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

3 Binghao Zhao^{1,2}; Lianli Zeng^{3,4}; Jiani Zhao^{3,4}; Qian Wu^{3,4}; Yifei Dong³; Fang Zou⁵;
4 Li Gan⁶; Yiping Wei¹; Wenxiong Zhang¹.

5 **Affiliations**

6 ¹Department of Cardio-Thoracic Surgery, The first affiliated hospital of Nanchang
7 University, Nanchang, China, 330006.

8 ²Departments of Neurosurgery, Peking Union Medical College Hospital, Chinese
9 Academy of Medical Sciences and Peking Union Medical College, Beijing, China,
10 100000.

11 ³Department of Cardiovascular Medicine, The second affiliated hospital of Nanchang
12 University, Nanchang, China, 330006.

13 ⁴Jiangxi medical college, Nanchang University, 330006, Nanchang, China

14 ⁵Department of Endocrinology, The second affiliated hospital of Nanchang University,
15 Nanchang, China, 330006.

16 ⁶Department of Neurology, The second affiliated hospital of Nanchang University,
17 Nanchang, China, 330006.

18 **Corresponding Author:** Wenxiong Zhang, MD, Department of Cardio-Thoracic
19 Surgery, The first affiliated hospital of Nanchang University, 17 Yongwai Main Street,
20 Nanchang, P. R. China 330006; E-mail: zwx123dr@126.com; Phone:
21 +8618720909414; Fax: 0791-86133161.

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

23 **Word count:** 4350

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4 24 **Abstract**

5
6 25 **Objective:** The detailed associations between type 2 diabetes (T2D) and total stroke
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8
9 26 and magnesium intake should be timely updated. And, we keep requiring evidence of
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11 27 significant prevention of the two diseases. We conducted a systematic review and
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14 28 meta-analysis to quantify the association and to determine the dose-response
15
16
17 29 relationships between magnesium intake and T2D and stroke.

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19 30 **Design:** Systematic review search, methodology and meta-analyses.

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21
22 31 **Data sources:** PubMed, EMBASE, Cochrane Library, Web of Science and
23
24
25 32 ClinicalTrials.gov.

26
27 33 **Eligibility criteria:** Prospective cohort studies about magnesium intake and risk of
28
29
30 34 T2D or stroke.

31
32 35 **Data synthesis:** Relative risk (RR) and 95% confidence intervals (95% CI) were
33
34
35 36 pooled for inclusion in random-effects models to calculate risk on T2D and stroke.

36
37 37 **Results:** Forty-one studies involving 53 cohorts were included. The magnitude of the
38
39 38 risk was significantly reduced by 22% for T2D (RR, 0.78 [95% CI, 0.75-0.81]; $P <$
40
41 39 0.001), 11% for total stroke (RR, 0.89 [95% CI, 0.83-0.94]; $P <$ 0.001), and 12% for
42
43 40 ischemic stroke (RR, 0.88 [95% CI, 0.81-0.95]; $P =$ 0.001) comparing the highest
44
45 41 magnesium intake to the lowest. The inverse association still existed when studies on
46
47 42 T2D were adjusted for cereal fiber (RR, 0.79 [95% CI, 0.73-0.85]; $P <$ 0.001) and
48
49 43 those on total stroke were adjusted for calcium (RR, 0.89 [95% CI, 0.80-0.99]; $P =$
50
51 44 0.040). Subgroup analyses suggested risk for total and ischemic stroke was
52
53 45 significantly decreased in females, participants with ≥ 25 mg/m² body mass index,
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4 46 and those with ≥ 12 y follow-up, the reduced risk in Asia was not so conspicuous as in
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6
7 47 North America and Europe.

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9 48 **Conclusions:** Magnesium intake has significantly inverse associations with T2D and
10
11
12 49 total stroke in a dose-dependent manner. Specific populations may receive more
13
14
15 50 benefits from magnesium-rich dietary pattern. Feasible costless dietary approach
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17
18 51 needs to be highlighted in the primary prevention of T2D and total stroke by the
19
20
21 52 public.

22 53

23 24 25 54 **Strength and limitation**

26
27 55 1. We conducted a quantitative analysis suggesting that magnesium intake has a
28
29 56 strong inverse association with T2D and total stroke.

30
31 57 2. Magnesium-rich food consumption should be recommended for high-risk
32
33 58 individuals in dietary guidelines.

34
35 59 3. Highlighting early management of T2D and stroke requires various efforts and
36
37 60 strategies.

38
39 61 4. This study, which includes a considerable amount of evidence, assists with
40
41 62 innovation of the global dietary pattern.

42
43 63 5. Although strong inverse associations for T2D and total stroke were reported,
44
45 64 individual-level studies having more detection power are required.

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51 66 **Keywords:** Magnesium Intake; Type 2 Diabetes; Stroke; Meta-Analysis.

67 **Introduction**

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

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

79 Actually, many adults in developed countries do not successfully meet the
80 recommended daily consumption of magnesium-rich foods such as whole grains, nuts,
81 and green leafy vegetables, and magnesium is less mentioned in dietary guidelines
82 and in studies about T2D or stroke prevention^{9,10}. With this regard, we chose T2D and
83 stroke as our outcome of interest (cardiovascular disease (CVD) was not elaborated
84 because there are so many items relating to CVD and the definitions about CVD
85 varied a lot among searched studies, which would enhance heterogeneity in the pooled
86 process and impair our interpretation of the final conclusion). And, emerging
87 studies¹¹⁻⁵¹ on this topic are limited, and the results still remain mixed possibly due to
88 the limitations of small sample sizes and differences in intervention duration, study

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4 89 design, characteristics of participants. Moreover, consecutive meta-analyses^{52,53} have
5
6 90 used less rigorous inclusion, the statistics were inadequate, the results were
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9 91 incomprehensive, and they did not completely address the influence of other
10
11 92 confounders (i.e., body mass index (BMI), cereal fiber, calcium, potassium) on the
12
13
14 93 relationship. Accordingly, we performed a meta-analysis to (1) establish a
15
16
17 94 comprehensive estimate and update the epidemiological evidence for clinical practice;
18
19 95 (2) discuss the results of stroke subtype and the impact of several statistical and
20
21 96 epidemiology confounders on the investigated association; and (3) highlight a detailed
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23
24 97 dose-response pattern for the participants in the studies analyzed.
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29

30 **Methods**

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32
33 100 This study was reported according to the Meta-analysis of Observational Studies in
34
35 101 Epidemiology (MOOSE) Guidelines Checklist and the Preferred Reporting Items for
36
37 102 Systematic Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**)
38
39 103 (Registration information: PROSPERO CRD42018092690).
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44

45 105 **Search Strategy**

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48 106 PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were
49
50 107 systematically reviewed through inception to March 15, 2019 for studies about
51
52 108 magnesium intake and T2D or stroke without language restrictions. The following key
53
54 109 words were used: “Magnesium”, “Type 2 Diabetes Mellitus”, “Type 2 Diabetes”,
55
56 110 “Stroke”, “Cerebrovascular Stroke”, “Cohort Studies”, and “Prospective Studies”. We
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4 111 also manually searched the reference lists of the retrieved literature (including
5
6 112 meta-analyses and brief reports), bibliographies and gray literature (including
7
8
9 113 presentations and unpublished literature) for further eligible articles.
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11
12 114

14 115 **Selection Criteria**

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17 116 (1) Eligible populations must be composed of individuals with plausible
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19 117 dietary/energy intake, who had no history of diabetes and/or insulin treatment for T2D
20
21
22 118 analysis and no current stroke for stroke analysis. (2) Their apparent life expectancy
23
24
25 119 was long enough for proper follow-up. (3) We only included prospective cohort
26
27 120 studies that reported magnesium intake and T2D and/or various types of stroke.
28
29
30 121 Notably, magnesium intake contained dietary magnesium intake and total magnesium
31
32 122 intake (dietary and supplementary magnesium).
33
34

35 123 Only studies containing the most comprehensive information on the population
36
37
38 124 or endpoints were included to avoid duplication. We excluded reviews, basic studies,
39
40 125 meta-analyses, etc.
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43 126

45 127 **Data Extraction and Quality Assessments**

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48 128 Two researchers independently extracted the following information: the first author,
49
50
51 129 publication year, period of cohort studies, duration of persistent exposure, basic
52
53 130 characteristics of the enrolled participants (weight, age, region, BMI, drinking and
54
55
56 131 smoking habits (previous plus current), etc.), median magnesium intake for each
57
58
59 132 quantile (tertile, quartile, or quintile), diabetes and total stroke cases, subtypes of total
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4 133 stroke, dietary and case assessments, adjusted confounding covariates. Importantly,
5
6 134 total stroke is classified as clinical ischemic stroke (87%), hemorrhagic stroke (13%)
7
8
9 135 and undetermined stroke⁵⁴. Hemorrhagic stroke is classified as subarachnoid
10
11
12 136 hemorrhage and intracerebral hemorrhage according to anatomical site or presumed
13
14 137 etiology⁵⁵. In cases of continuing disagreement, a final decision was reached after
15
16
17 138 discussion with a third member of the panel.

18
19 139 Methodological quality was described by the Newcastle-Ottawa Scale (NOS),
20
21
22 140 which was validated for assessment of the quality of nonrandomized controlled trials
23
24
25 141 in meta-analyses⁵⁶. As for 0-10 scale, each study was categorized as low (0-5),
26
27 142 medium (6-7), of high (8-10) quality.

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30 143

31 32 144 **Statistical Analysis**

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35 145 Articles providing data separately for men and women or black and white or different
36
37 146 types of disease within an article were treated as independent studies. Multivariate
38
39
40 147 relative risk (RR) and corresponding 95% confidence intervals (CI) for measuring the
41
42
43 148 quantitative associations between exposure and T2D, total stroke and other wanted
44
45
46 149 outcomes, particularly for the highest vs. the lowest categories of magnesium intake
47
48 150 were estimated by DerSimonian-Laird random effects model because the assumptions
49
50
51 151 involved account for the presence of within-study and between-study variability.
52
53 152 Statistical heterogeneity was determined with the Cochran Q chi-square test and the I^2 .
54
55
56 153 An $I^2 > 50\%$ or a P value for the Q test < 0.1 was considered to indicate significant
57
58 154 heterogeneity⁵⁷. We performed sensitivity analyses to test the robustness and
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4 155 post-subgroup analyses to detect source of heterogeneity. In addition, a
5
6 156 random-effects meta-regression analysis on BMI, sex, participants region, and dietary
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9 157 assessments with RR for each trial was performed to obtain an understanding of the
10
11 158 reasons for heterogeneity. RR and 95% CI might begin to significantly change as
12
13
14 159 publication years increased in T2D and total stroke etc., which would be validated by
15
16
17 160 cumulative meta-analyses.

18
19 161 The dose-response analyses for all outcomes were proposed by Greenland and
20
21
22 162 Longnecker⁵⁸ and Orsini⁵⁹ et al. The categories of magnesium intake, distributions of
23
24
25 163 cases and person-year, RR and 95 CI were extracted. Once the number of cases and/or
26
27
28 164 person-years was not available, variance-weighted least squares regression was used
29
30
31 165 to pool the risk estimate. For most studies, the median intake for each quantile (tertile,
32
33 166 quartile or quintile) of magnesium intake was assigned as the representative dose. For
34
35
36 167 continuous intake reported as category data with a range in some studies, we assigned
37
38 168 the mid-point category of the lower and upper bound to the RR in these studies; when
39
40
41 169 the highest category was open ended, we assumed the length of the open ended
42
43 170 interval to be 1.5 times as the adjacent interval; when the lowest category was open,
44
45
46 171 we assigned the adjacent interval of the category to be 1.5 times as the length of the
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48
49 172 open ended interval. We determined generalized least squares regression models to
50
51 173 calculate study-specific RR estimates per 50 mg/day, 100 mg/day, and 150 mg/day of
52
53
54 174 magnesium intake increment if there was evidence for linear relationships. In addition,
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57 175 the non-linear relationships between magnesium intake and all outcomes were
58
59 176 evaluated using restricted cubic splines with four knots located at the 5th, 35th, 65th,
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4 177 and 95th percentiles of the distribution. The P value for curve linearity or non-linearity
5
6 178 was calculated by testing the null hypothesis that the coefficient of the second spline
7
8
9 179 is equal to zero. All results were presented using two-stage dose-response model plots
10
11 180 (including linear and nonlinear relationships).Some results were demonstrated in
12
13
14 181 forest plots for < 50 mg/day, ≥ 50 and < 100 mg/day, ≥ 100 and < 150 mg/day, ≥ 150
15
16
17 182 mg/day increments.

18
19 183 Publication bias was assessed graphically by Begg's adjusted rank correlation
20
21
22 184 funnel plots⁶⁰ and Egger's linear regression tests⁶¹. All analyses were performed using
23
24
25 185 Stata version 14.0 (StataCorp, College Station, TX, USA); two-sided $P < 0.05$ was
26
27 186 considered statistically significant except where otherwise specified.

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31 32 188 **Patient and Public Involvement:**

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35 189 We did not involve patients or the public in this research at any stage.
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39 40 191 **Results**

41 42 192 **Study Characteristics and Quality Assessment**

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44
45 193 Of the total 8713 studies, 107 studies were considered for eligibility after screening of
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47
48 194 titles and abstracts (**Figure 1**). And a total of 41¹¹⁻⁵¹ prospective cohort studies
49
50
51 195 involving 53 cohorts, 1 912 634 participants and 76 678 cases were eligible for
52
53
54 196 current systematic review and meta-analysis (**Table S2**). Hodge et al¹⁸ only recorded
55
56 197 500 mg/day increment of magnesium for further pooled analyses; 2 studies^{33,51} failed
57
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59 198 to clearly distinguish the diabetes type, but the great majority of cases had T2D. We
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4 199 computed the subtype data in three studies^{14,27,36} after the extraction of total stroke,
5
6 200 and we considered ischemic stroke in three other studies^{28,30,42} as total stroke given
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8
9 201 ischemic stroke accounting for nearly 87% of total stroke. Participants were
10
11 202 predominately middle-age at baseline, with mean magnesium intake for the highest
12
13
14 203 category of 370 mg/day, mean for the lowest category of 232 mg/day. The mean
15
16
17 204 duration of all eligible studies was 10.7 years. Nineteen studies were conducted in
18
19 205 North America (America); 5 studies were in Europe (Sweden, the Netherlands and
20
21 206 Britain); 13 studies in Asia (China and Japan and Taipei); 4 studies enrolled
22
23
24 207 individuals in multiple nations. Most of the studies included used food frequency
25
26
27 208 questionnaires (FFQs) or semi-quantitative FFQs (SFFQs) to assess individual dietary
28
29
30 209 intake. Eighteen studies used dietary magnesium intake, and 21 studies recorded total
31
32 210 magnesium intake (dietary and supplementary magnesium intake). Of note,
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34
35 211 supplementary magnesium intake was assessed from the use of magnesium or
36
37
38 212 multivitamin supplements; nevertheless, dietary magnesium accounted for the
39
40
41 213 majority of magnesium intake. Adjusted confounders were mostly similar; however,
42
43 214 adjusted dietary confounders such as cereal fiber, potassium, and calcium still varied
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45
46 215 across individual studies. It was unclear whether included studies had adjusted for
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48
49 216 sodium because they did not provide the information. All these studies were written in
50
51 217 English.
52
53 218 After the quality assessments of the studies according to NOS, the average score was
54
55
56 219 8.85 (**Table S3**) and all studies were of high quality (NOS score 8-10).
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59 220

221 **Magnesium Intake and T2D Incidence**

222 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
223 participants and 56 540 T2D cases) reported the magnitude of the risk of T2D was
224 reduced by 22% (RR, 0.78 [95% CI, 0.75-0.81]; $P < 0.001$) comparing the highest
225 category of magnesium intake to the lowest with a little evidence of heterogeneity (I^2
226 = 35.6%; $P = 0.021$). The dose category-specific analysis suggested that for < 50
227 mg/day magnesium increment, the risk of T2D was reduced by 10% (RR, 0.90 [95%
228 CI, 0.88-0.93]; $P < 0.001$); for ≥ 50 and < 100 mg/day, the risk was decreased by 16%
229 (RR, 0.84 [95% CI, 0.82-0.87]; $P < 0.001$); for ≥ 100 and < 150 mg/day, the risk was
230 reduced by 22% (RR, 0.78 [95% CI, 0.74-0.83]; $P < 0.001$); and for ≥ 150 mg/day,
231 the risk was reduced by 21% (RR, 0.79 [95% CI, 0.74-0.84]; $P < 0.001$) (**Figure 2**).
232 Little evidence of publication bias was found (Egger's test: $P = 0.088$) (**Figure S1A**).

233

234 **Magnesium Intake and Stroke Incidence**

235 Eighteen cohorts from 15 publications^{13,14,21,27,28,30,36,38,40,42,44-47,50} (692 998
236 participants and 20 138 total stroke cases) reported the magnitude of the risk of total
237 stroke was decreased by 11% (RR, 0.89 [95% CI, 0.83-0.94]; $P < 0.001$) with no
238 heterogeneity ($I^2 = 0\%$; $P = 0.529$) in the highest category of magnesium intake VS.
239 the lowest. Dose category-specific analysis identified no significant association with
240 the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and < 150 mg/day of increments.
241 For the ≥ 150 mg/day increment, the risk of total stroke was decreased by 15% (RR,
242 0.85 [95% CI, 0.79-0.91]; $P < 0.001$) (**Figure S2**). Publication bias was evaluated for

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4 243 stroke subtypes respectively.
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6 244 Fifteen cohorts from 12 publications^{14,21,27,28,30,36,38,40,42,45,46,50} reported ischemic
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8
9 245 stroke. The magnitude of the risk of ischemic stroke was reduced by 12% (RR, 0.88
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11 246 [95% CI, 0.81-0.95]; $P = 0.001$) with no significant heterogeneity ($I^2 = 16.9\%$; $P =$
12
13
14 247 0.265). Dose category-specific analysis identified no significant association with the <
15
16
17 248 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and < 150 mg/day increments. A trend
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19
20 249 to decrease existed but remained insignificant. The original risk was reduced by
21
22 250 16% in the analysis of the ≥ 150 mg/day increment (RR, 0.84 [95% CI, 0.78-0.91]; $P <$
23
24
25 251 0.001) (**Figure S3**). No publication bias was observed in terms of ischemic stroke
26
27 252 (Egger's test: $P = 0.937$) (**Figure S1B**).
28
29

30 253 Ten cohorts from 8 studies^{14,21,27,36,38,45,46,50} reported that hemorrhagic stroke was
31
32
33 254 not significantly associated with magnesium intake (RR, 0.93 [95% CI, 0.82-1.06]; P
34
35 255 = 0.282). Dose category-specific analysis identified no significant association (**Figure**
36
37
38 256 **S4**). No significant heterogeneity or publication bias were identified with regard to
39
40
41 257 hemorrhagic stroke (Egger's test: $P = 0.809$) (**Figure S1C**).
42

43 258 Three publications involving 3 cohorts^{14,27,36} showed that high magnesium intake
44
45
46 259 had no significant efficacy in reducing subarachnoid hemorrhage risk (RR, 0.99 [95%
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48 260 CI, 0.71-1.39]; $P = 0.963$). Dose category-specific analysis identified no significant
49
50
51 261 association (**Figure S5**).
52

53 262 With respect to intracerebral hemorrhage, the pooled results from 3 cohorts^{14,27,36}
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56 263 in 3 publications revealed no significant advantages of intracerebral hemorrhage (RR,
57
58 264 0.92 [95% CI, 0.71-1.20]; $P = 0.540$). Dose category-specific analysis identified no
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4 265 significant association (**Figure S6**).

