1997(2)[12]	USA	1986-1992	F; 40-65 y	25.1	validated SFFQ	self-reported questionnaire	915 T2D (65173)	338 VS. 222 (0.62 (0.50-0.78))
Ascherio 1998[13]	USA	1986-1994	M; 40-75 y	NA	validated FFQ	self-reported questionnaire	328 stroke (43738)	425 VS. 243 (0.92 (0.58-1.46))
Iso 1999[14]	USA	1980-1994	F; 34-59 y	22.7	FFQ	self-reported questionnaire	690 stroke (85764)	381 VS. 211 (0.80 (0.63-1.01))
Kao 1999[15]	USA	NA	M/F; 45-64 y	27.2	FFQ	self-reported questionnaire	black: 367 T2D (2622) white: 739 T2D (9506)	374 VS. 264 (0.95 (0.52-1.74)) 418 VS. 308 (0.80 (0.56-1.14))
Liu 2000[16]	USA	1976-1984	F; 38-63 y	24.8	validated FFQ	self-reported questionnaire	1879 T2D (75521)	342 VS. 248 (0.75 (0.63-0.89))
Meyer 2000[17]	USA	1986-1992	F; 55-69 y	26.8	validated FFQ	self-reported questionnaire	1141 T2D (35998)	362 VS. 220 (0,67 (0.55-0.82))
Hodge 2004[18a]	multiple	1990-1994	M/F; 45-64 y	26.1	validated FFQ	self-reported questionnaire	365 T2D (31641)	500 increment per day
Lopez 2004[19]	USA	M: 1986-1998 W: 1980-1998	M; 40-75 y F; 30-35 y	25.4 24.3	validated SFFQ	self-reported questionnaire	1333 T2D (42872) 4085 T2D (85060)	457 VS. 314 (0.72 (0.58-0.89)) 373 VS. 222 (0.73 (0.65-0.82))
Song 2004[20]	USA	1993-2001	F; ⩾45 y[c]	26	SFFQ	self-reported questionnaire	918 T2D (38025)	433 VS. 255 (0.89 (0.71-1.10))
Song 2005[21]	USA	1993-2003	F; 39-89 y	26	FFQ	follow-up examination	368 stroke (39876)	433 VS. 255 (0.90 (0.65-1.26))
Liu 2006[22]	USA	1996-2006	F; 47-63 y	25.8	validated SFFQ	self-reported questionnaire	1603 T2D (37183)	340 VS. 307 (0.80 (0.67-0.95))
Pereira 2006[23]	USA	1986-1997	F; 56-66 y	26.7	validated FFQ	self-reported questionnaire	1418 T2D (28812)	334 VS. 281 (0.78(0.61-1.01))
Pittas 2006[24]	USA	1980-2000	F; 30-55 y	24.1	validated SFFQ	self-reported questionnaire	4843 T2D (83779)	352 VS. 258 (0.74 (0.67-0.82))
Van 2006[25]	multiple	1995-2003	F; 21-69 y	27.6	validated FFQ	self-reported questionnaire	1964 T2D (41186)	244 VS. 115 (0.65 (0.54-0.78))
Schulze2007[26]	multiple	1994-2005	M/F; 35-65 y	26.1	validated SFFQ	self-reported questionnaire	844 T2D (25067)	377 VS. 268 (0.99 (0.78-1.26))
Larsson 2008[27]	Sweden	1985-2004	M; 50-69 y	26.4	validated FFQ	follow-up examination	3370 stroke (26556)	575 VS. 382 (0.91 (0.77-1.07))
Weng 2008[28]	Taipei	1989-2002	M/F; ≥40 y	24.5	validated FFQ	Self-reported and cross-checked questionnaire	132 ischemic stroke (1772)	423 VS. 162 (0.69 (0.45-1.06))
Kirii 2009[29]	Japan	1993-1998	M; 40-69 y F; 40-69 y	23.6 23.5	FFQ	self-reported questionnaire	634 T2D (25876) 480 T2D (33919)	331 VS. 245 (0.93 (0.71-1.22)) 314 VS. 248 (0.76 (0.56-1.03))
Ohira 2009[30]	USA	1987-2004	M/F; 45-64 y	27.4	validated FFQ	follow-up examination	577 ischemic stroke (14221)	362 VS. 152 (0.80 (0.75-1.13))
Villegas 2009[31]	China	2000-2006	F; 40-70 y	23.8	validated FFQ	follow-up examination	2273 T2D (64191)	318 VS. 214 (0.80 (0.68-0.93))
Hopping 2010[32]	multiple	1993-2007	M; 45-75 y F; 45-75 y	NA	validated FFQ	self-reported questionnaire	4555 T2D (36256) 4032 T2D (39256)	278 VS. 86 (0.77 (0.70-0.85)) 300 VS. 93 (0.84 (0.76-0.93))
Kim 2010[33]	USA	1985-2005	M/F; 18-30 y	24.5	validated DHQ	self-reported questionnaire	330 T2D (4497)	302 VS. 182 (0.53 (0.32-0.86))