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8 9 267 **Meta-Regression and Cumulative Meta-Analysis**

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11 268 Meta-regression identified no evidence of BMI, sex, participant region and dietary
12
13 269 assessment for each individual trial bias in T2D (**Figure S7**), total stroke (**Figure S8**),
14
15 270 ischemic stroke (**Figure S9**) and hemorrhagic stroke events (**Figure S10**). The male
16
17 271 subgroup ($P = 0.041$) in the sex category might cast little heterogeneity on total stroke;
18
19 272 however, the sex category ($P = 0.112$) had no association with total stroke incidence.
20
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25 273 Analyses on T2D (**Figure S11**), total stroke (**Figure S12**) and ischemic stroke
26
27 274 demonstrated that the RRs of the final results became robust within a narrow range
28
29 275 and remained significant as publication years increased and as recent high quality
30
31 276 studies were included. After inclusion of the Iso et al¹⁴ study, the RR and 95% CI for
32
33 277 ischemic stroke decreased to less than 1 and became stable (**Figure S13**). Although
34
35 278 there was no significantly reduced risk in hemorrhagic stroke, clear evidence showed
36
37 279 that the confidence interval was becoming narrow, which had a trend toward
38
39 280 significance (**Figure S14**). Thus, risk for hemorrhagic stroke might be reduced, and
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41 281 further studies are still needed.
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49 50 283 **Sensitivity Analysis**

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53 284 When three²⁴⁻²⁶ studies were excluded in T2D analysis, the summary RR changed
54
55 285 from 0.78 ([95% CI, 0.75-0.81]) to 0.78 ([95% CI, 0.75-0.82]) with the heterogeneity
56
57 286 declining from ($I^2 = 35.6\%$; $P = 0.021$) to ($I^2 = 24.0\%$; $P = 0.112$). Among T2D
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4 287 analysis, eight studies^{19,22,23,26,33,39,48,49} adjusted for cereal fiber intake yield an RR of
5
6 288 0.79 ([95% CI, 0.73-0.85]; $P < 0.001$) and two studies^{15,35} for calcium yielded an RR
7
8
9 289 of 0.87 ([95% CI, 0.73-1.04]; $P = 0.128$). While among total stroke analysis, the
10
11 290 summary RR was 0.92 ([95% CI, 0.82-1.02]; $P = 0.097$) in five studies^{13,44-46,50}
12
13
14 291 adjusted for potassium intake and was 0.89 ([95% CI, 0.80-0.99]; $P = 0.040$) in five
15
16 292 studies^{14,44-46,50} adjusted for calcium. Only one study¹⁵ adjusted for potassium intake
17
18
19 293 in T2D, one study³⁶ for cereal fiber in total stroke.
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295 **Subgroup Analysis**

296 Stratified analyses by characteristics of the population and study design were
297 conducted on T2D (**Table 1**), total stroke, ischemic stroke and hemorrhagic stroke
298 (**Table 2**). The inverse association with T2D remained robust across all subgroups
299 with little evidence of heterogeneity. As for stroke incidence, a decreased risk of total
300 stroke and ischemic stroke was found in female participants (RR, 0.91 [95% CI,
301 0.83-0.99] for total stroke; 0.89 [95% CI, 0.79-1.00] for ischemic stroke) and
302 individuals with ≥ 25 kg/m² mean BMI (RR, 0.89 [95% CI, 0.82-0.96] for total stroke;
303 0.88 [95% CI, 0.81-0.96] for ischemic stroke). When restricted to a ≥ 12 y follow-up,
304 the risk of total stroke and ischemic stroke could be significantly reduced (RR, 0.89
305 [95% CI, 0.83-0.95] for total stroke; 0.88 [95% CI, 0.81-0.95] for ischemic stroke).
306 These risks were more reduced in North American and European individuals than
307 Asians. Cardiovascular events (CV events, coronary heart disease, heart failure, atrial
308 fibrillation, and self-reported heart disease etc. other than stroke),
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4 309 hypercholesterolemia and diabetes would blunt the effect of magnesium on total and
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6 310 ischemic stroke. However, magnesium intake could still, or at least, demonstrate the
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9 311 trend to decrease total and ischemic stroke in individuals even with those risk factors.
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11 312 Similarly, CV events, hypercholesterolemia and family diabetes history had no
12
13 313 substantial impact on the inverse association between T2D incidence and magnesium
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15 314 intake. We did not find significantly reduced risk in hemorrhagic stroke across the
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17 315 subgroup analyses.
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25 317 **Dose-Response Analysis**

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27 318 In this part, both linear and nonlinear relationships were found in T2D (**Figure 3A**), in
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29 319 total stroke (**Figure 3B**), and in ischemic stroke (**Figure 3C**). However, no linear or
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31 320 non-linear dose-response relationship was observed in hemorrhagic stroke (**Figure 3D**)
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33 321 along with the subtypes including subarachnoid hemorrhage and intracerebral
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35 322 hemorrhage (**Figure S15**).
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40 323 Specifically, we calculated RR for the magnesium increments if there was linear
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42 324 relationship found. The calculated RR was 0.94 ([95% CI, 0.93-0.95]) for the 100
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44 325 mg/day increment for T2D. For total stroke, the summary RR was 0.98 ([95% CI,
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46 326 0.97-0.99]) related to 100 mg/day increment in magnesium intake, RR for ischemic
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48 327 stroke was 0.98 ([95% CI, 0.97-0.99]) related to 100 mg/day increment in magnesium
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50 328 intake. Magnesium intake showed an inverse dose-response relationship with T2D,
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52 329 total stroke and ischemic stroke. Moreover, a more substantial reduction on risks was
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54 330 observed with more magnesium intake.
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6 332 **Discussion**

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9 333 This paper used a general and up-to-date search strategy to identify some additional
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11 334 studies that were missed in prior meta-analyses under real-world conditions. Our
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14 335 results support a significant inverse association between magnesium consumption and
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17 336 T2D, total stroke and ischemic stroke at the highest level vs. the lowest. No
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20 337 significant association for hemorrhagic stroke, subarachnoid hemorrhage and
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23 338 intracerebral hemorrhage was detected. Female obese participants (mean BMI \geq 25
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25 339 kg/m²) with longer follow-up period (\geq 12 y) might obtain a greater benefit from
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28 340 magnesium intake for preventing total and ischemic stroke. Enhancing magnesium
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31 341 intake seemed to be more effective for North American and European individuals to
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33 342 get lower stroke risks. Significant risk reduced by 6%, 2%, and 2% for T2D, total
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35 343 stroke and ischemic stroke respectively at per 100 mg/day increment in magnesium
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38 344 intake level. Overall, the correction of magnesium deficiencies and enhancement of
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41 345 magnesium intake appears to be useful for T2D and total stroke high-risk participants;
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43 346 our study supports the guidelines to address the role of magnesium intake for T2D and
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46 347 stroke early prevention. Even though, we still require more randomized controlled
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49 348 trials (RCTs) in the future to validate the causality.

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51 349 Dietary nutrients are hot topics for current clinical medicine, folic acid, vitamin
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54 350 D, and ω -3 fatty acids have been specifically recommended to pregnant women,
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56 351 infants and children, and the elderly^{62,63}, however, magnesium has been less
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59 352 extensively discussed. This is a noteworthy study for the following reasons. First, this
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4 353 study focused on an important and timely topic related to correlations between two
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6 354 chronic diseases and magnesium. Preventing T2D and stroke still requires
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9 355 high-quality evidence. Current study reinforces the possible role of magnesium in the
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11 356 prevention and management of these illnesses and causes new considerations on the
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14 357 avoidance of other chronic disease with potential diet strategy. Second, this
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17 358 comprehensive study with nearly two million individuals and abundant statistical
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19 359 power provides confirming evidence for medical practitioners, health educators and
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21 360 policy makers. Third, until this study, no related paper has discussed such detailed
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24 361 stratified analyses, which helps physicians to amplify the dietary benefits through
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27 362 individualized strategies. Interestingly, we detected North American and European
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29 363 participants seemed to receive more benefits from magnesium intake than Asians.
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31 364 Fourth, to our knowledge, this is the first study in which cumulative meta-analysis
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33 365 was performed to forecast the changing tendency of main risk estimates. Based on
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35 366 past and current cutting edge evidence about nutrition and T2D prevention, the US
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37 367 Diabetes Prevention Program (DPP) conducted a study that demonstrated that proper
38
39 368 lifestyle modification (exercise and Mediterranean diet) significantly reduced T2D
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41 369 risks irrespective of population baselines, and the benefit expanded with increased
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43 370 follow-up⁶⁴. The UK national health service (UK NHS) will launch an intervention
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45 371 program including weight loss, nutrition, monitoring and peer support targeting up to
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47 372 10 000 people prone to develop T2D⁶⁵.

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49 373 2018 American Diabetes Association (ADA) guidelines⁶⁶ recommend to enhance
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51 374 intake of nuts, berries, yogurt, coffee and tea in individuals who are at high risk of
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4 375 diabetes. The latest guidelines by the American Heart Association (AHA)/American
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6 376 Stroke Association (ASA)⁹ also validate considerable status of early management of
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9 377 stroke (ischemic stroke). In deed, a poor outcome on hemorrhagic stroke was
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11 378 observed in a RCT, however, high serum magnesium might be better for intracerebral
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14 379 hemorrhage prognosis⁶⁷. Most specific nutrients especially macronutrients are
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17 380 correlated with total energy intake. In included free-living human studies, variation of
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20 381 total energy intake is originated from physical activity, differences in body size, and
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22 382 differences in energy efficiency⁶⁸. Thus total energy intake can weaken the
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25 383 investigated association with considerable nutrients intake if this covariable is not
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28 384 properly removed. Epidemiologists should assess reproducibility and validity of
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30 385 energy-adjusted nutrients as well as absolute nutrients intake. Though micronutrient
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33 386 as magnesium is, inverse association could be still found in T2D, total stroke and
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36 387 ischemic stroke outcomes after total energy intake adjustment. As for other nutrients,
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38 388 potassium intake is proposed to lower blood pressure (BP) and improve vascular
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40 389 outcomes (including stroke); dietary potassium may also be influential in glucose
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43 390 control and limiting the risk of diabetes⁶⁹. Vitamin D and calcium may negatively
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46 391 influence glycemia, but the evidence is limited for mostly being based on
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48 392 cross-sectional observational studies⁷⁰. Calcium may be inversely associated with
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51 393 stroke in populations with low to moderate calcium intakes, but no significant
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54 394 association was found between calcium and CVD⁷¹. All things considered,
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56 395 magnesium-rich food such as nuts (151-567 mg/100g edibles), fruits (132-448
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58 396 mg/100g edibles), vegetables (132-1257 mg/100g edibles), legumes (138-243
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4 397 mg/100g edibles), fish (143-303 mg/100g edibles) and total grain (134-306 mg/100g
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7 398 edibles) should be recommended to populations with insufficient magnesium intake
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9 399 from T2D and total stroke.

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11 400 This seminar has several differences with previous studies. Dong et al⁵² found
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13 401 magnesium intake had an inverse association with T2D incidence (RR, 0.78 [95% CI,
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15 402 0.73-0.84]), and with an intake of 100 mg/day magnesium, the risk was reduced by
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17 403 14%. In fact, they failed to include adequate studies, and standard quality assessments
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19 404 of eligible studies were absent. Individuals from multiple nations in some
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21 405 studies^{18,25,26,32} were incorrectly assigned to Asia or the U.S. in the subgroups, and
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23 406 minor imperfections existed in the selection criteria because it was unclear whether
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25 407 they excluded participants with subclinical diabetes. BMI was not a potential modifier
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27 408 for T2D in our study due to the inclusion of more evidence which had longer
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29 409 follow-up period. Fang et al⁷² revealed dietary magnesium had a smaller effect on
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31 410 cardiovascular disease but significantly reduced T2D (RR, 0.74 [95% CI, 0.69-0.80])
32
33 411 and stroke (RR, 0.88 [95% CI, 0.82-0.95]) risks. The results were comparable, but
34
35 412 they just focused on dietary magnesium intake rather than overall magnesium intake
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37 413 (total or dietary), and subtypes of total stroke were missed. To our overall knowledge,
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39 414 BMI, follow-up, family diabetes history, etc. were crucial confounders for evaluating
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41 415 the association, which were not addressed in their study. Moreover, researchers had
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43 416 better investigate the likelihood of linear association in the dose-response pattern
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45 417 (using methods by Greenland and Orsini et al). Fang et al⁷³ found that the 100 mg/day
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47 418 intake of dietary magnesium was associated with an 8-13% reduction in T2D risk, and
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4 419 while a nonlinear relationship did not exist, a minor publication bias was present.
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6 420 Twenty-five studies were eligible; however, some of them focused not on dietary but
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9 421 on total magnesium intake. Moreover, there were two included studies focusing on
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11 422 red meat intake instead of magnesium intake. After excluding actual ineligible studies,
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14 423 we found no evidence of publication bias. Additionally, both linear and nonlinear
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16 424 relationships existed for T2D, because the RRs of the highest category of magnesium
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18 425 intake VS. the lowest in our pooled study were still used. A study by Larsson et
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21 426 al⁵³including 7 studies supported a modest but statistically significant inverse
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23 427 association between dietary magnesium intake and stroke. The sample size was quite
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25 428 small, and there was no useful information for stroke subtypes (e.g., ischemic stroke,
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27 429 hemorrhagic stroke) in the main analysis. In our opinion, a well-designed subgroup
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29 430 analysis is a compulsory undertaking, and a pooled stroke result restricted by
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31 431 potassium and calcium adjustment is recommended. The current study found
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33 432 magnesium intake was strongly inversely associated with total stroke and ischemic
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35 433 stroke, which still existed in the dose-response pattern.
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43 434 Future studies still have something to be addressed. At first, no significant
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45 435 efficacy was found in hemorrhagic stroke, however, the beneficial trend was observed
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47 436 in the cumulative meta-analysis, which addresses needs for more updated prospective
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49 437 studies and RCTs. Second, there is a key question regarding the optimal time to start
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51 438 prevention and methods to screen severe complications. Cardiovascular events occur
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53 439 in more than 50% and diabetic kidney disease occurs in 20-40% of patients with
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55 440 diabetes. Actually, cardiovascular events increase the risk of death three to four times
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4 441 compared with patients without such complications. A sustained period of intensive
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6 442 glucose control early in T2D has been confirmed to reduce complication rates⁷⁴. Most
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9 443 importantly, to the public, educators and guideline makers, boosting magnesium-rich
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11 444 food consumption brings considerable benefits to T2D and total stroke prevention,
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14 445 especially in high-risk populations.
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17 446 Several limitations deserve further discussion. First, this group-level
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19 447 meta-analysis is insufficient. Although strong inverse associations for T2D and total
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21 448 stroke were reported, individual-level studies having more detection power are
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23 449 required. Second, several variations cannot be totally understood, for example, we
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25 450 cannot exclude the possibility that other nutrients and/or dietary components
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27 451 correlated with dietary magnesium may have been responsible, either partially or
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29 452 entirely, for the observed associations. Based on eligible studies, we could not
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31 453 quantify the impact of supplementary magnesium (not combined with dietary intake)
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33 454 on T2D and stroke incidence. The real effect of some dietary supplements on T2D or
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35 455 cardiovascular disease seems very interesting to a number of medical experts,
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37 456 clinicians and nutrition educators. Third, FFQs/validated FFQs mostly used in
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39 457 primary studies could not characterize all the nutrients, which misclarified plausible
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41 458 associations. Finally, besides prospective cohort studies, we still required further
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43 459 RCTs, because observational studies might only reach the same conclusion (i.e.,
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45 460 magnesium intake is inversely associated with T2D incidence) but could not prove
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47 461 causality. However, there has been some evidence suggesting that magnesium
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49 462 achieves glucose and insulin metabolism through tyrosine kinase activity of the
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4 463 insulin receptor; magnesium also helps to eliminate calcium cation cytotoxicity and
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6 464 has vasodilatory effect⁷⁵.
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11 466 **Conclusion**

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14 467 Magnesium intake has a substantial inverse association with T2D and total stroke.
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17 468 Among these populations, magnesium consumption can be recommended as an
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20 469 optimization for T2D, total stroke and ischemic stroke primary prevention or early
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22 470 management. In particular, the greater the magnesium intake, the more the risk is
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25 471 reduced. As patients, physicians, policy makers and legislators debate on these issues,
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27 472 such a cost-effective alternative is needed to inform policy decisions and assist reform
28
29
30 473 in global dietary health care.
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39
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41
42
43 478 collection.
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45 479
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48 480 **Competing interests**

49
50 481 None declared
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55 483 **Provenance and peer review**

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58 484 Not commissioned; externally peer reviewed.
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6 486 **Data sharing statement**

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9 487 No additional data are available.

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14 489 **Patient consent for publication**

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17 490 Not required.

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36
37 498 and takes responsibility for the integrity of the data and the accuracy of the data
38
39 499 analysis.

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41 500 Concept and design: All authors.

42
43 501 Acquisition, analysis, or interpretation of data: All authors.

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45 502 Drafting of the manuscript: Binghao Zhao and Wenxiong Zhang.

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47 503 Critical revision of the manuscript for important intellectual content: Binghao Zhao,
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49 504 Lianli Zeng, Jiani Zhao, Qian Wu, Fang Zou, Li Gan and Yifei Dong.

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51 505 Statistical analysis: Binghao Zhao.

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53 506 Supervision: Wenxiong Zhang and Yiping Wei

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Table 1 Subgroup Analysis relating to Magnesium Intake and Type 2 Diabetes (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/m²)	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 frequency questionnaire; 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;

735 ^c, Two studies reported total magnesium and dietary magnesium intake outcome;

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

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

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

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

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742 **Table 2.** Subgroup Analyses Relating to Magnesium Intake and Total Stroke, Ischemic Stroke, Hemorrhagic stroke.
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Group	Total Stroke				Ischemic Stroke				Hemorrhagic stroke			
	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}
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/m²)	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	

1	intake	7	(0.81-0.96)		6	(0.77-1.03)		3		
2	Total energy adjustment	15		0.888	12		0.689	8		0.538
3			0.87			0.86				
4	Yes	5	(0.77-0.99)	27.00	2	(0.78-0.94)	0.00	2	0.93 (0.82-1.06)	0.00
5	No	10	0.89	0.00	10	0.88	26.60	6	0.90 (0.76-1.07)	11.40
6	Difference between top and bottom intake (mg/day)^d		(0.83-0.96)			(0.79-0.99)				
7		15		0.107	12		0.180	8		0.244
8										
9	≥ 180	7	0.83	0.00	5	0.83	0.00	6	1.07 (0.83-1.37)	0.00
10			(0.76-0.91)			(0.76-0.91)				
11	< 180	8	0.93	0.00	7	0.92	26.20	2	0.89 (0.76-1.03)	0.00
12			(0.86-1.00)			(0.81-1.03)				
13	Current CV events status^e	15		0.074	12		0.393	8		NA
14										
15	Yes	12	0.90	0.00	11	0.88	18.20	8	0.93 (0.82-1.06)	0.00
16			(0.85-0.96)			(0.81-0.96)				
17	Unknown	3	0.75	0.00	1	0.76	NA	0	NA	NA
18			(0.63-0.90)			(0.57-1.01)				
19	Hypercholesterolemia status^f	15		0.480	12		0.565	8		0.651
20										
21	Yes	7	0.91	0.00	6	0.90	6.90	5	0.90 (0.76-1.08)	0.00
22			(0.83-0.99)			(0.80-1.01)				
23	Unknown	8	0.86	13.10	6	0.86	32.40	3	0.94 (0.72-1.22)	40.30
24			(0.79-0.95)			(0.77-0.97)				
25	Current diabetes status^g	15		0.039	12		0.159	8		NA
26										
27	Yes	10	0.91	0.00	10	0.89	13.50	8	0.93 (0.82-1.06)	0.00
28			(0.82-0.97)			(0.82-0.97)				
29	Unknown	5	0.75	0.00	2	0.72	0.00	0	NA	NA
30			(0.64-0.88)			(0.56-0.92)				

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.

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3 744 **Figure Legends**
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5 745 **Figure 1.** Flow Chart for Literature Search and Screening Process
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7 746 **Figure 2.** Forest Plots for Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A)
8 and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and < 150 mg/day (D) and
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12 748 ≥ 150 mg/day Magnesium increments (E).
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14 749 **Figure 3.** Two-Stage Dose-Response Effect on the Relationships between Magnesium
15 Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and
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17 750
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19 751 Hemorrhagic Stroke (D).
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3 752 **Supplementary material online:**
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5 753 **Table S1.** PRISMA 2009 Checklist
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7 754 **Table S2.** Summary of Baseline Characteristics of Included Studies
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9 755 **Table S3.** Methodological Quality Assessments Of Studies Included With
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12 756 Newcastle-Ottawa Scales
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14 757 **Figure S1.** Funnel Plots for Magnesium Intake and Type 2 Diabetes (A), Ischemic
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16 758 Stroke (B) and Hemorrhagic Stroke (C).
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18 759 **Figure S2.** Forest Plots for Risk of Total Stroke for Magnesium Intake (A) and for <
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20 760 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and ≥ 150
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22 761 mg/day Magnesium increments (E).
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24 762 **Figure S3.** Forest Plots for Risk of Ischemic Stroke for Magnesium Intake (A) and for
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26 763 < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and ≥ 150
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28 764 mg/day Magnesium increments (E).
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30 765 **Figure S4.** Forest Plots for Risk of Hemorrhagic Stroke for Magnesium Intake (A)
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32 766 and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and
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34 767 ≥ 150 mg/day Magnesium increments (E).
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36 768 **Figure S5.** Forest Plots for Risk of Subarachnoid Hemorrhage for Magnesium Intake
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38 769 (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D)
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40 770 and ≥ 150 mg/day Magnesium increments (E)
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42 771 **Figure S6.** Forest Plots for Risk of Intracerebral Hemorrhage for Magnesium Intake
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44 772 (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D)
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46 773 and ≥ 150 mg/day Magnesium increments (E)
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48 774 **Figure S7.** Meta-Regression of Relative Risk for Type 2 Diabetes According to Body
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50 775 Mass Index (A, $P = 0.716$), Sex (B, $P = 0.284$), Participant Region (C, $P = 0.904$) and
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52 776 Dietary Assessment (D, $P = 0.521$).
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3 777 **Figure S8.** Meta-Regression of Relative Risk for Total Stroke According to Body
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5 778 Mass Index (A, $P = 0.606$), Sex (B, $P = 0.112$), Participant region (C, $P = 0.891$) and
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7 779 Dietary Assessment (D, $P = 0.891$).

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10 780 **Figure S9.** Meta-Regression of Relative Risk for Ischemic Stroke According to Body
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12 781 Mass Index (A, $P = 0.631$), Sex (B, $P = 0.134$), Participant Region (C, $P = 0.584$) and
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14 782 Dietary Assessment (D, no regression P -value due to limited data).

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17 783 **Figure S10.** Meta-Regression of Relative Risk for Hemorrhagic Stroke According to
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19 784 Body Mass Index (A, $P = 0.418$), Sex (B, $P = 0.872$), Participant Region (C, $P =$
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21 785 0.872) and Dietary Assessment (D, no regression P -value due to limited data).

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24 786 **Figure S11.** Cumulative Meta-Analysis Related to Magnesium Intake and Type 2
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26 787 Diabetes (T2D)

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29 788 **Figure S12.** Cumulative Meta-Analysis Related to Magnesium Intake and Total
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31 789 Stroke

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33 790 **Figure S13.** Cumulative Meta-Analysis Related to Magnesium Intake and Ischemic
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35 791 Stroke

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38 792 **Figure S14.** Cumulative Meta-Analysis Related to Magnesium Intake and
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40 793 Hemorrhagic Stroke

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42 794 **Figure S15.** Dose-Response Effect on the Relationships between Magnesium Intake
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44 795 and Subarachnoid Hemorrhage (A) and Intracerebral Hemorrhage (B).

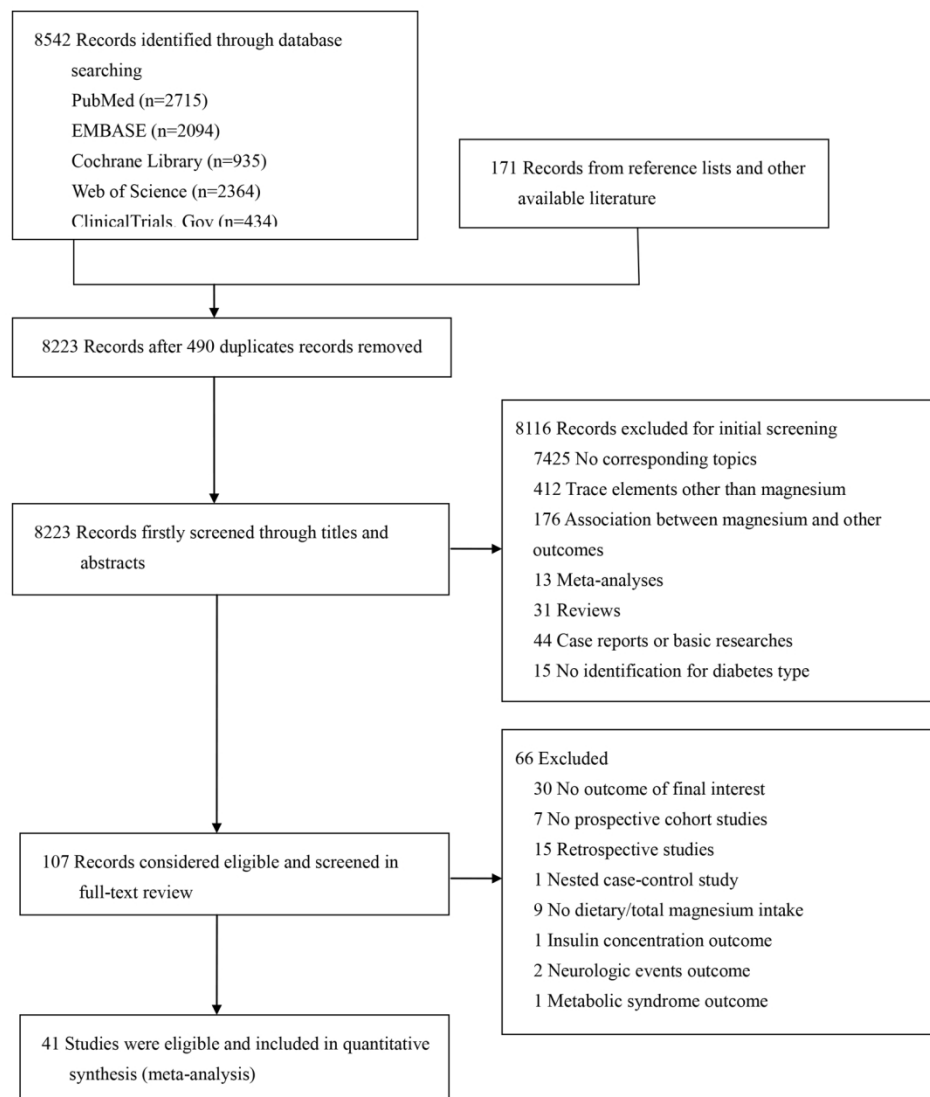


Figure 1. Flow Chart for Literature Search and Screening Process

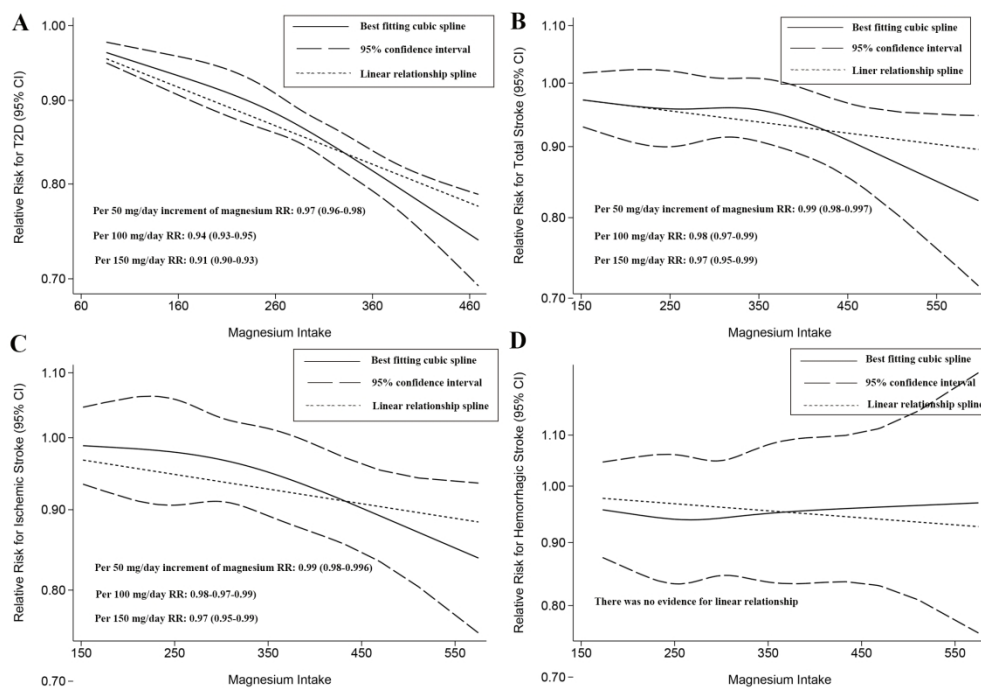


Figure 3. Two-Stage Dose-Response Effect on the Relationships between Magnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).



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

Page 1 of 2

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

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Page 2 of 2

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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))
Schulze 2007 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))

1	Nanri 2010 ³⁵	Japan	1990-1995	M; 40-65 y	NA	validated FFQ	self-reported questionnaire	634 T2D (25872)	348 VS. 213 (0.86 (0.63-1.16))
2				F; 40-65 y				480 T2D (33919)	333 VS. 213 (0.92 (0.66-1.28))
3	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))
4							follow-up examination or		
5	Weng 2012 ³⁷	Taipei	1993-2002	M/F; ≥30 y	24	validated FFQ	self-reported questionnaire	141 T2D (1604)	406 VS. 212 (0.44 (0.25-0.75))
6									
7	Zhang 2012 ³⁸	Japan	1988-2006/	M; 40-79 y	22.7	validated FFQ	follow-up examination	634 stroke (23083)	294 VS. 173 (1.03 (0.79-1.35))
8				F; 40-79 y	22.9			620 stroke (35533)	274 VS. 175 (0.90 (0.69-1.16))
9	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))
10							follow-up examination and		
11	Lin 2013 ⁴⁰	Taipei	1989-2002	M/F; ≥ 18 y	23.3	validated FFQ	self-reported questionnaire	123 stroke (2061)	378 VS. 210 (0.62 (0.40-0.97))
12									
13				M; 40-69 y	23.6			690 T2D (27769)	349 VS. 232 (0.84 (0.69-1.05))
14	Oba 2013 ⁴¹	Japan	1990-2000	F; 40-69 y	23.5	validated FFQ	self-reported questionnaire	500 T2D (36864)	356 VS. 211 (0.69 (0.54-0.88))
15									
16	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))
17	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))
18									
19	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))
20	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))
21									
22	Adebamowo 2015(2) ⁴⁶	USA	1976-2006	F; 30-55 y	26.4	validated FFQ	self-reported questionnaire	3237 stroke (86149)	411 VS. 233 (0.93 (0.79-1.08))
23			1989-2011	F; 25-42 y	25.7			543 stroke (94715)	
24	Bain 2015 ⁴⁷	Britain	2002-2008	M; 40-75 y	26.5	7-day diary recall	follow-up examination	364 stroke (2000)	456 VS. 266 (0.81 (0.53-1.22))
25				F; 40-75 y	26.2			511 stroke (2445)	374 VS. 456 (0.82 (0.54-1.24))
26	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))
27									
28			1984-2012	F; 30-55 y	24.8			7620 T2D (69176)	390 VS. 229 (0.80 (0.73-0.88))
29	Hruby 2017 ⁴⁹	USA	1991-2013	F; 25-42 y	24.6	validated SFFQ	self-reported questionnaire	6080 T2D (91471)	424 VS. 249 (0.89 (0.81-0.99))
30									
31			1986-2012	M; mean 53.5 y	24.8			3430 T2D (42096)	469 VS. 280 (0.88 (0.77-1.00))
32	Kokubo 2017 ^{50b}	Japan	1990-2009	M; 40-69 y	23.6	FFQ	follow-up examination	2576 stroke (39505)	348 VS. 213 (1.07 (0.86-1.33))
33									
34			1993-2010	F; 40-69 y	23.6			1846 stroke (45788)	333 VS. 213 (0.88 (0.67-1.14))
35	Konishi 2017 ⁵¹	Japan	1992-2002	M; ≥35 y	22.6	validated FFQ	self-reported questionnaire	266 T2D (5885)	469 VS. 310 (1.13 (0.76-1.70))
36				F; ≥35 y	22.1			172 T2D (7640)	432 VS. 285 (0.50 (0.30-0.84))

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

38 ^a, different ethnicities of participants are in multiple nations cohort;

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

40 ^c the range of enrolled participants age is not mentioned.

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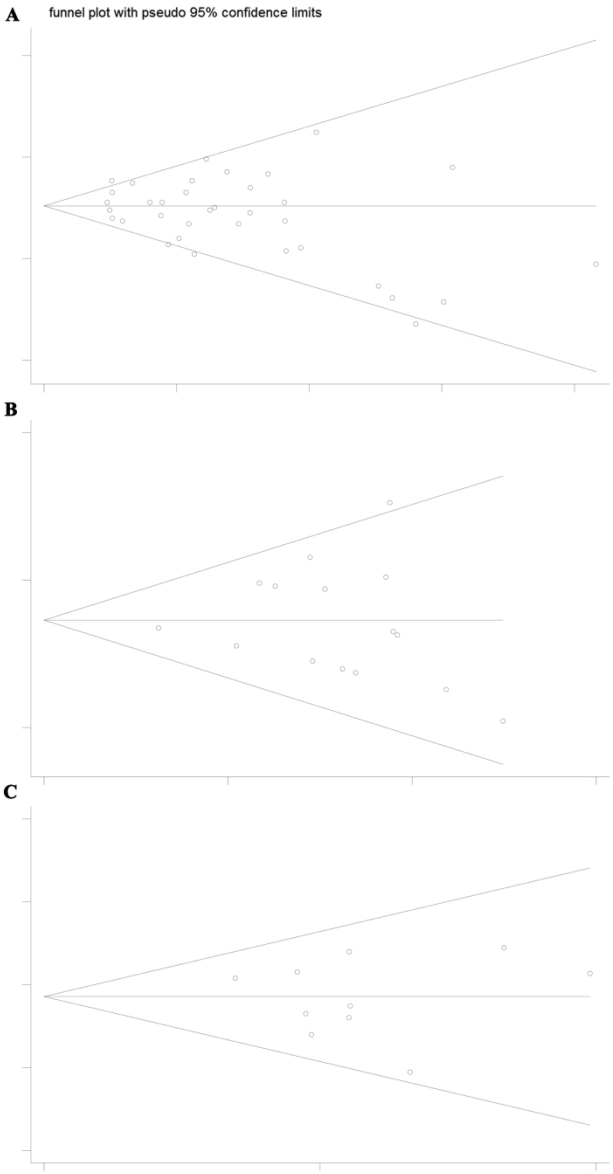
Table S3 Methodological Quality Assessments Of Included Studies With Newcastle-Ottwa Scales

	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	
7	1997	Salmeron et al, ¹¹	*	*	*	*	**	*	*	9
8	1997	Salmeron et al (2), ¹²	*	*	*	*	**	*	*	9
9	1998	Ascherio et al, ¹³	*	*	*	*	**	*	*	9
10	1999	Iso et al, ¹⁴	*	*	*	*	**	*	*	9
11	1999	Kao et al, ¹⁵	*	*	*	*	**	*	*	9
12	1999	Kao et al, ¹⁵	*	*	*	*	**	*	*	9
13	2000	Liu et al, ¹⁶	*	*	*	*	**	*	*	9
14	2000	Meyer et al, ¹⁷	*	*	*	*	**	*	*	9
15	2000	Meyer et al, ¹⁷	*	*	*	*	**	*	*	9
16	2004	Hodge et al, ¹⁸	*	*	*	*	*	*	*	7
17	2004	Hodge et al, ¹⁸	*	*	*	*	*	*	*	7
18	2004	Lopez et al, ¹⁹	*	*	*	*	**	*	*	9
19	2004	Lopez et al, ¹⁹	*	*	*	*	**	*	*	9
20	2004	Song et al, ²⁰	*	*	*	*	**	*	*	9
21	2004	Song et al, ²⁰	*	*	*	*	**	*	*	9
22	2005	Song et al, ²¹	*	*	*	*	**	*	*	9
23	2005	Song et al, ²¹	*	*	*	*	**	*	*	9
24	2006	Liu et al, ²²	*	*	*	*	**	*	*	9
25	2006	Liu et al, ²²	*	*	*	*	**	*	*	9
26	2006	Pereira et al, ²³	*	*	*	*	**	*	*	9
27	2006	Pereira et al, ²³	*	*	*	*	**	*	*	9
28	2006	Pittas et al, ²⁴	*	*	*	*	**	*	*	9
29	2006	Pittas et al, ²⁴	*	*	*	*	**	*	*	9
30	2006	Van et al, ²⁵	*	*	*	*	**	*	*	9
31	2006	Van et al, ²⁵	*	*	*	*	**	*	*	9
32	2007	Schulze et al, ²⁶	*	*	*	*	**	*	*	9
33	2007	Schulze et al, ²⁶	*	*	*	*	**	*	*	9
34	2008	Larsson et al, ²⁷	*	*	*	*	**	*	*	9
35	2008	Larsson et al, ²⁷	*	*	*	*	**	*	*	9
36	2008	Weng et al, ²⁸	*	*	*	*	**	*	*	9
37	2008	Weng et al, ²⁸	*	*	*	*	**	*	*	9
38	2009	Kirii et al, ²⁹	*	*	*	*	**	*	*	9
39	2009	Kirii et al, ²⁹	*	*	*	*	**	*	*	9
40	2009	Ohira et al, ³⁰	*	*	*	*	**	*	*	9
41	2009	Ohira et al, ³⁰	*	*	*	*	**	*	*	9
42	2009	Villegas et al, ³¹	*	*	*	*	**	*	*	9
43	2009	Villegas et al, ³¹	*	*	*	*	**	*	*	9
44	2010	Hopping et al, ³²	*	*	*	*	**	*	*	9
45	2010	Hopping et al, ³²	*	*	*	*	**	*	*	9
46	2010	Kim et al, ³³	*	*	*	*	**	*	*	8
47	2010	Kim et al, ³³	*	*	*	*	**	*	*	8
48	2010	Kirii et al, ³⁴	*	*	*	*	**	*	*	9
49	2010	Kirii et al, ³⁴	*	*	*	*	**	*	*	9
50	2010	Nanri et al, ³⁵	*	*	*	*	**	*	*	9
51	2010	Nanri et al, ³⁵	*	*	*	*	**	*	*	9
52	2011	Larsson et al, ³⁶	*	*	*	*	**	*	*	9
53	2011	Larsson et al, ³⁶	*	*	*	*	**	*	*	9
54	2012	Weng et al, ³⁷	*	*	*	*	**	*	*	8
55	2012	Weng et al, ³⁷	*	*	*	*	**	*	*	8
56	2012	Zhang et al, ³⁸	*	*	*	*	**	*	*	9
57	2012	Zhang et al, ³⁸	*	*	*	*	**	*	*	9

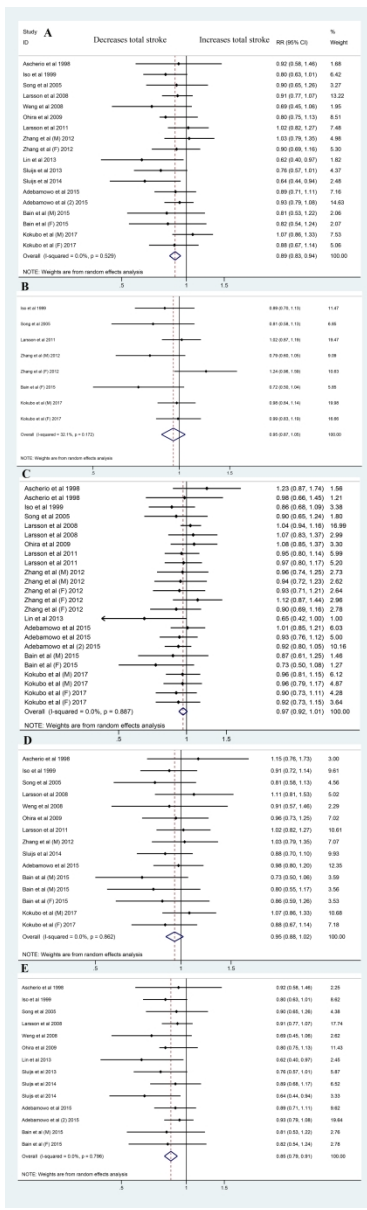
1	2013	Hata et al, ³⁹	*	*	*	*	**	*	*	*	9
2	2013	Lin et al, ⁴⁰	*	*	*	*	**	*	*	*	9
3	2013	Oba et al, ⁴¹	*	*	*	*	**	*	*	*	9
4	2013	Sluijs et al, ⁴²	*	*	*	*	**		*	*	8
5	2014	Hruby et al, ⁴³	*	*	*	*	**	*	*	*	9
6	2014	Sluijs et al, ⁴⁴	*	*	*	*	**	*	*	*	9
7	2015	Adebamowo et al, ⁴⁵	*	*	*	*	**	*	*	*	9
8	2015	Adebamowo et al (2), ⁴⁶	*	*	*	*	**	*	*	*	9
9	2015	Bain et al, ⁴⁷	*	*	*	*	**	*	*	*	9
10	2015	Huang et al, ⁴⁸	*	*	*		**	*	*	*	8
11	2017	Hruby et al, ⁴⁹	*	*	*	*	**	*	*	*	9
12	2017	Kokubo et al, ⁵⁰	*	*	*	*	**	*	*	*	9
13	2017	Konishi et al, ⁵¹	*	*	*	*	*	*	*	*	9