Kirii 2010[34]	Japan	NA	M/F; 40-65 y	22.9	validated FFQ	self-reported questionnaire	459 T2D (17592)	303 VS. 158 (0.64 (0.44-0.94))
Nanri 2010[35]	Japan	1990-1995	M; 40-65 y F; 40-65 y	NA	validated FFQ	self-reported questionnaire	634 T2D (25872) 480 T2D (33919)	348 VS. 213 (0.86 (0.63-1.16)) 333 VS. 213 (0.92 (0.66-1.28))
Larsson 2011[36]	Sweden	1998-2008	F; 49-83 y	25	validated FFQ	follow-up examination	1680 stroke (34670)	373 VS. 297 (1.02 (0.82-1.27))
Weng 2012[37]	Taipei	1993-2002	M/F; ≥30 y	24	validated FFQ	follow-up examination or self-reported questionnaire	141 T2D (1604)	406 VS. 212 (0.44 (0.25-0.75))
Zhang 2012[38]	Japan	1988-2006/	M; 40-79 y F; 40-79 y	22.7 22.9	validated FFQ	follow-up examination	634 stroke (23083) 620 stroke (35533)	294 VS. 173 (1.03 (0.79-1.35)) 274 VS. 175 (0.90 (0.69-1.16))
Hata 2013[39]	Japan	1988-2009	M/F; 40-79 y	22.9	validated SFFQ	self-reported questionnaire	417 T2D (1999)	215 VS. 133 (0.63 (0.44-0.90))
Lin 2013[40]	Taipei	1989-2002	M/F; ≥ 18 y	23.3	validated FFQ	follow-up examination and self-reported questionnaire	123 stroke (2061)	378 VS. 210 (0.62 (0.40-0.97))
Oba 2013[41]	Japan	1990-2000	M; 40-69 y F; 40-69 y	23.6 23.5	validated FFQ	self-reported questionnaire	690 T2D (27769) 500 T2D (36864)	349 VS. 232 (0.84 (0.69-1.05)) 356 VS. 211 (0.69 (0.54-0.88))
Sluijs 2013[42]	Netherland	NA	M/F; 21-70 y	NA	FFQ	NA	361 ischemic stroke (36359)	435 VS. 253 (0.76 (0.57-1.01))
Hruby 2014[43]	USA	1995-2001	M/F; 26-81 y	27	validated FFQ	self-reported questionnaire	179 T2D (2582)	395 VS. 235 (0.49 (0.27-0.88))
Sluijs 2014[44]	Netherland	NA	M/F; 21-70 y	NA	FFQ	follow-up examination	631 stroke (36094)	597 VS. 190 (0.64 (0.44-0.94))
Adebamowo 2015[45]	USA	1986-2010	M; 40-75 y	25.4	validated FFQ	self-reported questionnaire	1547 stroke (42669)	467 VS. 267 (0.89 (0.71-1.11))
Adebamowo 2015(2)[46]	USA	1976-2006 1989-2011	F; 30-55 y F; 25-42 y	26.4 25.7	validated FFQ	self-reported questionnaire	3237 stroke (86149) 543 stroke (94715)	411 VS. 233 (0.93 (0.79-1.08))
Bain 2015[47]	Britain	2002-2008	M; 40-75 y F; 40-75 y	26.5 26.2	7-day diary recall	follow-up examination	364 stroke (2000) 511 stroke (2445)	456 VS. 266 (0.81 (0.53-1.22)) 374 VS. 456 (0.82 (0.54-1.24))
Huang 2015[48]	Taipei	2000-2008	M/F; ≥65 y	NA	24 h dietary recall and SFFQ	follow-up examination	231 T2D (1400)	398 VS. 103 (0.59 (0.26-1.33))
Hruby 2017[49]	USA	1984-2012 1991-2013 1986-2012	F; 30-55 y F; 25-42 y M; mean 53.5 y	24.8 24.6 24.8	validated SFFQ	self-reported questionnaire	7620 T2D (69176) 6080 T2D (91471) 3430 T2D (42096)	390 VS. 229 (0.80 (0.73-0.88)) 424 VS. 249 (0.89 (0.81-0.99)) 469 VS. 280 (0.88 (0.77-1.00))
Kokubo 2017[50b]	Japan	1990-2009 1993-2010	M; 40-69 y F; 40-69 y	23.6 23.6	FFQ	follow-up examination	2576 stroke (39505) 1846 stroke (45788)	348 VS. 213 (1.07 (0.86-1.33)) 333 VS. 213 (0.88 (0.67-1.14))
Konishi 2017[51]	Japan	1992-2002	M; ≥35 y F; ≥35 y	22.6 22.1	validated FFQ	self-reported questionnaire	266 T2D (5885) 172 T2D (7640)	469 VS. 310 (1.13 (0.76-1.70)) 432 VS. 285 (0.50 (0.30-0.84))

Abbreviations: FFQ, food-frequency questionnaire; SFFQ, semi-quantitative food-frequency questionnaire; BMI, body mass index; T2D, type 2 diabetes; NA, not available.

[a], different ethnicities of participants are in multiple nations cohort;

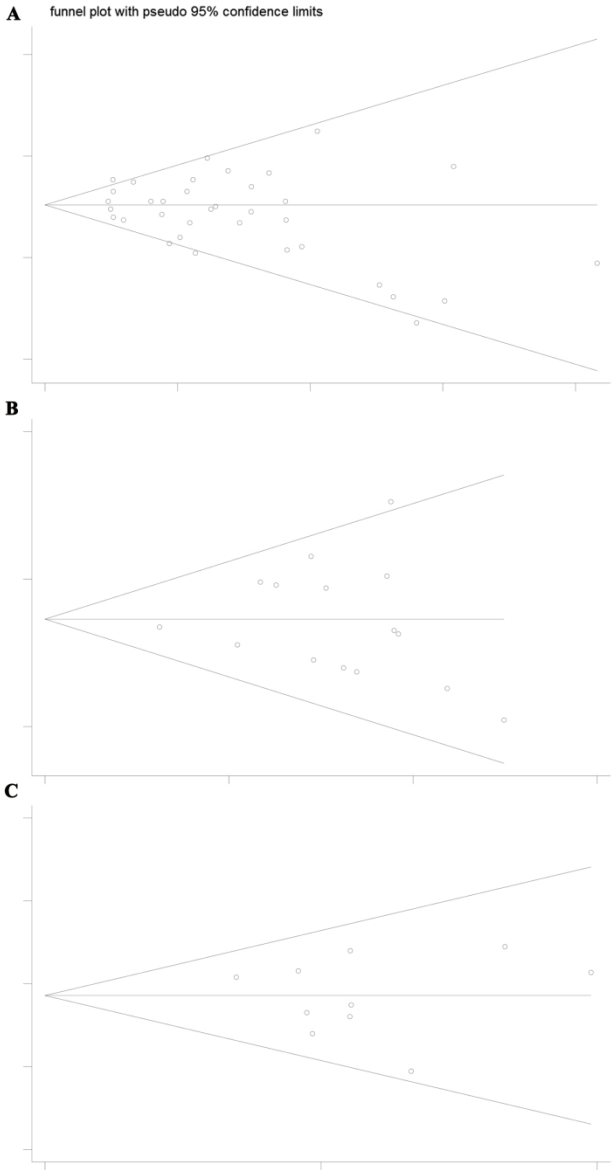
[b], the dose of magnesium intake which is not available in this study is retrieved from the same cohort reported in former publication;

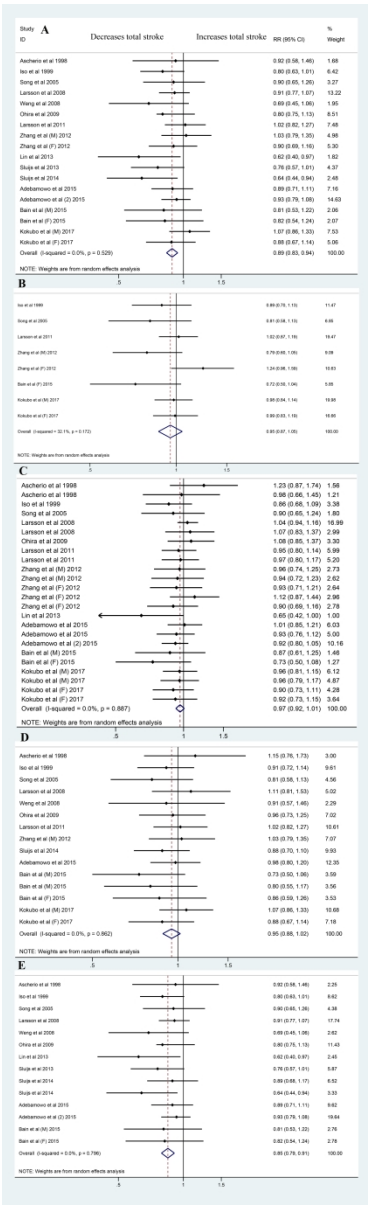
[c] the range of enrolled participants age is not mentioned.