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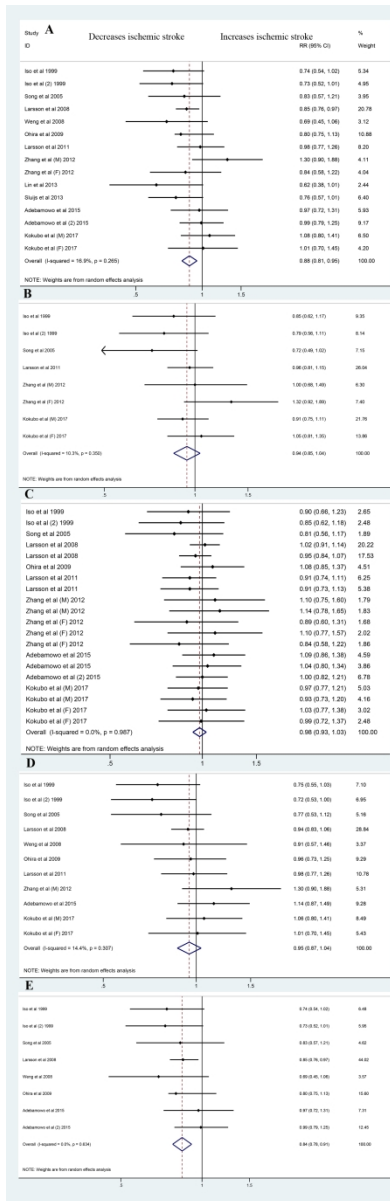
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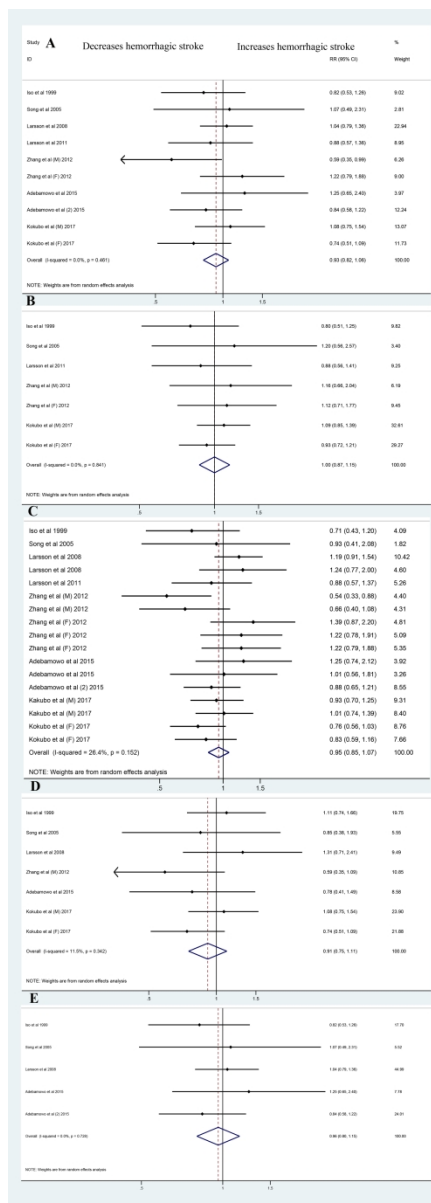
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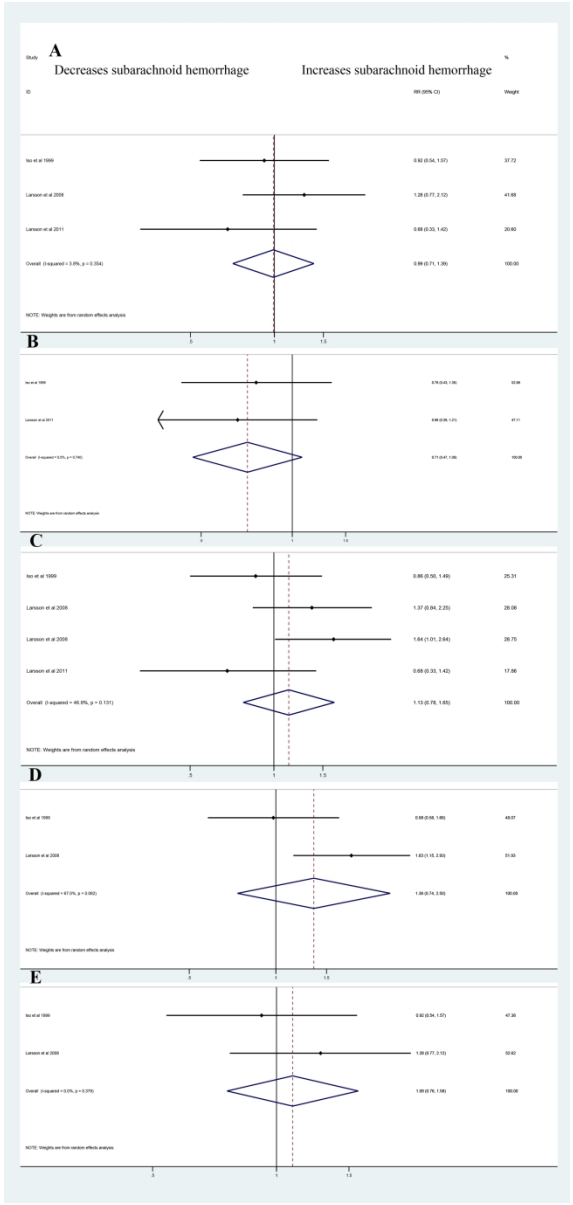
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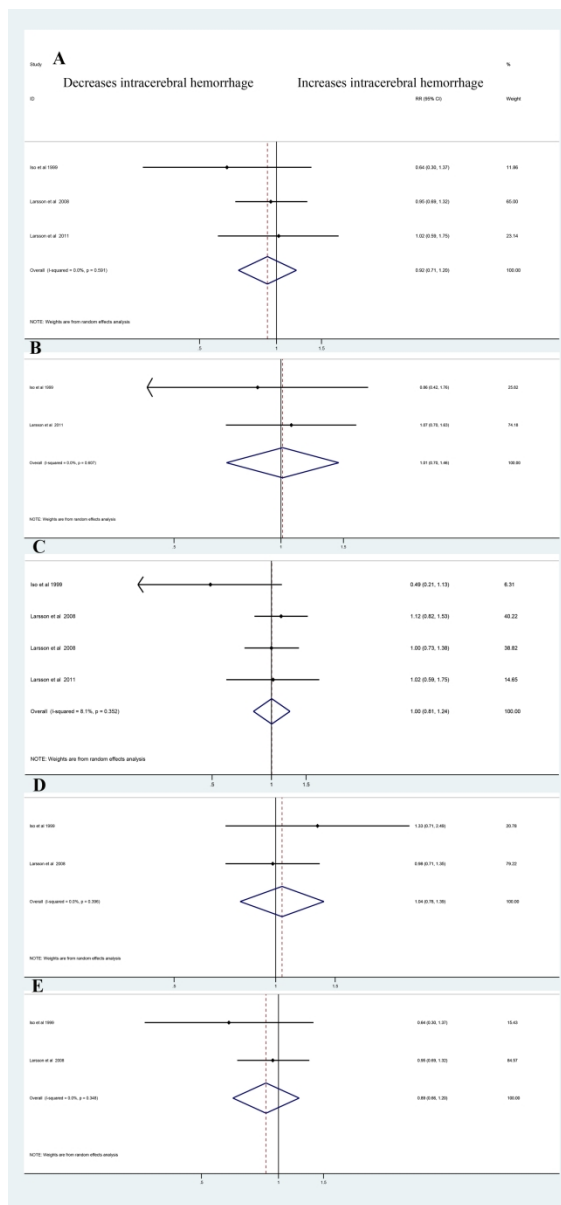
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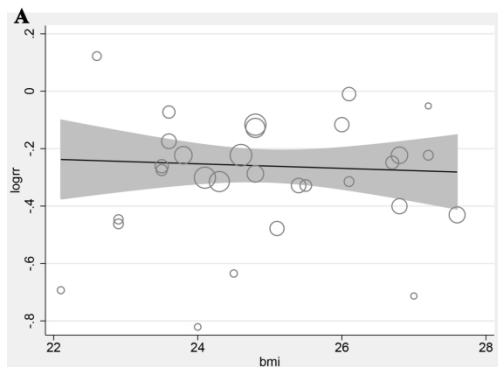


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```

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, wsize (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression              Number of obs =    35
RMSE 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    | -1.1314075  .0857798   -1.53  0.135   -1.3061323   -.0433174
sexnew2    | -.0630804   .0541113   -1.17  0.252   -1.733016   -.0471407
      _cons | -1.956565   .0461514   -4.24  0.000   -2.096637   -1.1016492
    
```

```

C
. tabulate participantregion, generate ( participantregionnew )

      participantregion | Freq.  Percent   Cum.
-----+-----
on                     |    35    100.00
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 participantregionnew1 participantregionnew2 participantregionnew3, wsize (selogrr) knapphartung reml
note: participantregionnew3 dropped because of collinearity

Meta-regression              Number of obs =    35
RMSE estimate of between-study variance      tau2 = .004698
% residual variation due to heterogeneity      I-squared_res = 35.22%
Proportion of between-study variance explained  Adj R-squared = -30.80%
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]
-----+-----
participantregionnew2 | .0027567  .0731865   0.04  0.970   -1.463193   .1518327
participantregionnew1 | -.001657  .0599158  -.034  0.739   -1.422102   .1018788
      _cons | -2.392399  .0510872  -4.68  0.000   -2.4833012  -1.1517166
    
```

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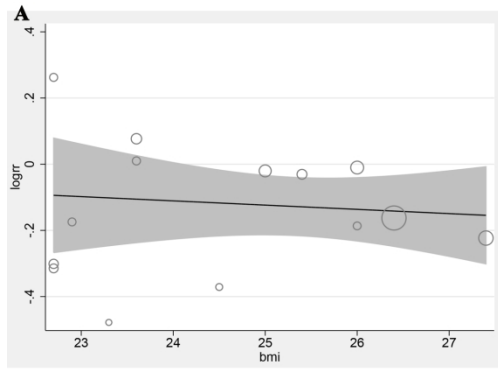
D
. tabulate dietaryassessment, generate ( dietaryassessmentnew )

      dietaryassessment | Freq.  Percent   Cum.
-----+-----
24h dietary recall and FFQ |     1     2.86   2.86
FFQ                        |     4    11.43  14.29
SPFQ                       |     1     2.86  17.14
validated DRQ              |     1     2.86  20.00
validated FFQ              |    17    48.57  68.57
validated SPFQ             |    11    31.43  100.00
-----+-----
Total                       |    35    100.00

. metareg logrr dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4 dietaryassessmentnew5 dietaryassessmentnew6 dietaryassessmentnew7 dietaryassessmentnew8 dietaryassessmentnew9 dietaryassessmentnew10 dietaryassessmentnew11 dietaryassessmentnew12 dietaryassessmentnew13 dietaryassessmentnew14 dietaryassessmentnew15 dietaryassessmentnew16 dietaryassessmentnew17 dietaryassessmentnew18 dietaryassessmentnew19 dietaryassessmentnew20 dietaryassessmentnew21 dietaryassessmentnew22 dietaryassessmentnew23 dietaryassessmentnew24 dietaryassessmentnew25 dietaryassessmentnew26 dietaryassessmentnew27 dietaryassessmentnew28 dietaryassessmentnew29 dietaryassessmentnew30 dietaryassessmentnew31 dietaryassessmentnew32 dietaryassessmentnew33 dietaryassessmentnew34 dietaryassessmentnew35 dietaryassessmentnew36 dietaryassessmentnew37 dietaryassessmentnew38 dietaryassessmentnew39 dietaryassessmentnew40 dietaryassessmentnew41 dietaryassessmentnew42 dietaryassessmentnew43 dietaryassessmentnew44 dietaryassessmentnew45 dietaryassessmentnew46 dietaryassessmentnew47 dietaryassessmentnew48 dietaryassessmentnew49 dietaryassessmentnew50 dietaryassessmentnew51 dietaryassessmentnew52 dietaryassessmentnew53 dietaryassessmentnew54 dietaryassessmentnew55 dietaryassessmentnew56 dietaryassessmentnew57 dietaryassessmentnew58 dietaryassessmentnew59 dietaryassessmentnew60 dietaryassessmentnew61 dietaryassessmentnew62 dietaryassessmentnew63 dietaryassessmentnew64 dietaryassessmentnew65 dietaryassessmentnew66 dietaryassessmentnew67 dietaryassessmentnew68 dietaryassessmentnew69 dietaryassessmentnew70 dietaryassessmentnew71 dietaryassessmentnew72 dietaryassessmentnew73 dietaryassessmentnew74 dietaryassessmentnew75 dietaryassessmentnew76 dietaryassessmentnew77 dietaryassessmentnew78 dietaryassessmentnew79 dietaryassessmentnew80 dietaryassessmentnew81 dietaryassessmentnew82 dietaryassessmentnew83 dietaryassessmentnew84 dietaryassessmentnew85 dietaryassessmentnew86 dietaryassessmentnew87 dietaryassessmentnew88 dietaryassessmentnew89 dietaryassessmentnew90 dietaryassessmentnew91 dietaryassessmentnew92 dietaryassessmentnew93 dietaryassessmentnew94 dietaryassessmentnew95 dietaryassessmentnew96 dietaryassessmentnew97 dietaryassessmentnew98 dietaryassessmentnew99 dietaryassessmentnew100, wsize (selogrr) knapphartung reml
note: dietaryassessmentnew2 through dietaryassessmentnew100 dropped because of collinearity

Meta-regression              Number of obs =    35
RMSE 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(15,29) = 0.16
With Knapp-Hartung modification               Prob > F = 0.5210

      logrr | Coef.  Std. Err.   t   P>|t|   [95% Conf. Interval]
-----+-----
dietaryassessmentnew1 | .1072405  .5101822   0.20  0.841   -1.07096   1.135451
dietaryassessmentnew2 | .0470373  .296468   1.58  0.124   -1.19403   1.073537
dietaryassessmentnew3 | -.1518405 .111752   -1.46  0.107   -1.152599   1.155849
dietaryassessmentnew4 | .1600754  .2811794   1.30  0.205   -1.194081   .8655519
dietaryassessmentnew5 | .1948872  .2812421   1.40  0.171   -1.057543   .6671218
dietaryassessmentnew6 | -.4388793 .279225   -1.57  0.131   -1.205958   -.0679791
    
```

```

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, wase (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   -0.4770662   -.0004339
sexnew2      -.0739192   .0940187  -0.79   0.447   -1.2787683   .1309299
      _cons      -.0480002   .0681983  -0.70   0.495   -1.1965933   .1005894
    
```

```

C . tabulate participantregion, generate ( participantregionnew )

participantregion
-----+-----
region      Freq.   Percent   Cum.
-----+-----
Asia        4     40.00    40.00
Europe      3     30.00    70.00
North America 4     40.00   100.00
-----+-----
Total      11    100.00

. metareg logrr participantregionnew1 participantregionnew2, wase (selogrr) knapphartung reml
note: participantregionnew3 dropped because of collinearity

Meta-regression              Number of obs =    15
REML estimate of between-study variance      tau2      = .0014
% residual variation due to heterogeneity     I-squared_res = 21.74%
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]
-----+-----
participantregionnew1      -.1089353   .1083661   1.01   0.335   -1.271992   .045197
participantregionnew2      .0517202   .0911749   0.53   0.598   -1.049328   .100332
      _cons      -.1429514   .0453255  -3.15   0.008   -.2024935   -.0804992
    
```

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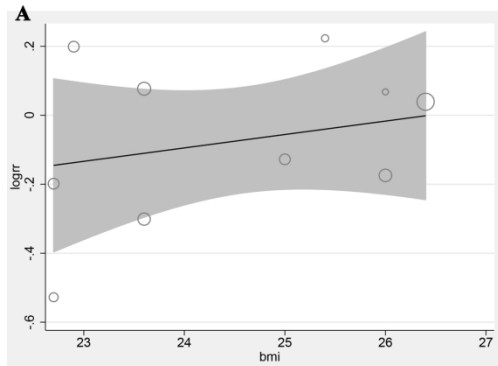
D . tabulate dietaryassessment, generate ( dietaryassessmentnew )

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

. metareg logrr dietaryassessmentnew1 dietaryassessmentnew2, wase (selogrr) knapphartung reml
note: dietaryassessmentnew3 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   -1.1528236   .2445382
      _cons      -.1429514   .0453255  -3.15   0.008   -.2024935   -.0804992
    
```



C

```
. tabulate participantregion, generate ( participantregionew )
```

participantregion	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 participantregionew1 participantregionew2 participantregionew3, wsize (selogrr) knapphartung reml
note: participantregionew3 dropped because of collinearity
```

Meta-regression

REML estimate of between-study variance	tau2	=	-.508835
% 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 # (2,3)	=	0.14
With Knapp-Hartung modification	Prob > F	=	0.8726

logrr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
participantregionew1	-.010555	.1797495	-0.06	0.954	-.4356955 .4143845
participantregionew2	.0796745	.1944402	0.41	0.694	-.3801034 .5394224
_cons	-.9943218	.1371043	-6.49	0.514	-.4195166 .228930