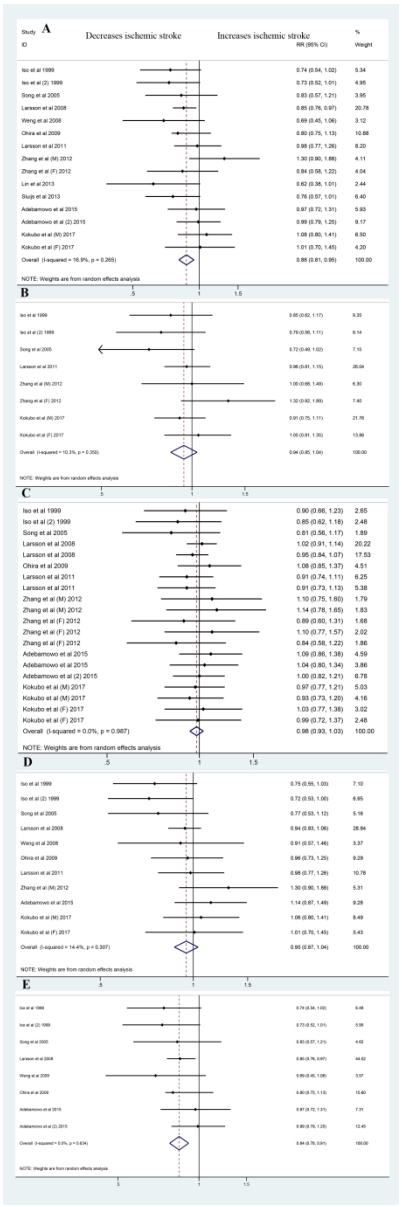
Table S5. Methodological Quality Assessments of the Included Studies with Newcastle-Ottawa Scales

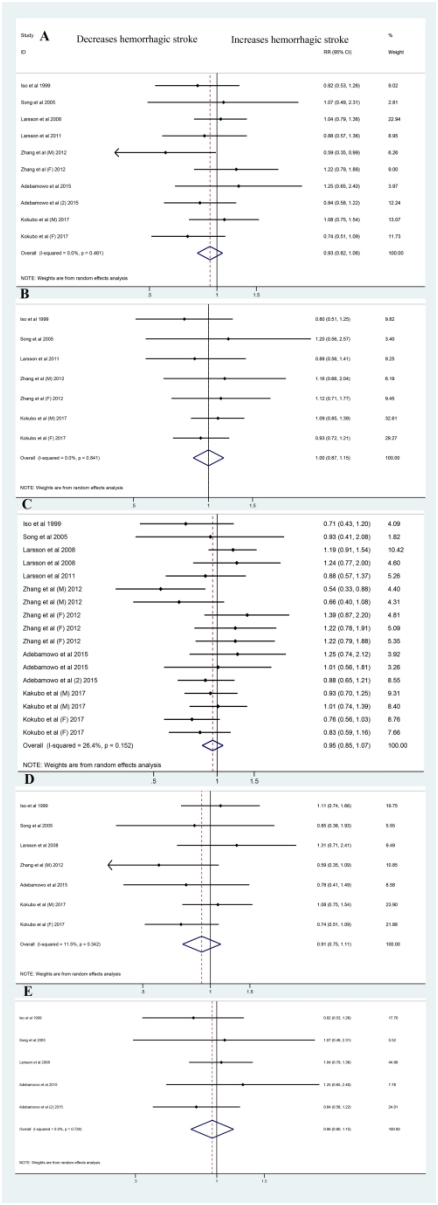
Study		Selection				Comparability	Outcome			Total score
		Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
1997	Salmeron et al,[11]	*	*	*	*	**	*	*		9
1997	Salmeron et al (2),[12]	*	*	*	*	**	*	*	*	9
1998	Ascherio et al,[13]	*	*	*	*	**	*	*	*	9
1999	Iso et al,[14]	*	*	*	*	**	*	*	*	9
1999	Kao et al,[15]	*	*	*	*	**	*	*	*	9
2000	Liu et al,[16]	*	*	*	*	**	*	*	*	9
2000	Meyer et al,[17]	*	*	*	*	**	*	*	*	9
2004	Hodge et al,[18]	*	*	*	*	*	*	*		7
2004	Lopez et al,[19]	*	*	*	*	**	*	*	*	9
2004	Song et al,[20]	*	*	*	*	**	*	*	*	9
2005	Song et al,[21]	*	*	*	*	**	*	*	*	9
2006	Liu et al,[22]	*	*	*	*	**	*	*	*	9
2006	Pereira et al,[23]	*	*	*	*	**	*	*	*	9
2006	Pittas et al,[24]	*	*	*	*	**	*	*	*	9
2006	Van et al,[25]	*	*	*	*	**	*	*	*	9
2007	Schulze et al,[26]	*	*	*	*	**	*	*	*	9
2008	Larsson et al,[27]	*	*	*	*	**	*	*	*	9
2008	Weng et al,[28]	*	*	*	*	**	*	*	*	9
2009	Kirii et al,[29]	*	*	*	*	**	*	*	*	9
2009	Ohira et al,[30]	*	*	*	*	**	*	*	*	9
2009	Villegas et al,[31]	*	*	*	*	**	*	*	*	9
2010	Hopping et al,[32]	*	*	*	*	**	*	*	*	9
2010	Kim et al,[33]	*	*	*		**	*	*	*	8
2010	Kirii et al,[34]	*	*	*	*	**	*	*	*	9
2010	Nanri et al,[35]	*	*	*	*	**	*	*	*	9
2011	Larsson et al,[36]	*	*	*	*	**	*	*	*	9
2012	Weng et al,[37]	*	*	*	*	**	*	*		8

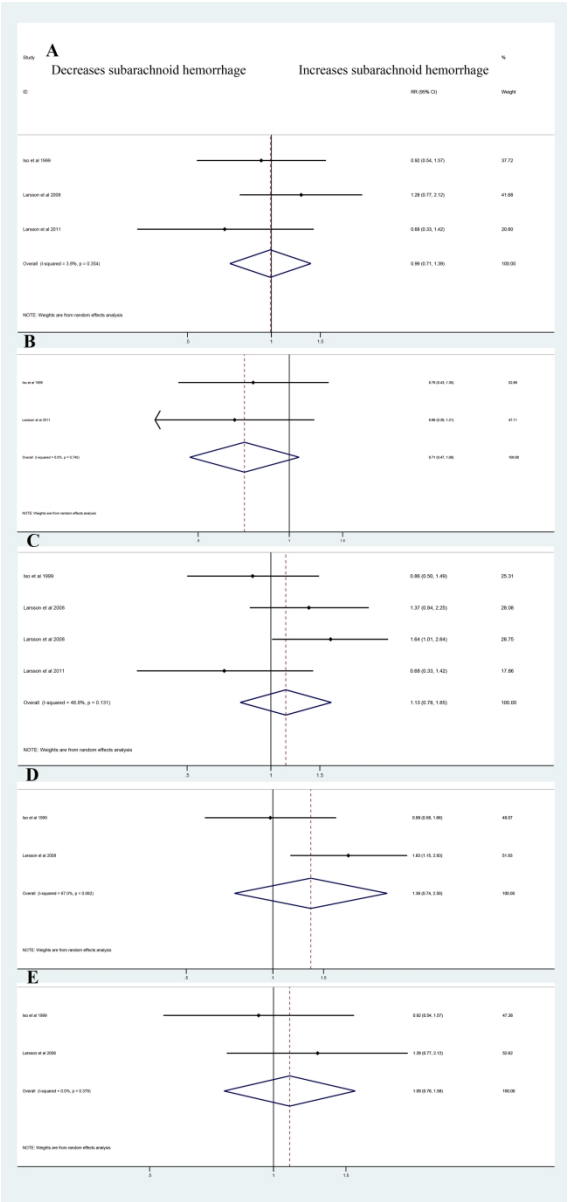
2012	Zhang et al,[38]	*	*	*	*	**	*	*	*	9
2013	Hata et al,[39]	*	*	*	*	**	*	*	*	9
2013	Lin et al,[40]	*	*	*	*	**	*	*	*	9
2013	Oba et al,[41]	*	*	*	*	**	*	*	*	9
2013	Sluijs et al,[42]	*	*	*	*	**		*	*	8
2014	Hruby et al,[43]	*	*	*	*	**	*	*	*	9
2014	Sluijs et al,[44]	*	*	*	*	**	*	*	*	9
2015	Adebamowo et al,[45]	*	*	*	*	**	*	*	*	9
2015	Adebamowo et al (2),[46]	*	*	*	*	**	*	*	*	9
2015	Bain et al,[47]	*	*	*	*	**	*	*	*	9
2015	Huang et al,[48]	*	*	*		**	*	*	*	8
2017	Hruby et al,[49]	*	*	*	*	**	*	*	*	9
2017	Kokubo et al,[50]	*	*	*	*	**	*	*	*	9
2017	Konishi et al,[51]	*	*	*	*	*	*	*	*	9

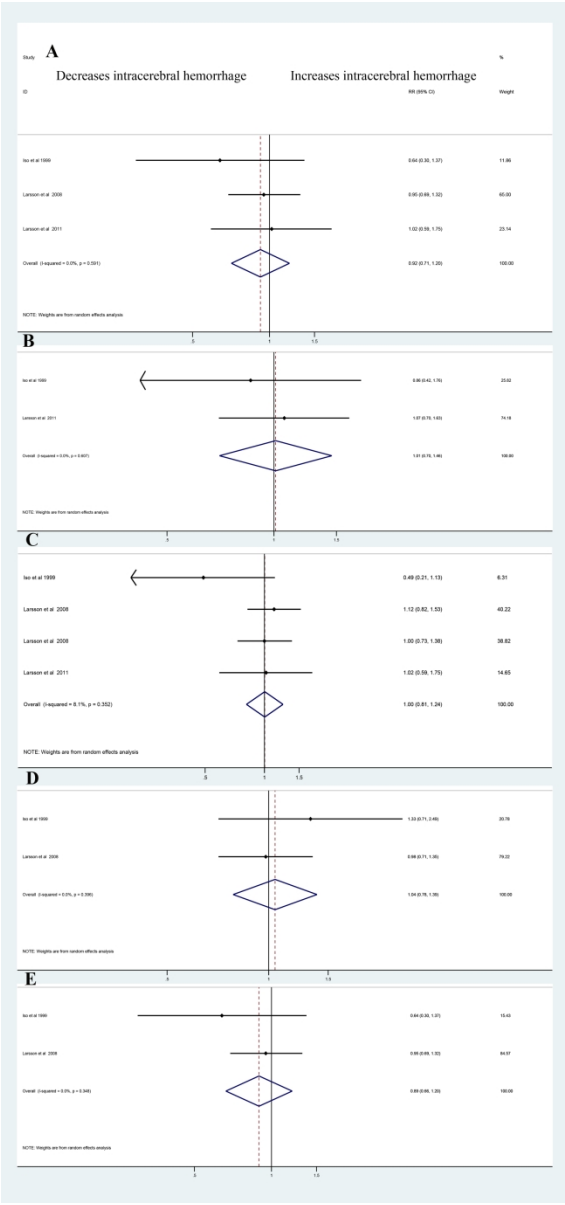

A
funnel plot with pseudo 95% confidence limits
B
C


A
Decreases total stroke
Increases total stroke
B
C
D
E

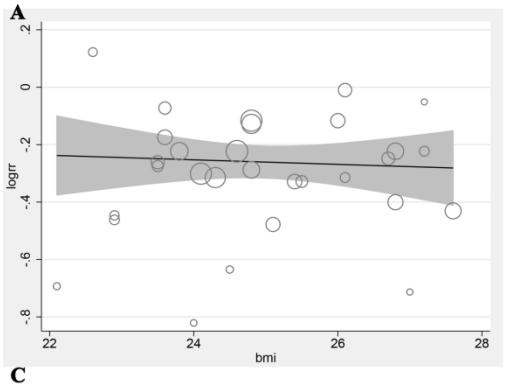

A
Decreases ischemic stroke
Increases ischemic stroke
B
C
D
E


A
Decreases hemorrhagic stroke
Increases hemorrhagic stroke
B
C
D
E


A
Decreases subarachnoid hemorrhage
Increases subarachnoid hemorrhage
B
C
D
E


A
Decreases intracerebral hemorrhage
Increases intracerebral hemorrhage
B
C
D
E

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	10	28.57	28.57
female	17	48.57	77.14
male	8	22.86	100.00
Total	35	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      35
REML estimate of between-study variance         tau2           = .004692
% residual variation due to heterogeneity       I-squared_res  =  36.58%
Proportion of between-study variance explained  Adj R-squared  = -26.08%
Joint test for all covariates                   Model F(2,32)  =    1.31
With Knapp-Hartung modification                 Prob > F       =  0.2841
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.1314075	.0857784	-1.53	0.135	-.3061323	.0433174
sexnew2	-.0630804	.0541113	-1.17	0.252	-.1733016	.0471407
_cons	-.1956565	.0461514	-4.24	0.000	-.2896637	-.1016492

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	13	37.14	37.14
Multiple nations	5	14.29	51.43
North America	17	48.57	100.00
Total	35	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      35
REML estimate of between-study variance         tau2           = .004868
% residual variation due to heterogeneity       I-squared_res  =  39.22%
Proportion of between-study variance explained  Adj R-squared  = -30.89%
Joint test for all covariates                   Model F(2,32)  =    0.10
With Knapp-Hartung modification                 Prob > F       =  0.9047
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew2	.0027567	.0731865	0.04	0.970	-.1463193	.1518327
participantsregionnew3	-.0201457	.0599158	-0.34	0.739	-.1422102	.1018788
_cons	-.2392399	.0510872	-4.68	0.000	-.3433012	-.1351786