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, wsize (selogrr) knapphartung reml
note: sexnew2 dropped because of collinearity
```

Meta-regression

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

D

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

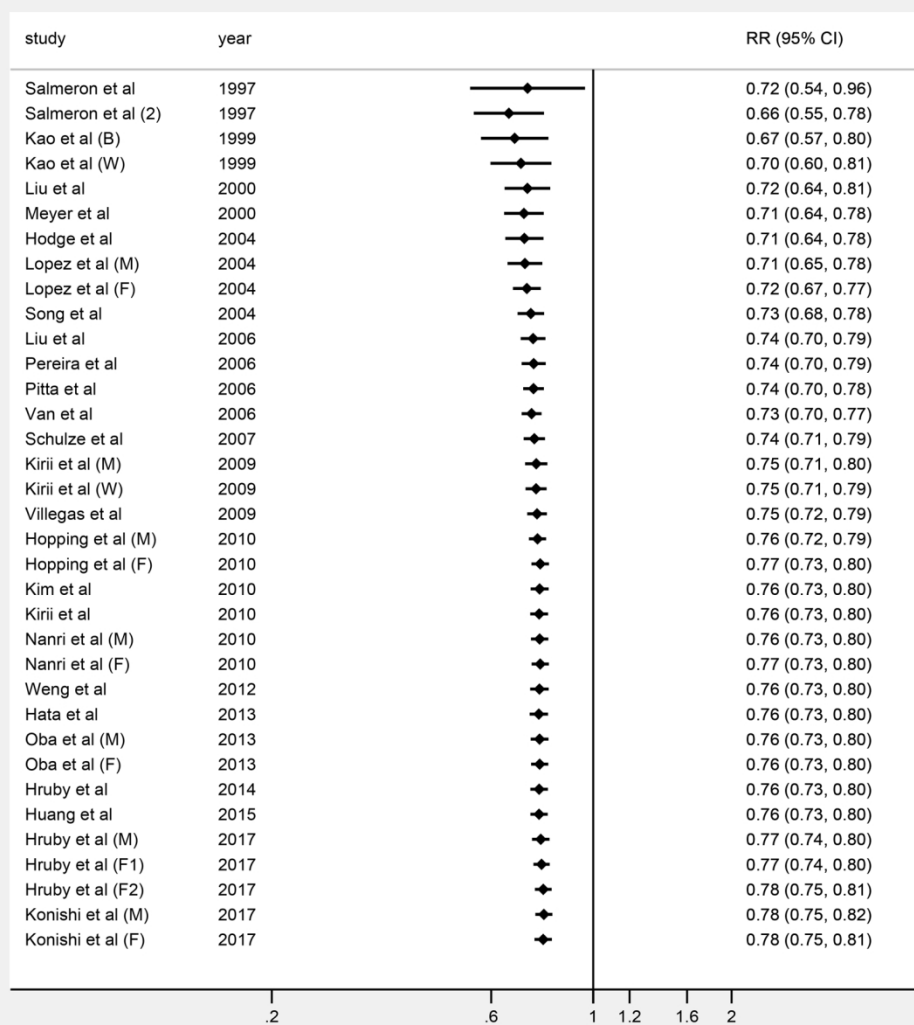
dietaryassessment	Freq.	Percent	Cum.
FFQ	4	40.00	40.00
validated FFQ	6	60.00	100.00
Total	10	100.00	

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

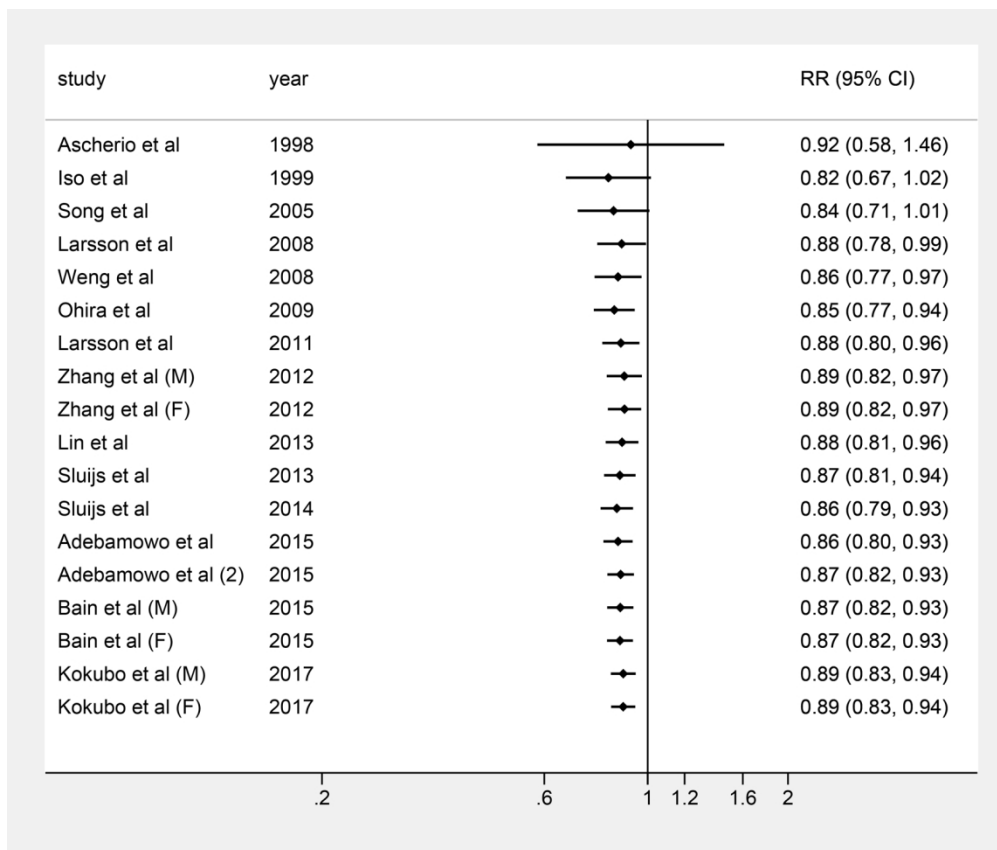
Meta-regression

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			

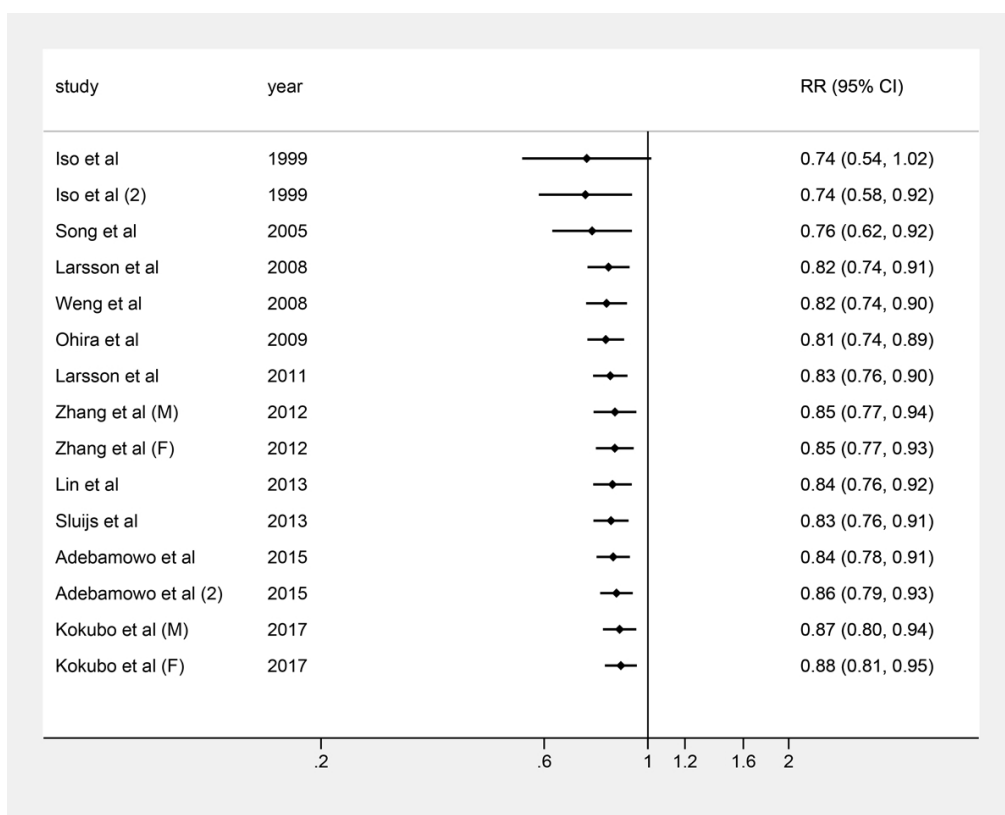
logrr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
dietaryassessmentnew1	.0642559	.1426454	0.45	0.644	-.2648051 .3911941
_cons	-.112665	.1133825	-0.99	0.349	-.2741255 .1487955



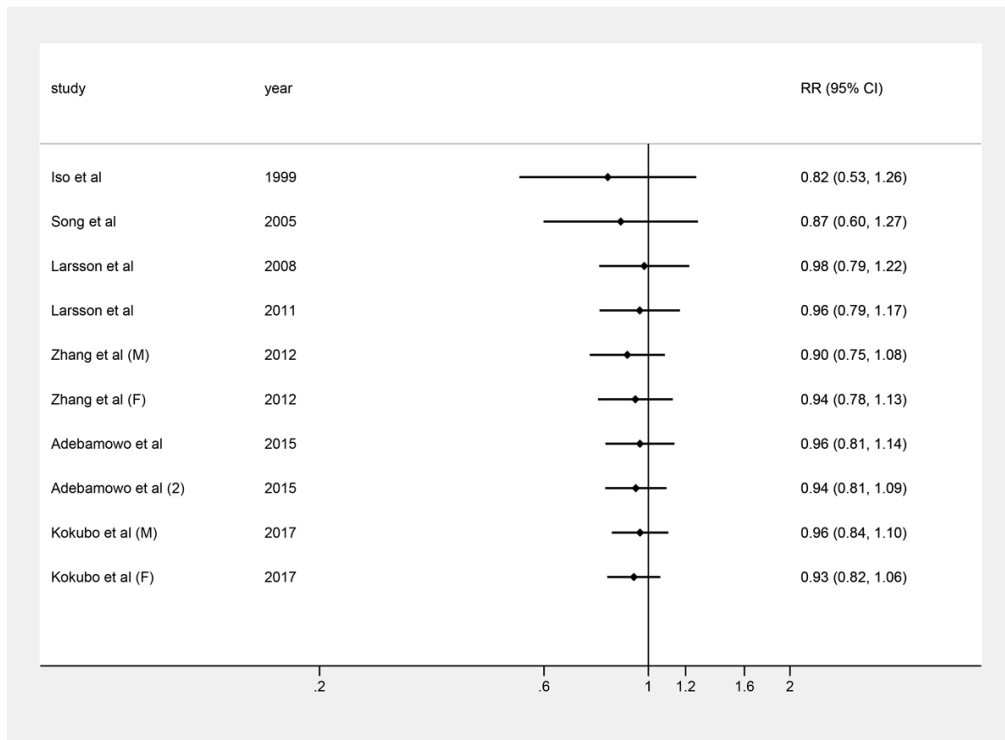
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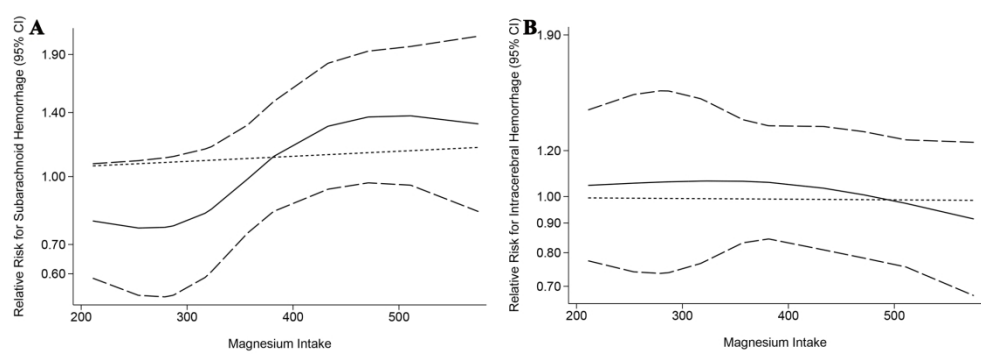




Table S1 PRISMA 2009 Checklist

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

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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.

BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032240.R1
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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
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1 **Magnesium intake has inverse association with type 2 diabetes and total stroke:**
2 **an updated systematic review and meta-analysis**

3 Binghao Zhao^{1,2}; Lianli Zeng^{3,4}; Jiani Zhao^{3,4}; Qian Wu^{3,4}; Yifei Dong³; Fang Zou⁵;
4 Li Gan⁶; Yiping Wei¹; Wenxiong Zhang¹.

5 **Affiliations**

6 ¹Department of Cardio-Thoracic Surgery, The Second Affiliated Hospital of
7 Nanchang University, Nanchang, China, 330006.

8 ²Departments of Neurosurgery, Peking Union Medical College Hospital, Chinese
9 Academy of Medical Sciences and Peking Union Medical College, Beijing, China,
10 100000.

11 ³Department of Cardiovascular Medicine, The Second Affiliated Hospital of
12 Nanchang University, Nanchang, China, 330006.

13 ⁴Jiangxi medical college, Nanchang University, 330006, Nanchang, China

14 ⁵Department of Endocrinology, The Second Affiliated Hospital of Nanchang
15 University, Nanchang, China, 330006.

16 ⁶Department of Neurology, The Second Affiliated Hospital of Nanchang University,
17 China, 330006.

18 **Corresponding Author:** Wenxiong Zhang, MD, Department of Cardio-Thoracic
19 Surgery, The Second Affiliated Hospital of Nanchang University, 1 Minde Road,
20 Nanchang, China, 330006; E-mail: zwx123dr@126.com; Phone: +8618720909414;
21 Fax: 0791-86133161.

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

23 **Word count:** 4971.

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4 **Abstract**

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

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

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

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21 **Eligibility criteria:** Prospective cohort studies about the two diseases

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

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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/m² body mass index, and those with \geq
12y follow-up, the reduced risk in Asia was not so conspicuous as in North America
and Europe.

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4 46 **Conclusions:** Magnesium intake has significantly inverse associations with T2D and
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6 47 total stroke in a dose-dependent manner. Feasible magnesium-rich dietary pattern
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9 48 may highly benefit specific populations, and can be highlighted in the primary
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12 49 prevention of T2D and total stroke by the public.

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14 50 PROSPERO registration number CRD42018092690
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18 19 52 **Strengths and limitations of this study**

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21
22 53 1. An inverse association between magnesium intake and T2D and stroke is
23
24 54 established.
25
26 55 2. Magnesium-rich food consumption may be recommended for high-risk individuals
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28 56 in dietary guidelines.
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30 57 3. Considerable evidence assists with innovation of the global dietary pattern.
31
32 58 4. Event ascertainment is limited by FFQ or self-reports.
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34 59 5. More individual-level studies are required for reducing potential bias.
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40 61 **Keywords:** Magnesium Intake; Type 2 Diabetes; Stroke; Meta-Analysis.
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62 **Introduction**

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

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

74 Actually, many adults in developed countries do not successfully meet the
75 recommended daily consumption of magnesium-rich foods such as whole grains, nuts,
76 and green leafy vegetables, and magnesium is less mentioned in dietary guidelines
77 and in studies about T2D or stroke prevention^{9,10}. With this regard, we chose T2D and
78 stroke as our outcome of interest (cardiovascular disease (CVD) was not elaborated
79 because there are so many items relating to CVD and the definitions about CVD
80 varied a lot among searched studies, which would enhance heterogeneity in the pooled
81 process and impair our interpretation of the final conclusion). And, emerging
82 studies¹¹⁻⁵¹ on this topic are limited, and the results still remain mixed, for example,
83 most of the studies support magnesium intake has inverse association with T2D or

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4 84 total stroke incidence, however, several studies reveal there is an inverse trend but not
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6 85 significant association, which possibly due to the limitations of small sample sizes and
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9 86 differences in intervention duration, study design, characteristics of participants.
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11 87 Moreover, consecutive meta-analyses^{52,53} have used less rigorous inclusion, the results
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14 88 were incomprehensive, and they did not completely address the influence of other
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17 89 confounders (i.e., body mass index (BMI), cereal fiber, calcium, potassium) on the
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20 90 relationship. Accordingly, we performed a meta-analysis to (1) establish a
21
22 91 comprehensive estimate and update the epidemiological evidence for clinical practice;
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25 92 (2) discuss the results of stroke subtype and the impact of several statistical and
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27 93 epidemiology confounders on the investigated association; and (3) highlight a detailed
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30 94 dose-response pattern for the participants in the studies analyzed.
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35 96 **Methods**

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38 97 This study was reported according to the Preferred Reporting Items for Systematic
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40 98 Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**) and the Meta-analysis
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42 99 of Observational Studies in Epidemiology (MOOSE) Guidelines Checklist (**Table S2**)
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45 100 (Registration information: PROSPERO CRD42018092690).
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102 102 **Search Strategy**

103 103 PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were
104 104 systematically reviewed through inception to March 15, 2019 for studies about
105 105 magnesium intake and T2D or stroke without language restrictions. The following key
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4 106 words were used: “Magnesium”, “Type 2 Diabetes Mellitus”, “Type 2 Diabetes”,
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6 107 “Stroke”, “Cerebrovascular Stroke”, “Cohort Studies”, and “Prospective Studies”. We
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9 108 also manually searched the reference lists of the retrieved literature (including
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11 109 meta-analyses and brief reports), bibliographies and gray literature (including
12
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14 110 presentations and unpublished literature) for further eligible articles. The search
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16
17 111 strategy could be found in **Table S3**.

112 113 **Selection Criteria**

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

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

127

128 **Data Extraction and Quality Assessments**

129 Two researchers independently extracted the following information: the first author,
130 publication year, period of cohort studies, duration of persistent exposure, basic
131 characteristics of the enrolled participants (weight, age, region, BMI, drinking and
132 smoking habits (previous plus current), etc.), median magnesium intake for each
133 quantile (tertile, quartile, or quintile), diabetes and total stroke cases, subtypes of total
134 stroke, dietary and case assessments, adjusted confounding covariates. Importantly,
135 total stroke is classified as clinical ischemic stroke (87%), hemorrhagic stroke (13%)
136 and undetermined stroke⁵⁴. Hemorrhagic stroke is classified as subarachnoid
137 hemorrhage and intracerebral hemorrhage according to anatomical site or presumed
138 etiology⁵⁵. In cases of continuing disagreement, a final decision was reached after
139 discussion with a third member of the panel.

140 Methodological quality was described by the Newcastle-Ottawa Scale (NOS),
141 which was validated for assessment of the quality of nonrandomized controlled trials
142 in meta-analyses⁵⁶. As for 0-10 scale, each study was categorized as low (0-5),
143 medium (6-7), of high (8-10) quality.

145 **Statistical Analysis**

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

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4 150 T2D, total stroke and other wanted outcomes, particularly for the highest vs. the
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7 151 lowest categories of magnesium intake were estimated by DerSimonian-Laird random
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9 152 effects model because the assumptions involved account for the presence of
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11 153 within-study and between-study variability. Statistical heterogeneity was determined
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14 154 with the Cochran Q chi-square test and the I^2 . An $I^2 > 50\%$ or a P value for the Q test
15
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17 155 < 0.1 was considered to indicate significant heterogeneity⁵⁷. We performed sensitivity
18
19
20 156 analyses to test the robustness and post-subgroup analyses to detect source of
21
22 157 heterogeneity. In addition, a random-effects meta-regression analysis on BMI, sex,
23
24 158 participants region, and dietary assessments with RR for each trial was performed to
25
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27 159 obtain an understanding of the reasons for heterogeneity. RR and 95% CI might begin
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30 160 to significantly change as publication years increased in T2D and total stroke etc.,
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33 161 which would be validated by cumulative meta-analyses.

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35 162 The dose-response analyses for all outcomes were proposed by Greenland and
36
37 163 Longnecker⁵⁸ and Orsini⁵⁹ et al. The categories of magnesium intake, distributions of
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40 164 cases and person-year, RR and 95 CI were extracted. Once the number of cases and/or
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43 165 person-years was not available, variance-weighted least squares regression was used
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46 166 to pool the risk estimate. For most studies, the median intake for each quantile (tertile,
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48 167 quartile or quintile) of magnesium intake was assigned as the representative dose. For
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51 168 continuous intake reported as category data with a range in some studies, we assigned
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54 169 the mid-point category of the lower and upper bound to the RR in these studies; when
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56 170 the highest category was open ended, we assumed the length of the open ended
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59 171 interval to be 1.5 times as the adjacent interval; when the lowest category was open,
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4 172 we assigned the adjacent interval of the category to be 1.5 times as the length of the
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7 173 open ended interval. We determined generalized least squares regression models to
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10 174 calculate study-specific RR estimates per 50 mg/day, 100 mg/day, and 150 mg/day of
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12 175 magnesium intake increment if there was evidence for linear relationships. In addition,
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14 176 the non-linear relationships between magnesium intake and all outcomes were
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17 177 evaluated using restricted cubic splines with four knots located at the 5th, 35th, 65th,
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19 178 and 95th percentiles of the distribution. The P value for curve linearity or non-linearity
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22 179 was calculated by testing the null hypothesis that the coefficient of the second spline
23
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25 180 is equal to zero. All results were presented using two-stage dose-response model plots
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28 181 (including linear and nonlinear relationships).Some results were demonstrated in
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30 182 forest plots for < 50 mg/day, ≥ 50 and < 100 mg/day, ≥ 100 and < 150 mg/day, ≥ 150
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33 183 mg/day increments.

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35 184 Publication bias was assessed graphically by Begg's adjusted rank correlation
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38 185 funnel plots⁶⁰ and Egger's linear regression tests⁶¹. All analyses were performed using
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41 186 Stata version 14.0 (StataCorp, College Station, TX, USA); two-sided $P < 0.05$ was
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44 187 considered statistically significant except where otherwise specified.

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47 48 189 **Patient and Public Involvement**

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51 190 No patients were involved in setting the research question or the outcome measures,
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54 191 and no patients were involved in developing plans for design or implementation of the
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57 192 study. Furthermore, no patients were asked to advice on interpretation or writing up of
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60 193 results. Since this study used aggregated data from previous publications, it is not easy

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4 194 to disseminate the results of the research to study participants directly.
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8 9 196 **Results**

10 11 12 197 **Study Characteristics and Quality Assessment**

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14 198 Of the total 8713 studies, 107 studies were considered for eligibility after screening of
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17 199 titles and abstracts (**Figure 1**). And a total of 41¹¹⁻⁵¹ prospective cohort studies
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20 200 involving 53 cohorts, 1 912 634 participants and 76 678 cases were eligible for
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22 201 current systematic review and meta-analysis (**Table S4**). Hodge et al¹⁸ only recorded
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25 202 500 mg/day increment of magnesium for further pooled analyses; 2 studies^{33,51} failed
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27 203 to clearly distinguish the diabetes type, but the great majority of cases had T2D. We
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30 204 computed the subtype data in three studies^{14,27,36} after the extraction of total stroke,
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33 205 and we considered ischemic stroke in three other studies^{28,30,42} as total stroke given
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35 206 ischemic stroke accounting for nearly 87% of total stroke. Participants were
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38 207 predominately middle-age at baseline, with mean magnesium intake for the highest
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41 208 category of 370 mg/day, mean for the lowest category of 232 mg/day. The mean
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43 209 duration of all eligible studies was 10.7 years. Nineteen studies were conducted in
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46 210 North America (America); 5 studies were in Europe (Sweden, the Netherlands and
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48 211 Britain); 13 studies in Asia (China and Japan and Taipei); 4 studies enrolled
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51 212 individuals in multiple nations. Most of the studies included used food frequency
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53 213 questionnaires (FFQs) or semi-quantitative FFQs (SFFQs) to assess individual dietary
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56 214 intake. Eighteen studies used dietary magnesium intake, and 21 studies recorded total
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59 215 magnesium intake (dietary and supplementary magnesium intake). Of note,
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4 216 supplementary magnesium intake was assessed from the use of magnesium or
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7 217 multivitamin supplements; nevertheless, dietary magnesium accounted for the
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9 218 majority of magnesium intake. Adjusted confounders were mostly similar; however,
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12 219 adjusted dietary confounders such as cereal fiber, potassium, and calcium still varied
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15 220 across individual studies. It was unclear whether included studies had adjusted for
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17 221 sodium because they did not provide the information. All these studies were written in
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20 222 English.

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22 223 After the quality assessments of the studies according to NOS, the average score was
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25 224 8.85 (**Table S5**) and all studies were of high quality (NOS score 8-10).
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27 28 29 30 226 **Magnesium Intake and T2D Incidence**

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32 227 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
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35 228 participants and 56 540 T2D cases) reported the magnitude of the risk of T2D was
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38 229 reduced by 22% (RR, 0.78 [95% CI, 0.75-0.81]; $P < 0.001$; AR reduction, 0.120%)
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41 230 comparing the highest category of magnesium intake to the lowest with a little
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43 231 evidence of heterogeneity ($I^2 = 35.6%$; $P = 0.021$). The dose category-specific
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45 232 analysis suggested that for < 50 mg/day magnesium increment, the risk of T2D was
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48 233 reduced by 10% (RR, 0.90 [95% CI, 0.88-0.93]; $P < 0.001$); for ≥ 50 and < 100
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51 234 mg/day, the risk was decreased by 16% (RR, 0.84 [95% CI, 0.82-0.87]; $P < 0.001$);
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54 235 for ≥ 100 and < 150 mg/day, the risk was reduced by 22% (RR, 0.78 [95% CI,
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56 236 0.74-0.83]; $P < 0.001$); and for ≥ 150 mg/day, the risk was reduced by 21% (RR, 0.79
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58 237 [95% CI, 0.74-0.84]; $P < 0.001$) (**Figure 2**). Little evidence of publication bias was
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4 238 found (Egger's test: $P = 0.088$) (**Figure S1A**).

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8 9 240 **Magnesium Intake and Stroke Incidence**

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12 241 Eighteen cohorts from 15 publications^{13,14,21,27,28,30,36,38,40,42,44-47,50} (692 998

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14 242 participants and 20 138 total stroke cases) reported the magnitude of the risk of total

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17 243 stroke was decreased by 11% (RR, 0.89 [95% CI, 0.83-0.94]; $P < 0.001$; AR

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20 244 reduction, 0.281%) with no heterogeneity ($I^2 = 0\%$; $P = 0.529$) in the highest category

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22 245 of magnesium intake VS. the lowest. Dose category-specific analysis identified no

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24 246 significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and $<$

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27 247 150 mg/day of increments. For the ≥ 150 mg/day increment, the risk of total stroke