D

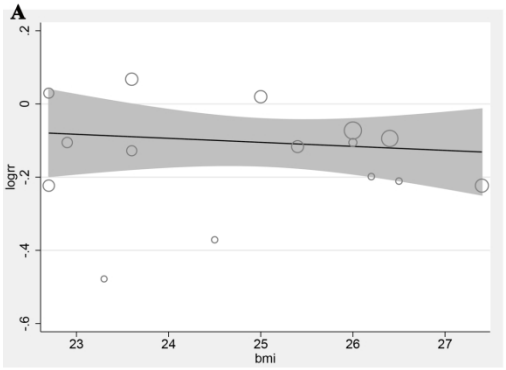
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

dietaryassessment	Freq.	Percent	Cum.
24h dietary recall and SFFQ	1	2.86	2.86
FFQ	4	11.43	14.29
SFFQ	1	2.86	17.14
validated DHQ	1	2.86	20.00
validated FFQ	17	48.57	68.57
validated SFFQ	11	31.43	100.00
Total	35	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4 dietaryassessmentnew5 dietary
> assessmentnew6, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew4 dropped because of collinearity

Meta-regression                                 Number of obs  =      35
REML estimate of between-study variance         tau2           = .004258
% residual variation due to heterogeneity       I-squared_res  =  38.44%
Proportion of between-study variance explained  Adj R-squared  = -14.42%
Joint test for all covariates                   Model F(5,29)  =    0.86
With Knapp-Hartung modification                 Prob > F       =  0.5210
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew1	.1072455	.5318922	0.20	0.841	-.97894	1.193431
dietaryassessmentnew2	.4672073	.294548	1.58	0.124	-.1393423	1.073757
dietaryassessmentnew3	.5183445	.311752	1.66	0.107	-.1192599	1.155949
dietaryassessmentnew5	.3650754	.2813784	1.30	0.205	-.2104981	.9405589
dietaryassessmentnew6	.3944872	.2812621	1.40	0.171	-.1807583	.9697328
_cons	-.6348783	.279223	-2.27	0.031	-1.205958	-.0637991

A



B

```
. tabulate sex, generate (sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	3	20.00	20.00
female	7	46.67	66.67
male	5	33.33	100.00
Total	15	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   0.00%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    2.64
With Knapp-Hartung modification                 Prob > F       =  0.1120
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew2	.1870375	.0983982	1.90	0.082	-.0273537	.4014286
sexnew3	.2312472	.1011998	2.29	0.041	.0107518	.4517427
_cons	-.2844281	.0870478	-3.27	0.007	-.4740889	-.0947673

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	6	33.33	33.33
Europe	6	33.33	66.67
North America	6	33.33	100.00
Total	18	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml random
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      18
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   1.81%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,15)  =    0.32
With Knapp-Hartung modification                 Prob > F       =  0.7332
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	.0566278	.0763754	0.74	0.470	-.1061625	.2194181
participantsregionnew2	.0028959	.0725841	0.04	0.969	-.1518136	.1576053
_cons	-.1370955	.0474962	-2.87	0.012	-.2387575	-.0354336

D

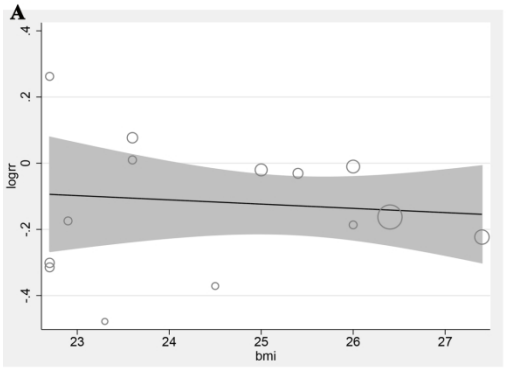
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

dietaryassessment	Freq.	Percent	Cum.
7-day diary recall	2	11.11	11.11
FFQ	6	33.33	44.44
validated FFQ	9	50.00	94.44
validated SFFQ	1	5.56	100.00
Total	18	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4, wsse (selogrr) knapphartung
> reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      18
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   8.20%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(3,14)  =    0.21
With Knapp-Hartung modification                 Prob > F       =  0.8911
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0596066	.167476	0.36	0.727	-.2995937	.418807
dietaryassessmentnew3	.0984932	.1614344	0.61	0.552	-.2481701	.4651645
dietaryassessmentnew4	.1211665	.291519	0.42	0.684	-.5044595	.7464325
_cons	-.2045601	.1567379	-1.31	0.213	-.5407374	.1316013

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
both male and female	4	26.67	26.67
female	7	46.67	73.33
male	4	26.67	100.00
Total	15	100.00	

```
. metareg logrr  sexnew1 sexnew2 sexnew3, wsse (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .004782
% residual variation due to heterogeneity       I-squared_res  =   1.79%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    2.39
With Knapp-Hartung modification                 Prob > F       =  0.1339
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.2383161	.109578	-2.17	0.050	-.4770662	.0004339
sexnew2	-.0739192	.0940187	-0.79	0.447	-.2787683	.1309299
_cons	-.048002	.0681983	-0.70	0.495	-.1965933	.1005894

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	6	40.00	40.00
Europe	3	20.00	60.00
North America	6	40.00	100.00
Total	15	100.00	

```
. metareg logrr  participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .00114
% residual variation due to heterogeneity       I-squared_res  =  21.76%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,12)  =    0.56
With Knapp-Hartung modification                 Prob > F       =  0.5842
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	.1089103	.1083661	1.01	0.335	-.1271992	.3450197
participantsregionnew2	.0117202	.0911749	0.13	0.900	-.1869328	.2103732
_cons	-.1629514	.0653255	-2.49	0.028	-.3052835	-.0206192

D

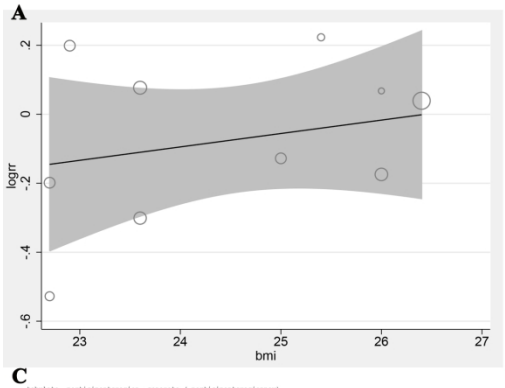
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

dietaryassessment	Freq.	Percent	Cum.
FFQ	6	40.00	40.00
validated FFQ	9	60.00	100.00
Total	15	100.00	

```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      15
REML estimate of between-study variance         tau2           = .001922
% residual variation due to heterogeneity       I-squared_res  =  21.79%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0410573	.0897444	0.46	0.655	-.1528236	.2349382
_cons	-.162938	.0753946	-2.16	0.050	-.3258182	-.0000578

A



B

```
. tabulate  sex, generate ( sexnew)
```

sex	Freq.	Percent	Cum.
female	6	60.00	60.00
male	4	40.00	100.00
Total	10	100.00	

```
. metareg logrr  sexnew1 sexnew2, wsse (selogrr) knapphartung reml
note: sexnew2 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           =       0
% residual variation due to heterogeneity       I-squared_res  =   0.42%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
sexnew1	-.1120692	.1333867	-0.84	0.425	-.4196595	.1955211
_cons	-.0110753	.0978042	-0.11	0.913	-.2366123	.2144617

C

```
. tabulate  participantsregion, generate ( participantsregionnew)
```

participantsregion	Freq.	Percent	Cum.
Asia	4	40.00	40.00
Europe	2	20.00	60.00
North America	4	40.00	100.00
Total	10	100.00	

```
. metareg logrr participantsregionnew1 participantsregionnew2 participantsregionnew3, wsse (selogrr) knapphartung reml
note: participantsregionnew3 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           = .008835
% residual variation due to heterogeneity       I-squared_res  =  15.78%
Proportion of between-study variance explained  Adj R-squared  =      .%
Joint test for all covariates                   Model F(2,7)   =    0.14
With Knapp-Hartung modification                 Prob > F       =  0.8726
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
participantsregionnew1	-.0106555	.1797495	-0.06	0.954	-.4356955	.4143845
participantsregionnew2	.0796745	.1944402	0.41	0.694	-.3801034	.5394524
_cons	-.0943118	.1371063	-0.69	0.514	-.4185166	.229893

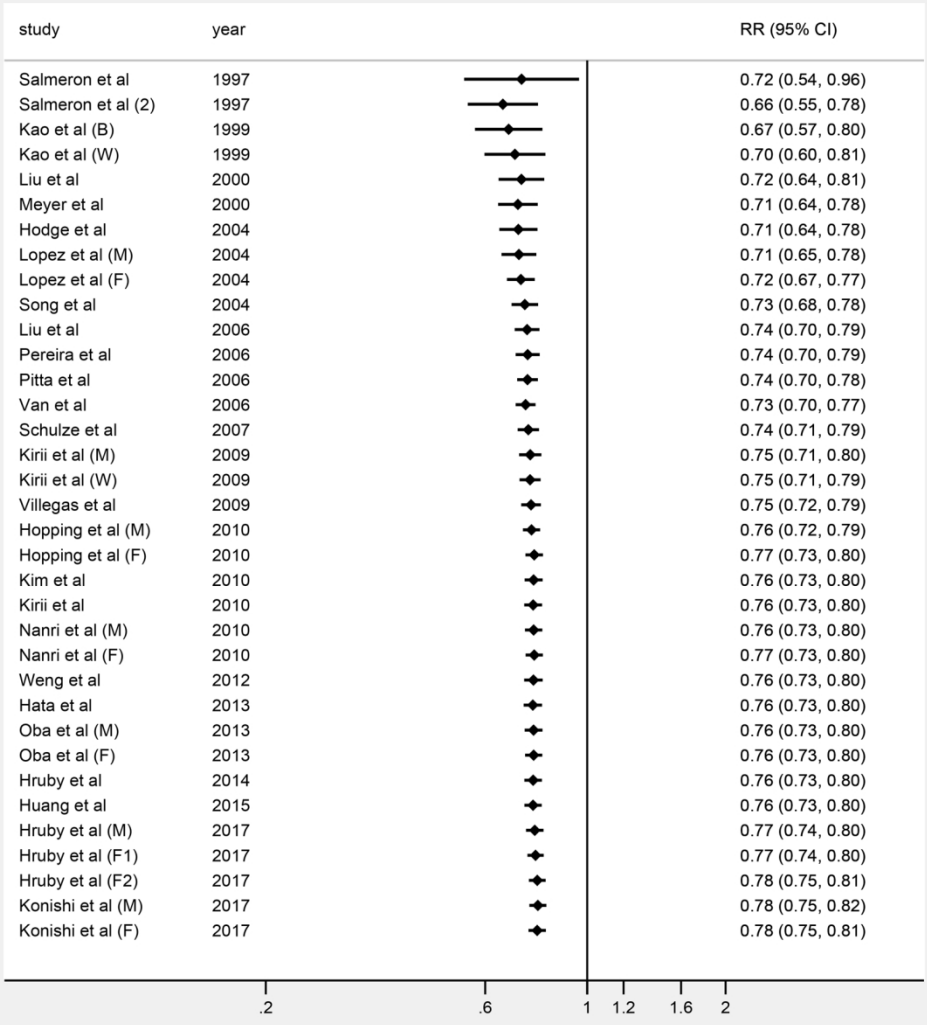
D

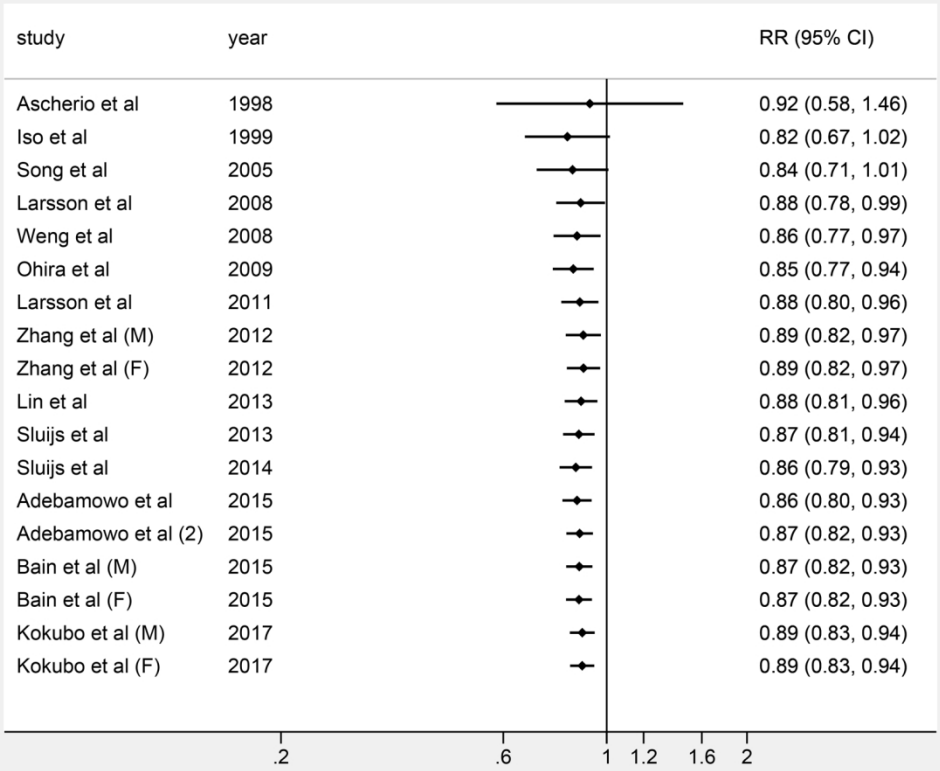
```
. tabulate  dietaryassessment, generate ( dietaryassessmentnew)
```