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30 248 was decreased by 15% (RR, 0.85 [95% CI, 0.79-0.91]; $P < 0.001$) (**Figure S2**).

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33 249 Publication bias was evaluated for stroke subtypes respectively.

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35 250 Fifteen cohorts from 12 publications^{14,21,27,28,30,36,38,40,42,45,46,50} reported ischemic

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38 251 stroke. The magnitude of the risk of ischemic stroke was reduced by 12% (RR, 0.88

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41 252 [95% CI, 0.81-0.95]; $P = 0.001$; AR reduction, 0.246%) with no significant

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43 253 heterogeneity ($I^2 = 16.9\%$; $P = 0.265$). Dose category-specific analysis identified no

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45
46 254 significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and $<$

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48
49 255 150 mg/day increments. A trend to decrease existed but remained insignificant. The

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51 256 original risk was reduced by 16% in the analysis of the ≥ 150 mg/day increment (RR,

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54 257 0.84 [95% CI, 0.78-0.91]; $P < 0.001$) (**Figure S3**). No publication bias was observed

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56
57 258 in terms of ischemic stroke (Egger's test: $P = 0.937$) (**Figure S1B**).

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59 259 Ten cohorts from 8 studies^{14,21,27,36,38,45,46,50} reported that hemorrhagic stroke was

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4 260 not significantly associated with magnesium intake (RR, 0.93 [95% CI, 0.82-1.06]; P
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6 261 = 0.282). Dose category-specific analysis identified no significant association (**Figure**
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9 262 **S4**). No significant heterogeneity or publication bias were identified with regard to
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11 263 hemorrhagic stroke (Egger's test: $P = 0.809$) (**Figure S1C**).

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14 264 Three publications involving 3 cohorts^{14,27,36} showed that high magnesium intake
15
16 265 had no significant efficacy in reducing subarachnoid hemorrhage risk (RR, 0.99 [95%
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18 266 CI, 0.71-1.39]; $P = 0.963$). Dose category-specific analysis identified no significant
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20 267 association (**Figure S5**).

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24 268 With respect to intracerebral hemorrhage, the pooled results from 3 cohorts^{14,27,36}
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26 269 in 3 publications revealed no significant advantages of intracerebral hemorrhage (RR,
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28 270 0.92 [95% CI, 0.71-1.20]; $P = 0.540$). Dose category-specific analysis identified no
29
30 271 significant association (**Figure S6**).

272 273 **Meta-Regression and Cumulative Meta-Analysis**

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275 274 Meta-regression identified no evidence of BMI, sex, participant region and dietary
276
277 275 assessment for each individual trial bias in T2D (**Figure S7**), total stroke (**Figure S8**),
278
279 276 ischemic stroke (**Figure S9**) and hemorrhagic stroke events (**Figure S10**). The male
280
281 277 subgroup ($P = 0.041$) in the sex category might cast little heterogeneity on total stroke;
282
283 278 however, the sex category ($P = 0.112$) had no association with total stroke incidence.

284
285 279 Analyses on T2D (**Figure S11**), total stroke (**Figure S12**) and ischemic stroke
286
287 280 demonstrated that the RRs of the final results became robust within a narrow range
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289 281 and remained significant as publication years increased and as recent high quality
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4 282 studies were included. After inclusion of the Iso et al¹⁴ study, the RR and 95% CI for
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6 283 ischemic stroke decreased to less than 1 and became stable (**Figure S13**). Although
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9 284 there was no significantly reduced risk in hemorrhagic stroke, clear evidence showed
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11 285 that the confidence interval was becoming narrow, which had a trend toward
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14 286 significance (**Figure S14**). Thus, risk for hemorrhagic stroke might be reduced, and
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17 287 further studies are still needed.
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289 **Sensitivity Analysis**

290 When three²⁴⁻²⁶ studies were excluded in T2D analysis, the summary RR changed
291 from 0.78 ([95% CI, 0.75-0.81]) to 0.78 ([95% CI, 0.75-0.82]) with the heterogeneity
292 declining from ($I^2 = 35.6\%$; $P = 0.021$) to ($I^2 = 24.0\%$; $P = 0.112$). Among T2D
293 analysis, eight studies^{19,22,23,26,33,39,48,49} adjusted for cereal fiber intake yield an RR of
294 0.79 ([95% CI, 0.73-0.85]; $P < 0.001$) and two studies^{15,35} for calcium yielded an RR
295 of 0.87 ([95% CI, 0.73-1.04]; $P = 0.128$). While among total stroke analysis, the
296 summary RR was 0.92 ([95% CI, 0.82-1.02]; $P = 0.097$) in five studies^{13,44-46,50}
297 adjusted for potassium intake and was 0.89 ([95% CI, 0.80-0.99]; $P = 0.040$) in five
298 studies^{14,44-46,50} adjusted for calcium. Only one study¹⁵ adjusted for potassium intake
299 in T2D, one study³⁶ for cereal fiber in total stroke.
300

301 **Subgroup Analysis**

302 Stratified analyses by characteristics of the population and study design were
303 conducted on T2D (**Table 1**), total stroke, ischemic stroke and hemorrhagic stroke
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4 304 (**Table 2**). The inverse association with T2D remained robust across all subgroups
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7 305 with little evidence of heterogeneity. As for stroke incidence, a decreased risk of total
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10 306 stroke and ischemic stroke was found in female participants (RR, 0.91 [95% CI,
11
12 307 0.83-0.99] for total stroke; 0.89 [95% CI, 0.79-1.00] for ischemic stroke) and
13
14 308 individuals with ≥ 25 kg/m² mean BMI (RR, 0.89 [95% CI, 0.82-0.96] for total stroke;
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16
17 309 0.88 [95% CI, 0.81-0.96] for ischemic stroke). When restricted to a ≥ 12 y follow-up,
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20 310 the risk of total stroke and ischemic stroke could be significantly reduced (RR, 0.89
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22 311 [95% CI, 0.83-0.95] for total stroke; 0.88 [95% CI, 0.81-0.95] for ischemic stroke).
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25 312 These risks were more reduced in North American and European individuals than
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28 313 Asians. Cardiovascular events (CV events, coronary heart disease, heart failure, atrial
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30 314 fibrillation, and self-reported heart disease etc. other than stroke),
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33 315 hypercholesterolemia and diabetes would blunt the effect of magnesium on total and
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36 316 ischemic stroke. However, magnesium intake could still, or at least, demonstrate the
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39 317 trend to decrease total and ischemic stroke in individuals even with those risk factors.
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42 318 Similarly, CV events, hypercholesterolemia and family diabetes history had no
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45 319 substantial impact on the inverse association between T2D incidence and magnesium
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48 320 intake. We did not find significantly reduced risk in hemorrhagic stroke across the
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51 321 subgroup analyses.

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323 **Dose-Response Analysis**

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56 324 In this part, both linear and nonlinear relationships were found in T2D (**Figure 3A**), in
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59 325 total stroke (**Figure 3B**), and in ischemic stroke (**Figure 3C**). However, no linear or
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4 326 non-linear dose-response relationship was observed in hemorrhagic stroke (**Figure 3D**)
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6 327 along with the subtypes including subarachnoid hemorrhage and intracerebral
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9 328 hemorrhage (**Figure S15**).

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11 329 Specifically, we calculated RR for the magnesium increments if there was linear
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14 330 relationship found. The calculated RR was 0.94 ([95% CI, 0.93-0.95]) for the 100
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17 331 mg/day increment for T2D. For total stroke, the summary RR was 0.98 ([95% CI,
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19 332 0.97-0.99]) related to 100 mg/day increment in magnesium intake, RR for ischemic
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22 333 stroke was 0.98 ([95% CI, 0.97-0.99]) related to 100 mg/day increment in magnesium
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25 334 intake. There was no RR cut-off point at which the decreasing trend reversed, but the
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28 335 RR decreased a bit rapidly with any slightly decreases at approximately 260 mg/day
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31 336 for T2D and 350 mg/day for total/ischemic stroke. But there was substantial
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33 337 uncertainty in the lower range of this distribution (**Figure 3A, 3B, 3C**).

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37 339 **Discussion**

40 340 **Main findings**

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43 341 This paper used a general and up-to-date search strategy to identify some additional
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46 342 studies that were missed in prior meta-analyses under real-world conditions. Our
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49 343 results support a significant inverse association between magnesium consumption and
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52 344 T2D, total stroke and ischemic stroke at the highest level vs. the lowest. No
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55 345 significant association for hemorrhagic stroke, subarachnoid hemorrhage and
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58 346 intracerebral hemorrhage was detected. Female obese participants (mean BMI \geq 25
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60 347 kg/m²) with longer follow-up period (\geq 12 y) might obtain a greater benefit from

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4 348 magnesium intake with a lower risk of total and ischemic stroke incidence. In
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6 349 subgroup analyses, RR of stroke risk was highly decreased among North American
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9 350 and European individuals. Significant risk reduced by 6%, 2%, and 2% for T2D, total
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11 351 stroke and ischemic stroke respectively at per 100 mg/day increment in magnesium
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14 352 intake level. Overall, our study supports the guidelines to address the role of
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17 353 magnesium intake for T2D and stroke early prevention. Even though, we still require
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19 354 more randomized controlled trials (RCTs) in the future to validate the causality.
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356 **Clinical implications**

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

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4 370 in which cumulative meta-analysis was performed to forecast the changing tendency
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6 371 of main risk estimates. Based on past and current cutting edge evidence about
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9 372 nutrition and T2D prevention, the US Diabetes Prevention Program (DPP) conducted
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11 373 a study that demonstrated that proper lifestyle modification (exercise and
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13 374 Mediterranean diet) significantly reduced T2D risks irrespective of population
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15 375 baselines, and the benefit expanded with increased follow-up⁶⁴. The UK national
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17 376 health service (UK NHS) will launch an intervention program including weight loss,
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19 377 nutrition, monitoring and peer support targeting up to 10 000 people prone to develop
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21 378 T2D⁶⁵.

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27 379 2018 American Diabetes Association (ADA) guidelines⁶⁶ recommend to enhance
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29 380 intake of nuts, berries, yogurt, coffee and tea in individuals who are at high risk of
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31 381 diabetes. The latest guidelines by the American Heart Association (AHA)/American
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33 382 Stroke Association (ASA)⁹ also validate considerable status of early management of
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35 383 stroke (ischemic stroke). In fact, magnesium is a cofactor of enzyme systems that
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37 384 regulate diversity biomedical reactions including protein synthesis, muscle and nerve
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39 385 transmission, neuromuscular conduction, signal transduction blood glucose control
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41 386 and blood pressure management⁶⁷. Magnesium played a role in transporting calcium
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43 387 and potassium ions across cell membrane, also is crucial for structural function of
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45 388 proteins, nucleic acids or mitochondria⁶⁸. In diabetes, magnesium achieves glucose
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47 389 and insulin metabolism through tyrosine kinase activity of the insulin receptor, intake
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49 390 of magnesium also influences phosphorylase B kinase activity by releasing
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51 391 glucose-1-phosphate from glycogen. Magnesium regulates glucose translocation into
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4 392 the cell⁶⁹. In stroke higher magnesium level deregulates glutamate and calcium cation
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6 393 influx by reducing NMDA receptor activity, and blocks voltage-gated calcium
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9 394 channel eliminating calcium cation cytotoxicity. Additionally, magnesium has
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11 395 vasodilatory effect which may do benefit to ischemic stroke patients⁷⁰. In deed, a poor
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14 396 outcome on hemorrhagic stroke was observed in a RCT, however, high serum
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17 397 magnesium might be better for intracerebral hemorrhage prognosis⁷¹.

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19 398 Most specific nutrients especially macronutrients are correlated with total energy
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22 399 intake. In included free-living human studies, variation of total energy intake is
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24 400 originated from physical activity, differences in body size, and differences in energy
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27 401 efficiency⁷². Thus total energy intake can weaken the investigated association with
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30 402 considerable nutrients intake if this covariable is not properly removed.
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32 403 Epidemiologists should assess reproducibility and validity of energy-adjusted
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35 404 nutrients as well as absolute nutrients intake. Though micronutrient as magnesium is,
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38 405 inverse association could be still found in T2D, total stroke and ischemic stroke
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41 406 outcomes after total energy intake adjustment. As for other nutrients, potassium intake
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43 407 is proposed to lower blood pressure (BP) and improve vascular outcomes (including
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46 408 stroke); dietary potassium may also be influential in glucose control and limiting the
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48 409 risk of diabetes⁷³. Vitamin D and calcium may negatively influence glycemia, but the
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51 410 evidence is limited for mostly being based on cross-sectional observational studies⁷⁴.
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53 411 Calcium may be inversely associated with stroke in populations with low to moderate
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56 412 calcium intakes, but no significant association was found between calcium and CVD⁷⁵.
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58 413 All things considered, magnesium-rich food such as nuts (151-567 mg/100g edibles),
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4 414 fruits (132-448 mg/100g edibles), vegetables (132-1257 mg/100g edibles), legumes
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6 415 (138-243 mg/100g edibles), fish (143-303 mg/100g edibles) and total grain (134-306
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9 416 mg/100g edibles) should be recommended to populations with insufficient magnesium
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11 417 intake.

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17 419 **Compared with other similar studies**

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19 420 This seminar has several differences with previous studies. Dong et al⁵² found
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21 421 magnesium intake had an inverse association with T2D incidence (RR, 0.78 [95% CI,
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23 422 0.73-0.84]), and with an intake of 100 mg/day magnesium, the risk was reduced by
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25 423 14%. In fact, they failed to include adequate studies, and standard quality assessments
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27 424 of eligible studies were absent. Individuals from multiple nations in some
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29 425 studies^{18,25,26,32} were incorrectly assigned to Asia or the U.S. in the subgroups, and
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31 426 minor imperfections existed in the selection criteria because it was unclear whether
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33 427 they excluded participants with subclinical diabetes. BMI was not a potential modifier
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35 428 for T2D in our study due to the inclusion of more evidence which had longer
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37 429 follow-up period. Fang et al⁷⁶ revealed dietary magnesium was significantly
38
39 430 associated with reduced risk of T2D (RR, 0.74 [95% CI, 0.69-0.80]) and stroke (RR,
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41 431 0.88 [95% CI, 0.82-0.95]). The results were comparable, but they just focused on
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43 432 dietary magnesium intake rather than overall magnesium intake (total or dietary), and
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45 433 subtypes of total stroke were missed. To our overall knowledge, BMI, follow-up,
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47 434 family diabetes history, etc. were crucial confounders for evaluating the association,
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49 435 which were not addressed in their study. Moreover, researchers had better investigate
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4 436 the likelihood of linear association in the dose-response pattern (using methods by
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7 437 Greenland and Orsini et al). Fang et al⁷⁷ found that the 100 mg/day intake of dietary
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9 438 magnesium was associated with an 8-13% reduction in T2D risk, and while a
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12 439 nonlinear relationship did not exist, a minor publication bias was present. Twenty-five
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15 440 studies were eligible; however, some of them focused not on dietary but on total
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17 441 magnesium intake. Moreover, there were two included studies focusing on red meat
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20 442 intake instead of magnesium intake. After excluding actual ineligible studies, we
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23 443 found no evidence of publication bias. Additionally, both linear and nonlinear
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25 444 relationships existed for T2D, because the RRs of the highest category of magnesium
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27 445 intake VS. the lowest in our pooled study were still used. A study by Larsson et
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30 446 al⁵³including 7 studies supported a modest but statistically significant inverse
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33 447 association between dietary magnesium intake and stroke. The sample size was quite