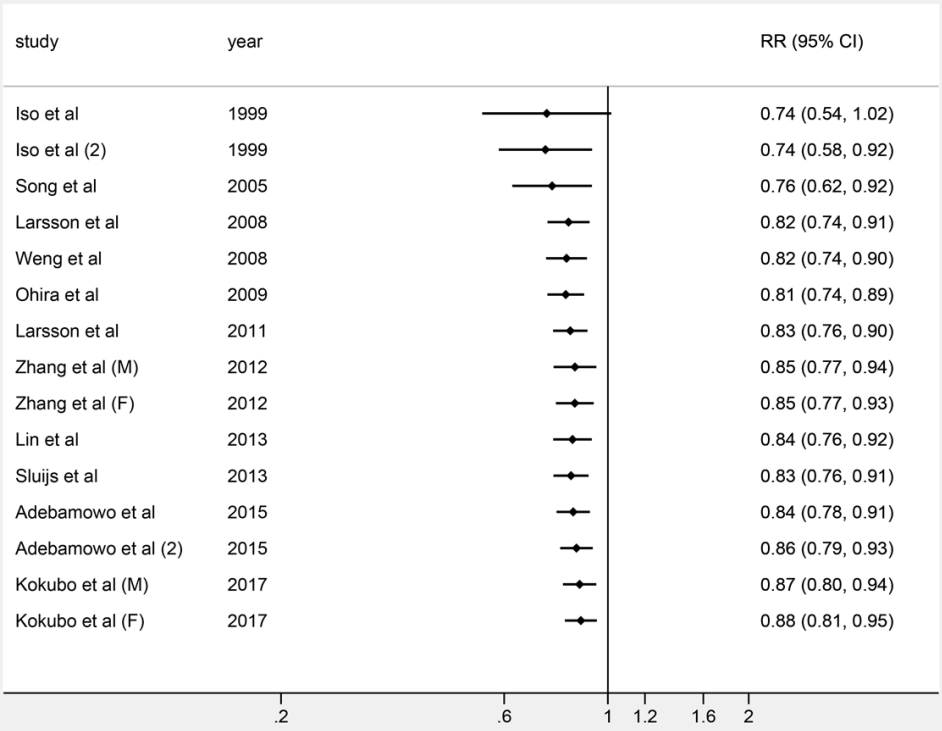
dietaryassessment	Freq.	Percent	Cum.
FFQ	4	40.00	40.00
validated FFQ	6	60.00	100.00
Total	10	100.00	

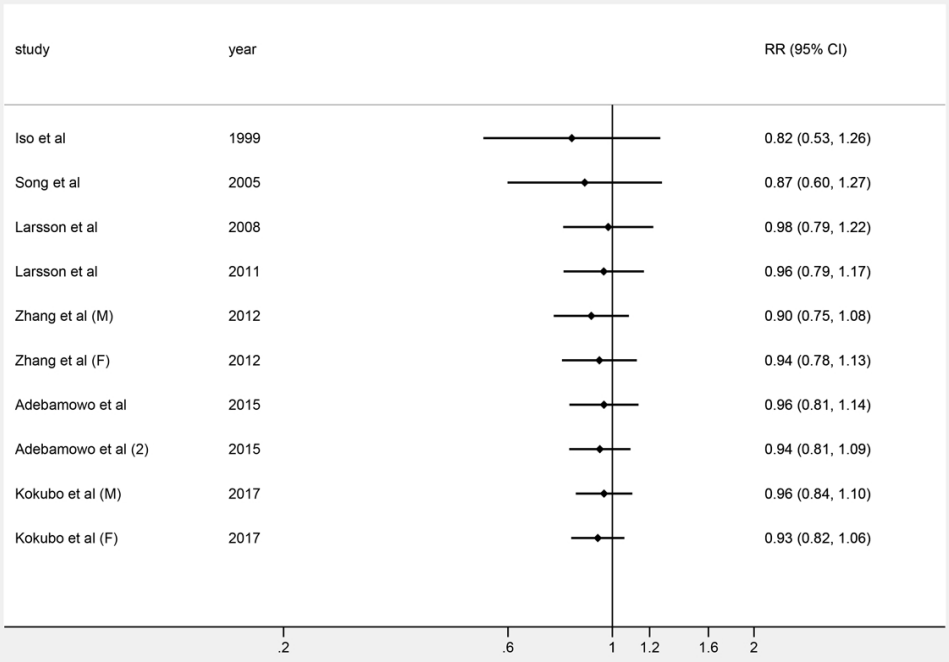
```
. metareg logrr  dietaryassessmentnew1 dietaryassessmentnew2, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew1 dropped because of collinearity

Meta-regression                                 Number of obs  =      10
REML estimate of between-study variance         tau2           = .001097
% residual variation due to heterogeneity       I-squared_res  =   6.09%
Proportion of between-study variance explained  Adj R-squared  =      .%
With Knapp-Hartung modification
```

logrr	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
dietaryassessmentnew2	.0642559	.1426454	0.45	0.664	-.2646851	.3931968
_cons	-.112665	.1133825	-0.99	0.349	-.3741255	.1487955