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36 448 small, and there was no useful information for stroke subtypes (e.g., ischemic stroke,
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38 449 hemorrhagic stroke) in the main analysis. In our opinion, a well-designed subgroup
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41 450 analysis is a compulsory undertaking, and a pooled stroke result restricted by
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44 451 potassium and calcium adjustment is recommended. The current study found
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47 452 magnesium intake was strongly inversely associated with total stroke and ischemic
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50 453 stroke, which still existed in the dose-response pattern.

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53 455 **Directions for further research**

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56 456 Future studies still have something to be addressed. At first, no significant association
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59 457 was found in hemorrhagic stroke, however, the beneficial trend was observed in the
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4 458 cumulative meta-analysis, which addresses needs for more updated prospective
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7 459 studies and RCTs. Second, there is a key question regarding the optimal time to start
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9 460 prevention and methods to screen severe complications. Cardiovascular events occur
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11 461 in more than 50% and diabetic kidney disease occurs in 20-40% of patients with
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14 462 diabetes. Actually, cardiovascular events increase the risk of death three to four times
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17 463 compared with patients without such complications. A sustained period of intensive
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19 464 glucose control early in T2D has been confirmed to reduce complication rates⁷⁸. Most
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22 465 importantly, to the public, educators and guideline makers, boosting magnesium-rich
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25 466 food consumption relates to considerable benefits to T2D and total stroke prevention,
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27 467 especially in high-risk populations.
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31 32 469 **Limitations**

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35 470 Several limitations deserve further discussion. First, this group-level meta-analysis is
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37 471 insufficient. Although strong inverse associations for T2D and total stroke were
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40 472 reported, individual-level studies having more detection power are required. Second,
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43 473 several variations cannot be totally understood, for example, we cannot exclude the
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46 474 possibility that other nutrients and/or dietary components correlated with dietary
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48 475 magnesium may have been responsible, either partially or entirely, for the observed
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51 476 associations. Based on eligible studies, we could not quantify the impact of
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54 477 supplementary magnesium (not combined with dietary intake) on T2D and stroke
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56 478 incidence. The real effect of some dietary supplements on T2D or cardiovascular
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59 479 disease seems very interesting to a number of medical experts, clinicians and nutrition
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4 480 educators. Third, FFQs/validated FFQs mostly used in primary studies could not
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6 481 characterize all the nutrients, which misclarified plausible associations. It was
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9 482 suggested that magnesium specific food questionnaire and/or food records should be
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11 483 reasonably used for accurate magnesium intake estimation. Finally, we still required
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14 484 further RCTs, because observational studies might only reach the same conclusion
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16
17 485 (i.e., magnesium intake is inversely associated with T2D incidence) but could not
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19 486 prove causality.
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23 24 25 488 **Conclusion**

26
27 489 Magnesium intake has a substantial inverse association with T2D and total stroke.
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30 490 Among these populations, magnesium consumption can be recommended as an
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32 491 optimization for T2D, total stroke and ischemic stroke primary prevention or early
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35 492 management. In particular, the greater the magnesium intake, the more reduced risk is
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38 493 observed. As patients, physicians, policy makers and legislators debate on these issues,
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40 494 such a cost-effective alternative is needed to inform policy decisions and assist reform
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43 495 in global dietary health care.
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56 500 collection.
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4 502 **Competing interests**

5
6 503 None declared

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11 505 **Provenance and peer review**

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14 506 Not commissioned; externally peer reviewed.

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19 508 **Data availability statement**

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22 509 All data relevant to the study are included in the article or uploaded as supplementary
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24 510 information.

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29 512 **Patient consent for publication**

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32 513 Not required.

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36
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50
51 521 manuscript and takes responsibility for the integrity of the data and the accuracy of
52
53 522 the data analysis.

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55 523 Concept and design: All authors.

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57 524 Acquisition, analysis, or interpretation of data: All authors.

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59 525 Drafting of the manuscript: Binghao Zhao and Wenxiong Zhang.

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4 526 Critical revision of the manuscript for important intellectual content: Binghao Zhao,
5 527 Lianli Zeng, Jiani Zhao, Qian Wu, Fang Zou, Li Gan and Yifei Dong.

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7 528 Statistical analysis: Binghao Zhao.

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9 529 Supervision: Wenxiong Zhang and Yiping Wei

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Table 1 Subgroup Analysis relating to Magnesium Intake and Type 2 Diabetes (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/m²)	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 frequency questionnaire; 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;

765 ^c, Two studies reported total magnesium and dietary magnesium intake outcome;

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

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

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

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

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772 **Table 2.** Subgroup Analyses Relating to Magnesium Intake and Total Stroke, Ischemic Stroke, Hemorrhagic stroke.
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Group	Total Stroke				Ischemic Stroke				Hemorrhagic stroke			
	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}
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/m²)	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	

1	intake	7	(0.81-0.96)		6	(0.77-1.03)		3		
2	Total energy adjustment	15		0.888	12		0.689	8		0.538
3			0.87			0.86				
4	Yes	5	(0.77-0.99)	27.00	2	(0.78-0.94)	0.00	2	0.93 (0.82-1.06)	0.00
5	No	10	0.89	0.00	10	0.88	26.60	6	0.90 (0.76-1.07)	11.40
6	Difference between top and bottom intake (mg/day)^d		(0.83-0.96)			(0.79-0.99)				
7		15		0.107	12		0.180	8		0.244
8										
9	≥ 180	7	0.83	0.00	5	0.83	0.00	6	1.07 (0.83-1.37)	0.00
10			(0.76-0.91)			(0.76-0.91)				
11	< 180	8	0.93	0.00	7	0.92	26.20	2	0.89 (0.76-1.03)	0.00
12			(0.86-1.00)			(0.81-1.03)				
13	Current CV events status^e			0.074	12		0.393	8		NA
14	Yes	12	0.90	0.00	11	0.88	18.20	8	0.93 (0.82-1.06)	0.00
15			(0.85-0.96)			(0.81-0.96)				
16	Unknown	3	0.75	0.00	1	0.76	NA	0	NA	NA
17			(0.63-0.90)			(0.57-1.01)				
18	Hypercholesterolemia status^f			0.480	12		0.565	8		0.651
19	Yes	7	0.91	0.00	6	0.90	6.90	5	0.90 (0.76-1.08)	0.00
20			(0.83-0.99)			(0.80-1.01)				
21	Unknown	8	0.86	13.10	6	0.86	32.40	3	0.94 (0.72-1.22)	40.30
22			(0.79-0.95)			(0.77-0.97)				
23	Current diabetes status^g			0.039	12		0.159	8		NA
24	Yes	10	0.91	0.00	10	0.89	13.50	8	0.93 (0.82-1.06)	0.00
25			(0.82-0.97)			(0.82-0.97)				
26	Unknown	5	0.75	0.00	2	0.72	0.00	0	NA	NA
27			(0.64-0.88)			(0.56-0.92)				

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.

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3 **774 Figure Legends**
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5 **775 Figure 1.** Flow Chart for Literature Search and Screening Process
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7 **776 Figure 2.** Forest Plots for Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A)
8 and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and < 150 mg/day (D) and
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10 ≥ 150 mg/day Magnesium increments (E).
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14 **779 Figure 3.** Two-Stage Dose-Response Effect on the Relationships between Magnesium
15 Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and
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780 Hemorrhagic Stroke (D).
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3 782 **Supplementary material online:**
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5 783 **Table S1.** PRISMA 2009 Checklist
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7 784 **Table S2.** MOOSE Checklist
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9 785 **Table S3.** The complete search terms for Pubmed
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11 786 **Table S4.** Summary of Baseline Characteristics of Included Studies
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13 787 **Table S5.** Methodological Quality Assessments Of Studies Included With
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17 788 Newcastle-Ottawa Scales

18 789 **Figure S1.** Funnel Plots for Magnesium Intake and Type 2 Diabetes (A), Ischemic
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20
21 790 Stroke (B) and Hemorrhagic Stroke (C).
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23 791 **Figure S2.** Forest Plots for Risk of Total Stroke for Magnesium Intake (A) and for <
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26 792 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and ≥ 150
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28 793 mg/day Magnesium increments (E).
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30 794 **Figure S3.** Forest Plots for Risk of Ischemic Stroke for Magnesium Intake (A) and for
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33 795 < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and ≥ 150
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35 796 mg/day Magnesium increments (E).
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37 797 **Figure S4.** Forest Plots for Risk of Hemorrhagic Stroke for Magnesium Intake (A)
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40 798 and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and
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42 799 ≥ 150 mg/day Magnesium increments (E).
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44 800 **Figure S5.** Forest Plots for Risk of Subarachnoid Hemorrhage for Magnesium Intake
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47 801 (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D)
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49 802 and ≥ 150 mg/day Magnesium increments (E)
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51 803 **Figure S6.** Forest Plots for Risk of Intracerebral Hemorrhage for Magnesium Intake
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54 804 (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D)
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56 805 and ≥ 150 mg/day Magnesium increments (E)
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58 806 **Figure S7.** Meta-Regression of Relative Risk for Type 2 Diabetes According to Body
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3 807 Mass Index (A, $P = 0.716$), Sex (B, $P = 0.284$), Participant Region (C, $P = 0.904$) and
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5 808 Dietary Assessment (D, $P = 0.521$).

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8 809 **Figure S8.** Meta-Regression of Relative Risk for Total Stroke According to Body
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10 810 Mass Index (A, $P = 0.606$), Sex (B, $P = 0.112$), Participant region (C, $P = 0.891$) and
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12 811 Dietary Assessment (D, $P = 0.891$).

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15 812 **Figure S9.** Meta-Regression of Relative Risk for Ischemic Stroke According to Body
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17 813 Mass Index (A, $P = 0.631$), Sex (B, $P = 0.134$), Participant Region (C, $P = 0.584$) and
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19 814 Dietary Assessment (D, no regression P -value due to limited data).

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21 815 **Figure S10.** Meta-Regression of Relative Risk for Hemorrhagic Stroke According to
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23 816 Body Mass Index (A, $P = 0.418$), Sex (B, $P = 0.872$), Participant Region (C, $P =$
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25 817 0.872) and Dietary Assessment (D, no regression P -value due to limited data).

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28 818 **Figure S11.** Cumulative Meta-Analysis Related to Magnesium Intake and Type 2
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30 819 Diabetes (T2D)

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33 820 **Figure S12.** Cumulative Meta-Analysis Related to Magnesium Intake and Total
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35 821 Stroke

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38 822 **Figure S13.** Cumulative Meta-Analysis Related to Magnesium Intake and Ischemic
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40 823 Stroke

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42 824 **Figure S14.** Cumulative Meta-Analysis Related to Magnesium Intake and
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44 825 Hemorrhagic Stroke

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47 826 **Figure S15.** Dose-Response Effect on the Relationships between Magnesium Intake
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49 827 and Subarachnoid Hemorrhage (A) and Intracerebral Hemorrhage (B).

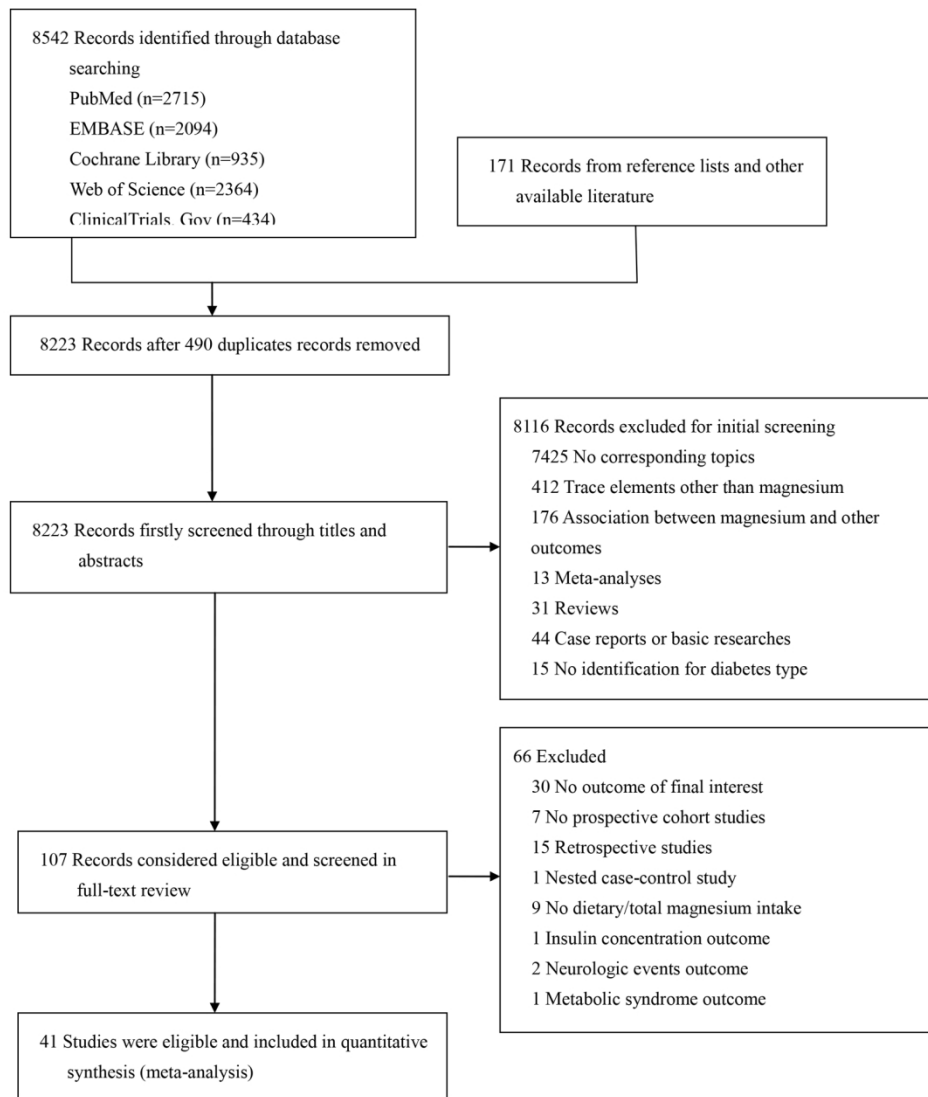


Figure 1. Flow Chart for Literature Search and Screening Process

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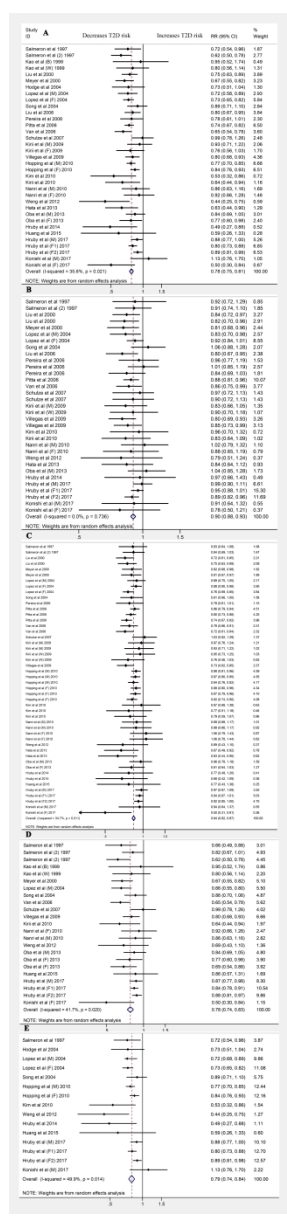


Figure 2. Forest Plots for Risk of Type 2 Diabetes (T2D) for Magnesium Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and < 150 mg/day (D) and ≥ 150 mg/day Magnesium increments (E).

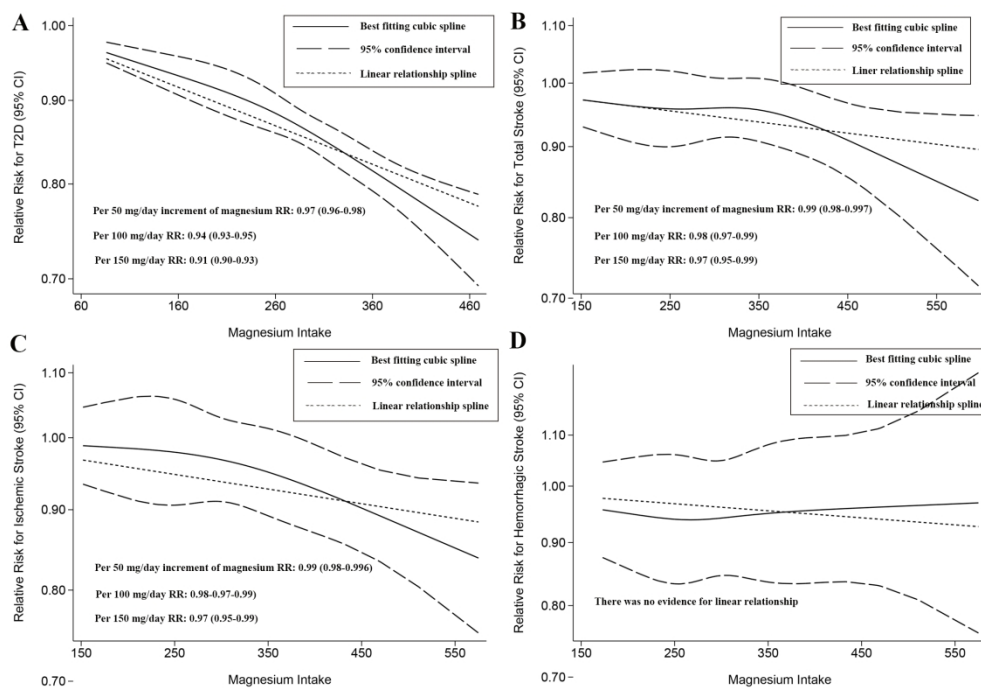


Figure 3. Two-Stage Dose-Response Effect on the Relationships between Magnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).



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

Page 1 of 2

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.

Page 2 of 2

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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))
Schulze 2007 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))

1	Nanri 2010 ³⁵	Japan	1990-1995	M; 40-65 y	NA	validated FFQ	self-reported questionnaire	634 T2D (25872)	348 VS. 213 (0.86 (0.63-1.16))
2				F; 40-65 y				480 T2D (33919)	333 VS. 213 (0.92 (0.66-1.28))
3	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))
4							follow-up examination or		
5	Weng 2012 ³⁷	Taipei	1993-2002	M/F; ≥30 y	24	validated FFQ	self-reported questionnaire	141 T2D (1604)	406 VS. 212 (0.44 (0.25-0.75))
6									
7	Zhang 2012 ³⁸	Japan	1988-2006/	M; 40-79 y	22.7	validated FFQ	follow-up examination	634 stroke (23083)	294 VS. 173 (1.03 (0.79-1.35))
8				F; 40-79 y	22.9			620 stroke (35533)	274 VS. 175 (0.90 (0.69-1.16))
9	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))
10							follow-up examination and		
11	Lin 2013 ⁴⁰	Taipei	1989-2002	M/F; ≥ 18 y	23.3	validated FFQ	self-reported questionnaire	123 stroke (2061)	378 VS. 210 (0.62 (0.40-0.97))
12									
13				M; 40-69 y	23.6			690 T2D (27769)	349 VS. 232 (0.84 (0.69-1.05))
14	Oba 2013 ⁴¹	Japan	1990-2000	F; 40-69 y	23.5	validated FFQ	self-reported questionnaire	500 T2D (36864)	356 VS. 211 (0.69 (0.54-0.88))
15									
16	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))
17	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))
18									
19	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))
20	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))
21									
22	Adebamowo 2015(2) ⁴⁶	USA	1976-2006	F; 30-55 y	26.4	validated FFQ	self-reported questionnaire	3237 stroke (86149)	411 VS. 233 (0.93 (0.79-1.08))
23									
24				F; 25-42 y	25.7			543 stroke (94715)	
25	Bain 2015 ⁴⁷	Britain	2002-2008	M; 40-75 y	26.5	7-day diary recall	follow-up examination	364 stroke (2000)	456 VS. 266 (0.81 (0.53-1.22))
26				F; 40-75 y	26.2			511 stroke (2445)	374 VS. 456 (0.82 (0.54-1.24))
27	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))
28									
29				F; 30-55 y	24.8			7620 T2D (69176)	390 VS. 229 (0.80 (0.73-0.88))
30	Hruby 2017 ⁴⁹	USA	1991-2013	F; 25-42 y	24.6	validated SFFQ	self-reported questionnaire	6080 T2D (91471)	424 VS. 249 (0.89 (0.81-0.99))
31									
32				M; mean 53.5 y	24.8			3430 T2D (42096)	469 VS. 280 (0.88 (0.77-1.00))
33	Kokubo 2017 ^{50b}	Japan	1990-2009	M; 40-69 y	23.6	FFQ	follow-up examination	2576 stroke (39505)	348 VS. 213 (1.07 (0.86-1.33))
34									
35				F; 40-69 y	23.6			1846 stroke (45788)	333 VS. 213 (0.88 (0.67-1.14))
36	Konishi 2017 ⁵¹	Japan	1992-2002	M; ≥35 y	22.6	validated FFQ	self-reported questionnaire	266 T2D (5885)	469 VS. 310 (1.13 (0.76-1.70))
37				F; ≥35 y	22.1			172 T2D (7640)	432 VS. 285 (0.50 (0.30-0.84))

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

38 ^a, different ethnicities of participants are in multiple nations cohort;

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

40 ^c the range of enrolled participants age is not mentioned.

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

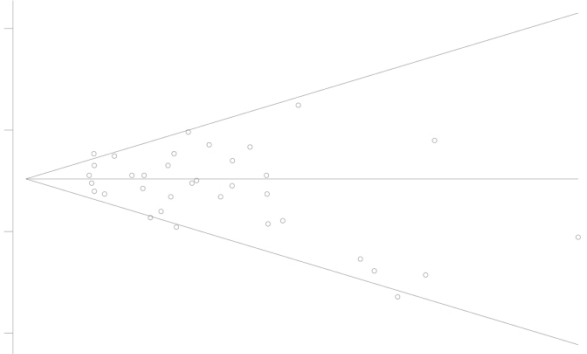
	Study	Selection				Comparability	Outcome			Total score
		Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
1997	Salmeron et al, ¹¹	*	*	*	*	**	*	*		9
1997	Salmeron et al (2), ¹²	*	*	*	*	**	*	*	*	9
1998	Ascherio 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

1	2013	Hata et al, ³⁹	*	*	*	*	**	*	*	*	9
2	2013	Lin et al, ⁴⁰	*	*	*	*	**	*	*	*	9
3	2013	Oba et al, ⁴¹	*	*	*	*	**	*	*	*	9
4	2013	Sluijs et al, ⁴²	*	*	*	*	**		*	*	8
5	2014	Hruby et al, ⁴³	*	*	*	*	**	*	*	*	9
6	2014	Sluijs et al, ⁴⁴	*	*	*	*	**	*	*	*	9
7	2015	Adebamowo et al, ⁴⁵	*	*	*	*	**	*	*	*	9
8	2015	Adebamowo et al (2), ⁴⁶	*	*	*	*	**	*	*	*	9
9	2015	Bain et al, ⁴⁷	*	*	*	*	**	*	*	*	9
10	2015	Huang et al, ⁴⁸	*	*	*		**	*	*	*	8
11	2017	Hruby et al, ⁴⁹	*	*	*	*	**	*	*	*	9
12	2017	Kokubo et al, ⁵⁰	*	*	*	*	**	*	*	*	9
13	2017	Konishi et al, ⁵¹	*	*	*	*	*	*	*	*	9

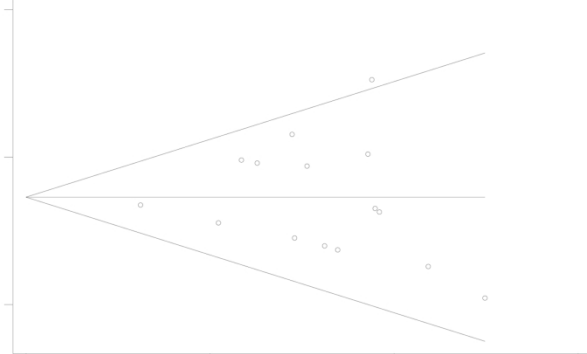
For peer review only

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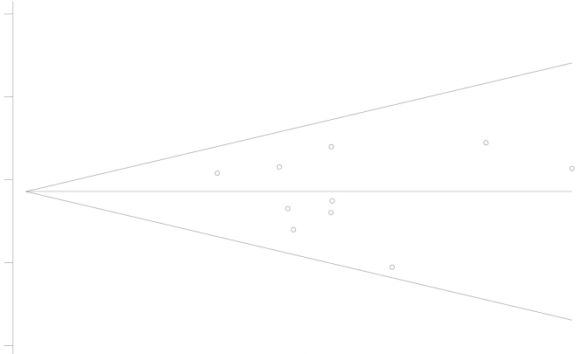
A funnel plot with pseudo 95% confidence limits



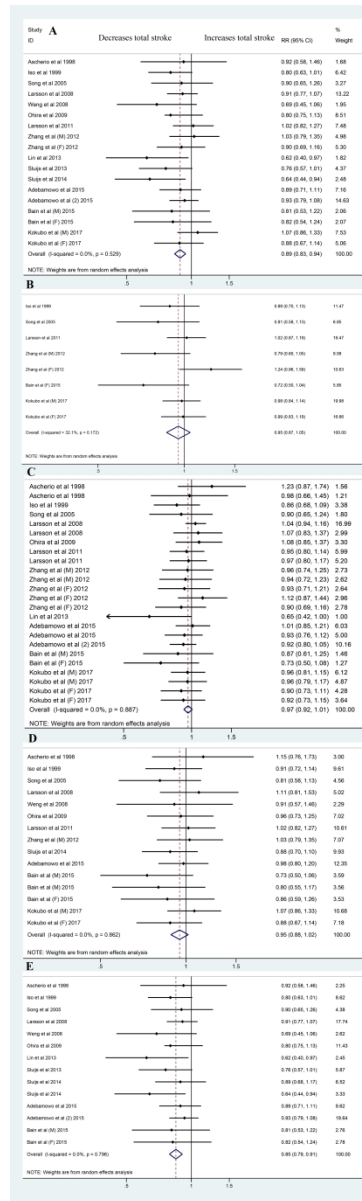
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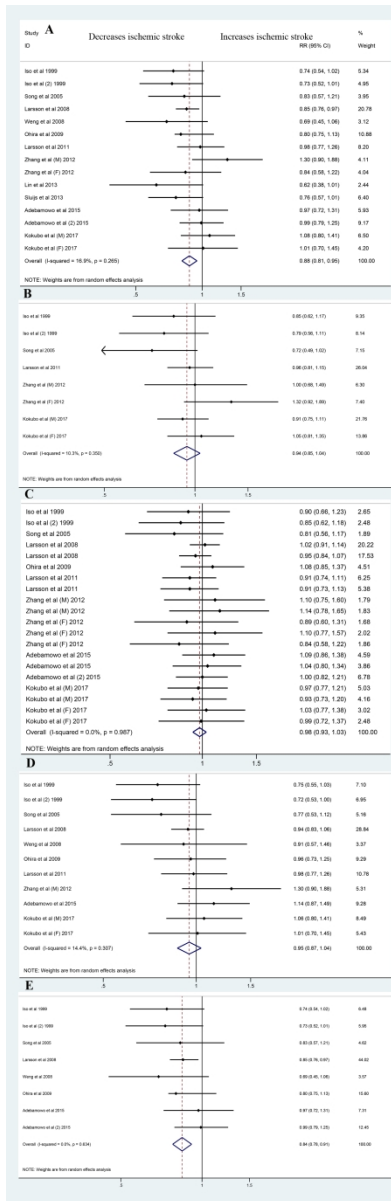
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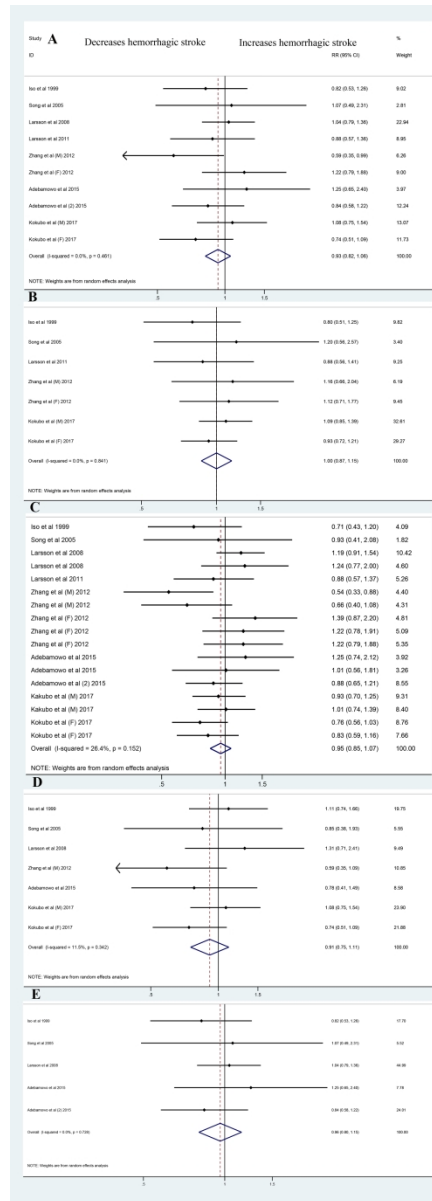
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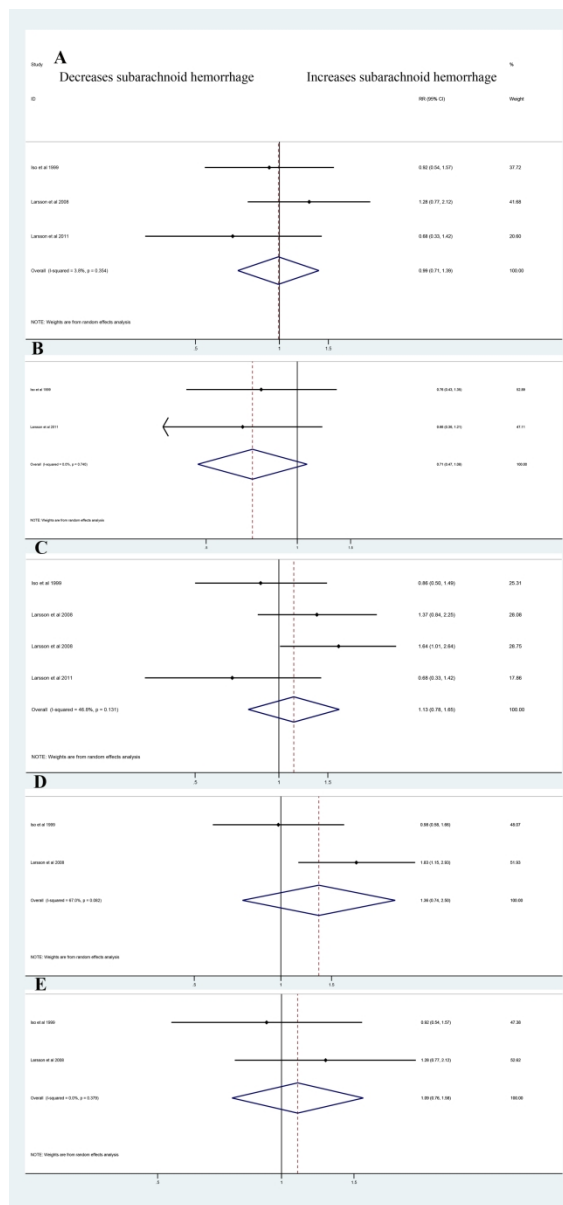
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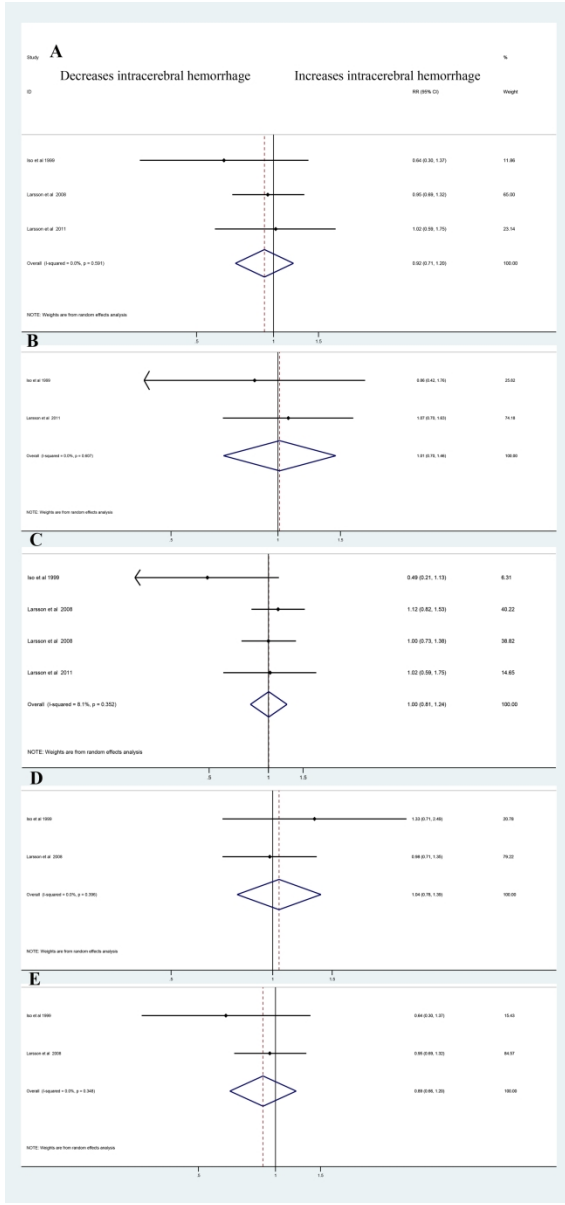
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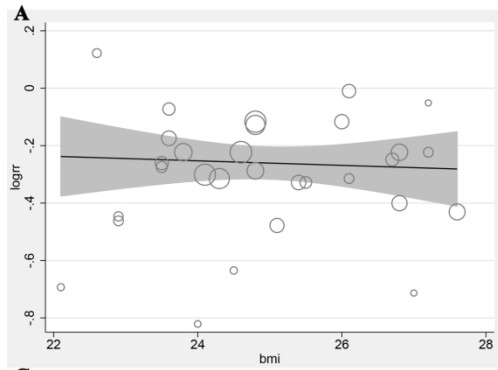


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B
. tabulate sex, generate ( sexnew )

      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, wsize (selogrr) knapphartung reml
note: sexnew3 dropped because of collinearity

Meta-regression              Number of obs =    35
RMSE 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    | -1.1314075  .0857798   -1.53  0.135  -1.3061323  -.0433174
sexnew2    | -0.630804   .0541113   -1.17  0.252  -1.733016  -.0471407
      _cons | -1.956565   .0461514   -4.24  0.000  -2.096637  -1.1016492
    
```

```

C
. tabulate participantregion, generate ( participantregionnew )

      participantregion | Freq.  Percent  Cum.
-----+-----
on                     |    35    100.00
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 participantregionnew1 participantregionnew2 participantregionnew3, wsize (selogrr) knapphartung reml
note: participantregionnew3 dropped because of collinearity

Meta-regression              Number of obs =    35
RMSE estimate of between-study variance      tau2 = .004698
% residual variation due to heterogeneity     I-squared_res = 35.22%
Proportion of between-study variance explained  Adj R-squared = -30.80%
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]
-----+-----
participantregionnew2 | .0027567  .0731865   0.04  0.970  -1.463193  .1518327
participantregionnew1 | -.001657  .0599158  -0.34  0.739  -1.422102  .1018788
      _cons         | -2.2392399  .0510872  -4.68  0.000  -2.3433012  -1.1351766
    
```