study
year
RR (95% CI)
Salmeron et al 1997 0.72 (0.54, 0.96)
Salmeron et al (2) 1997 0.66 (0.55, 0.78)
Kao et al (B) 1999 0.67 (0.57, 0.80)
Kao et al (W) 1999 0.70 (0.60, 0.81)
Liu et al 2000 0.72 (0.64, 0.81)
Meyer et al 2000 0.71 (0.64, 0.78)
Hodge et al 2004 0.71 (0.64, 0.78)
Lopez et al (M) 2004 0.71 (0.65, 0.78)
Lopez et al (F) 2004 0.72 (0.67, 0.77)
Song et al 2004 0.73 (0.68, 0.78)
Liu et al 2006 0.74 (0.70, 0.79)
Pereira et al 2006 0.74 (0.70, 0.79)
Pitta et al 2006 0.74 (0.70, 0.78)
Van et al 2006 0.73 (0.70, 0.77)
Schulze et al 2007 0.74 (0.71, 0.79)
Kirii et al (M) 2009 0.75 (0.71, 0.80)
Kirii et al (W) 2009 0.75 (0.71, 0.79)
Villegas et al 2009 0.75 (0.72, 0.79)
Hopping et al (M) 2010 0.76 (0.72, 0.79)
Hopping et al (F) 2010 0.77 (0.73, 0.80)
Kim et al 2010 0.76 (0.73, 0.80)
Kirii et al 2010 0.76 (0.73, 0.80)
Nanri et al (M) 2010 0.76 (0.73, 0.80)
Nanri et al (F) 2010 0.77 (0.73, 0.80)
Weng et al 2012 0.76 (0.73, 0.80)
Hata et al 2013 0.76 (0.73, 0.80)
Oba et al (M) 2013 0.76 (0.73, 0.80)
Oba et al (F) 2013 0.76 (0.73, 0.80)
Hruby et al 2014 0.76 (0.73, 0.80)
Huang et al 2015 0.76 (0.73, 0.80)
Hruby et al (M) 2017 0.77 (0.74, 0.80)
Hruby et al (F1) 2017 0.77 (0.74, 0.80)
Hruby et al (F2) 2017 0.78 (0.75, 0.81)
Konishi et al (M) 2017 0.78 (0.75, 0.82)
Konishi et al (F) 2017 0.78 (0.75, 0.81)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Ascherio et al 1998 0.92 (0.58, 1.46)
Iso et al 1999 0.82 (0.67, 1.02)
Song et al 2005 0.84 (0.71, 1.01)
Larsson et al 2008 0.88 (0.78, 0.99)
Weng et al 2008 0.86 (0.77, 0.97)
Ohira et al 2009 0.85 (0.77, 0.94)
Larsson et al 2011 0.88 (0.80, 0.96)
Zhang et al (M) 2012 0.89 (0.82, 0.97)
Zhang et al (F) 2012 0.89 (0.82, 0.97)
Lin et al 2013 0.88 (0.81, 0.96)
Sluijs et al 2013 0.87 (0.81, 0.94)
Sluijs et al 2014 0.86 (0.79, 0.93)
Adebamowo et al 2015 0.86 (0.80, 0.93)
Adebamowo et al (2) 2015 0.87 (0.82, 0.93)
Bain et al (M) 2015 0.87 (0.82, 0.93)
Bain et al (F) 2015 0.87 (0.82, 0.93)
Kokubo et al (M) 2017 0.89 (0.83, 0.94)
Kokubo et al (F) 2017 0.89 (0.83, 0.94)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Iso et al 1999 0.74 (0.54, 1.02)
Iso et al (2) 1999 0.74 (0.58, 0.92)
Song et al 2005 0.76 (0.62, 0.92)
Larsson et al 2008 0.82 (0.74, 0.91)
Weng et al 2008 0.82 (0.74, 0.90)
Ohira et al 2009 0.81 (0.74, 0.89)
Larsson et al 2011 0.83 (0.76, 0.90)
Zhang et al (M) 2012 0.85 (0.77, 0.94)
Zhang et al (F) 2012 0.85 (0.77, 0.93)
Lin et al 2013 0.84 (0.76, 0.92)
Sluijs et al 2013 0.83 (0.76, 0.91)
Adebamowo et al 2015 0.84 (0.78, 0.91)
Adebamowo et al (2) 2015 0.86 (0.79, 0.93)
Kokubo et al (M) 2017 0.87 (0.80, 0.94)
Kokubo et al (F) 2017 0.88 (0.81, 0.95)
.2
.6
1
1.2
1.6
2


study
year
RR (95% CI)
Iso et al
1999
0.82 (0.53, 1.26)
Song et al
2005
0.87 (0.60, 1.27)
Larsson et al
2008
0.98 (0.79, 1.22)
Larsson et al
2011
0.96 (0.79, 1.17)
Zhang et al (M)
2012
0.90 (0.75, 1.08)
Zhang et al (F)
2012
0.94 (0.78, 1.13)
Adebamowo et al
2015
0.96 (0.81, 1.14)
Adebamowo et al (2)
2015
0.94 (0.81, 1.09)
Kokubo et al (M)
2017
0.96 (0.84, 1.10)
Kokubo et al (F)
2017
0.93 (0.82, 1.06)
.2
.6
1
1.2
1.6
2

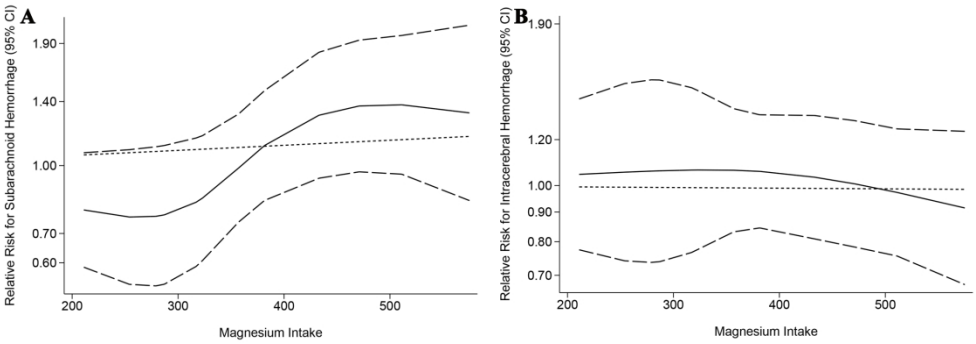

A
Relative Risk for Subarachnoid Hemorrhage (95% CI)
1.90
1.40
1.00
0.70
0.60
200
300
400
500
Magnesium Intake
B
Relative Risk for Intracerebral Hemorrhage (95% CI)
1.90
1.20
1.00
0.90
0.80
0.70
200
300
400
500
Magnesium Intake

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			1
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			2-3
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2-3
INTRODUCTION			4-5
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4-5
METHODS			5-9
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6-8

Table S1 PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8-9
RESULTS			9-16
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-16
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-16
DISCUSSION			16-22
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	16-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21-22
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			23
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	23

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

MOOSE Checklist for Meta-analyses of Observational Studies

Item No	Recommendation	Reported on Page No
Reporting of background should include		
1	Problem definition	4
2	Hypothesis statement	4
3	Description of study outcome(s)	5
4	Type of exposure or intervention used	5
5	Type of study designs used	5
6	Study population	4-5
Reporting of search strategy should include		
7	Qualifications of searchers (eg, librarians and investigators)	6-7
8	Search strategy, including time period included in the synthesis and key words	5-6
9	Effort to include all available studies, including contact with authors	5-6
10	Databases and registries searched	5-6
11	Search software used, name and version, including special features used (eg, explosion)	5-6
12	Use of hand searching (eg, reference lists of obtained articles)	5-6
13	List of citations located and those excluded, including justification	6
14	Method of addressing articles published in languages other than English	6
15	Method of handling abstracts and unpublished studies	6
16	Description of any contact with authors	6
Reporting of methods should include		
17	Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	7-8
18	Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	6-7
19	Documentation of how data were classified and coded (eg, multiple raters, blinding and interrater reliability)	6-7
20	Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	7-9
21	Assessment of study quality, including blinding of quality assessors, stratification or regression on possible predictors of study results	7-9
22	Assessment of heterogeneity	7-9
23	Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or	7-9

	cumulative meta-analysis) in sufficient detail to be replicated	
24	Provision of appropriate tables and graphics	9
Reporting of results should include		
25	Graphic summarizing individual study estimates and overall estimate	10-14
26	Table giving descriptive information for each study included	10-11, Table S4
27	Results of sensitivity testing (eg, subgroup analysis)	14
28	Indication of statistical uncertainty of findings	16

Item No	Recommendation	Reported on Page No
Reporting of discussion should include		
29	Quantitative assessment of bias (eg, publication bias)	11-14
30	Justification for exclusion (eg, exclusion of non-English language citations)	10
31	Assessment of quality of included studies	11, Table S5
Reporting of conclusions should include		
32	Consideration of alternative explanations for observed results	16-22
33	Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	16, 23
34	Guidelines for future research	17-20, 22
35	Disclosure of funding source	None