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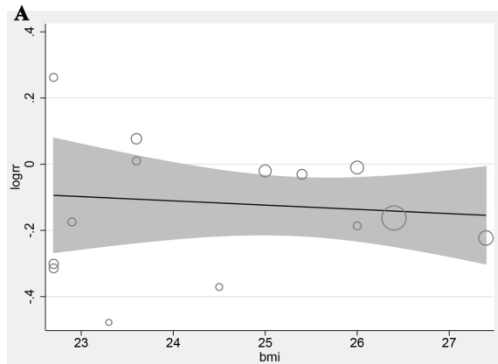
D
. tabulate dietaryassessment, generate ( dietaryassessmentnew )

      dietaryassessment | Freq.  Percent  Cum.
-----+-----
24h dietary recall and FFQ |     1     2.86   2.86
FFQ                        |     4    11.43  14.29
SPFQ                       |     1     2.86  17.14
validated DRQ              |     1     2.86  20.00
validated FFQ              |    17    48.57  68.57
validated SPFQ             |    11    31.43  100.00
-----+-----
Total                       |    35    100.00

. metareg logrr dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4 dietaryassessmentnew5 dietaryassessmentnew6 dietaryassessmentnew7 dietaryassessmentnew8 dietaryassessmentnew9 dietaryassessmentnew10 dietaryassessmentnew11 dietaryassessmentnew12 dietaryassessmentnew13 dietaryassessmentnew14 dietaryassessmentnew15 dietaryassessmentnew16 dietaryassessmentnew17 dietaryassessmentnew18 dietaryassessmentnew19 dietaryassessmentnew20 dietaryassessmentnew21 dietaryassessmentnew22 dietaryassessmentnew23 dietaryassessmentnew24 dietaryassessmentnew25 dietaryassessmentnew26 dietaryassessmentnew27 dietaryassessmentnew28 dietaryassessmentnew29 dietaryassessmentnew30 dietaryassessmentnew31 dietaryassessmentnew32 dietaryassessmentnew33 dietaryassessmentnew34 dietaryassessmentnew35 dietaryassessmentnew36 dietaryassessmentnew37 dietaryassessmentnew38 dietaryassessmentnew39 dietaryassessmentnew40 dietaryassessmentnew41 dietaryassessmentnew42 dietaryassessmentnew43 dietaryassessmentnew44 dietaryassessmentnew45 dietaryassessmentnew46 dietaryassessmentnew47 dietaryassessmentnew48 dietaryassessmentnew49 dietaryassessmentnew50 dietaryassessmentnew51 dietaryassessmentnew52 dietaryassessmentnew53 dietaryassessmentnew54 dietaryassessmentnew55 dietaryassessmentnew56 dietaryassessmentnew57 dietaryassessmentnew58 dietaryassessmentnew59 dietaryassessmentnew60 dietaryassessmentnew61 dietaryassessmentnew62 dietaryassessmentnew63 dietaryassessmentnew64 dietaryassessmentnew65 dietaryassessmentnew66 dietaryassessmentnew67 dietaryassessmentnew68 dietaryassessmentnew69 dietaryassessmentnew70 dietaryassessmentnew71 dietaryassessmentnew72 dietaryassessmentnew73 dietaryassessmentnew74 dietaryassessmentnew75 dietaryassessmentnew76 dietaryassessmentnew77 dietaryassessmentnew78 dietaryassessmentnew79 dietaryassessmentnew80 dietaryassessmentnew81 dietaryassessmentnew82 dietaryassessmentnew83 dietaryassessmentnew84 dietaryassessmentnew85 dietaryassessmentnew86 dietaryassessmentnew87 dietaryassessmentnew88 dietaryassessmentnew89 dietaryassessmentnew90 dietaryassessmentnew91 dietaryassessmentnew92 dietaryassessmentnew93 dietaryassessmentnew94 dietaryassessmentnew95 dietaryassessmentnew96 dietaryassessmentnew97 dietaryassessmentnew98 dietaryassessmentnew99 dietaryassessmentnew100, wsize (selogrr) knapphartung reml
note: dietaryassessmentnew2 through dietaryassessmentnew100 dropped because of collinearity

Meta-regression              Number of obs =    35
RMSE 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(15,29) = 0.16
With Knapp-Hartung modification              Prob > F = 0.5210

      logrr | Coef.  Std. Err.  t  P>|t|  [95% Conf. Interval]
-----+-----
dietaryassessmentnew1 | .1072405  .5101822   0.20  0.841  -1.07096  1.1334551
dietaryassessmentnew2 | .0470373  .294068  1.58  0.124  -0.139403  1.073757
dietaryassessmentnew3 | -.1518405  .111752  -1.46  0.107  -1.152599  1.155949
dietaryassessmentnew4 | .1600754  .1811794   1.30  0.205  -0.1204983  .4805589
dietaryassessmentnew5 | .1948872  .1012421  1.92  0.171  -0.1057583  .4907228
dietaryassessmentnew6 | -.6388793  .279225  -2.27  0.031  -1.205958  -.067950
    
```

```

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, wase (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  -0.4770662   .0004339
sexnew2    | -.0739192  .0940187  -0.79  0.447  -0.2787683   .1309299
   _cons   | -.0480002  .0681983  -0.70  0.495  -0.1965933   .1005894
    
```

```

C . tabulate participantregion, generate ( participantregionnew )

participantregion | Freq.  Percent   Cum.
-----+-----
Asia              |      4    40.00    40.00
Europe            |      3    30.00    70.00
North America    |      8    80.00   100.00
-----+-----
Total            |     15   100.00

. metareg logrr participantregionnew1 participantregionnew2, wase (selogrr) knapphartung reml
note: participantregionnew3 dropped because of collinearity

Meta-regression              Number of obs =    15
REML estimate of between-study variance      tau2 = .0014
% residual variation due to heterogeneity     I-squared_res = 21.74%
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]
-----+-----
participantregionnew1 | -.1089353  .1083661   1.01  0.335  -0.1271992   .1450197
participantregionnew2 | -.0117202  .0911749   0.13  0.900  -0.1849328   .1610732
   _cons             | -.1429514  .0453255  -3.16  0.008  -0.2052493  -.0806492
    
```

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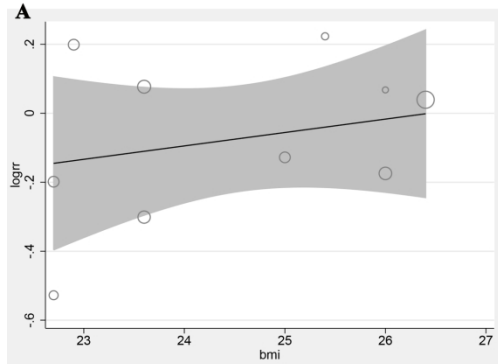
D . tabulate dietaryassessment, generate ( dietaryassessmentnew )

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, wase (selogrr) knapphartung reml
note: dietaryassessmentnew3 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  -0.1508236   .2445382
   _cons              | -.1429338  .0753946  -1.89  0.099  -0.3258102  -.0000578
    
```



C

```
. tabulate participantregion, generate ( participantregionew )
```

participantregion	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 participantregionew1 participantregionew2 participantregionew3, wsize (selogrr) knapphartung reml
note: participantregionew3 dropped because of collinearity
```

Meta-regression

REML estimate of between-study variance	tau2	=	-.508835
% 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 # (2,3)	=	0.14
With Knapp-Hartung modification	Prob > F	=	0.8726

logrr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
participantregionew1	-.010555	.1797495	-0.06	0.954	-.4356955 .4143845
participantregionew2	.0796745	.1944402	0.41	0.694	-.3801034 .5394224
_cons	-.9943118	.1371043	-6.49	0.514	-1.1951164 -.7935071

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, wsize (selogrr) knapphartung reml
note: sexnew2 dropped because of collinearity
```

Meta-regression

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

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	

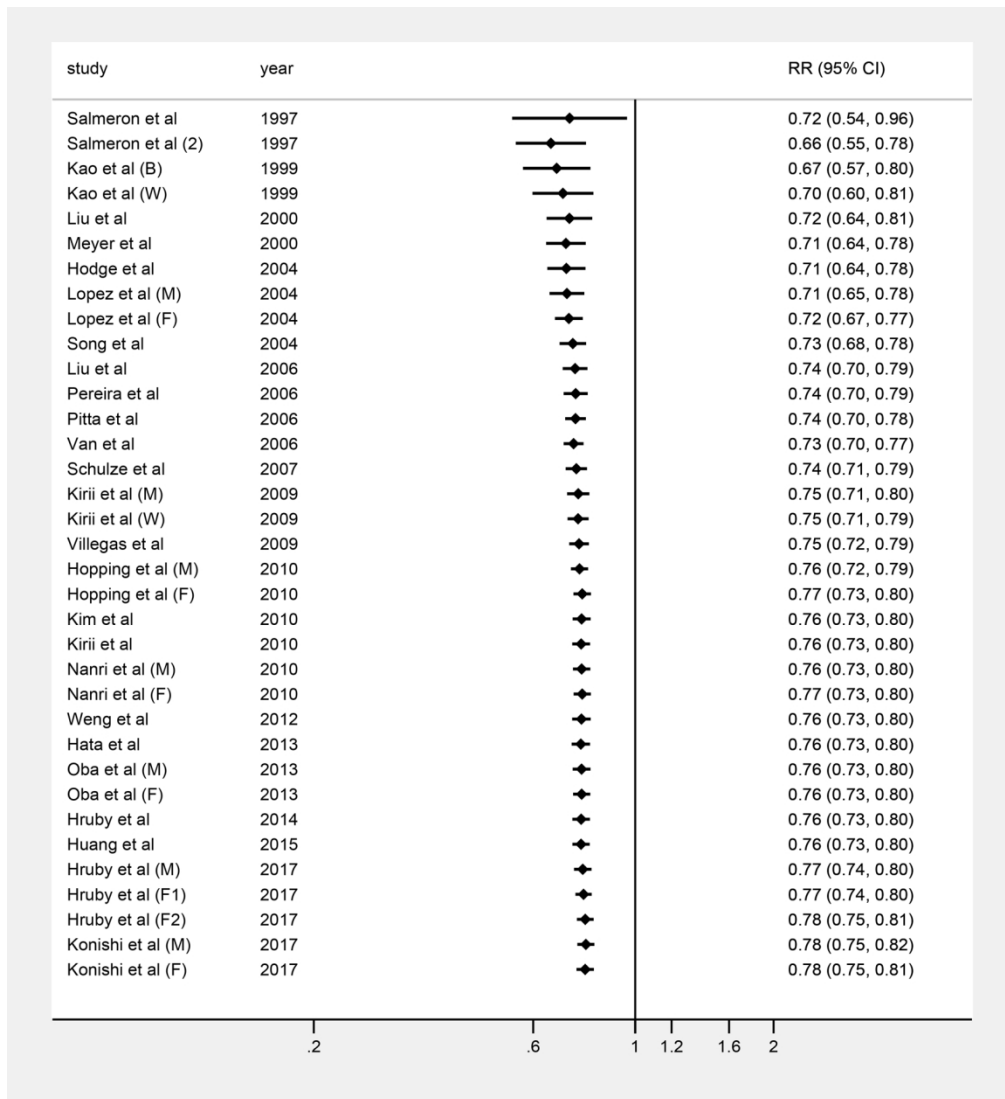
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. metareg logrr dietaryassessmentnew1 dietaryassessmentnew2, wsize (selogrr) knapphartung reml
note: dietaryassessmentnew2 dropped because of collinearity
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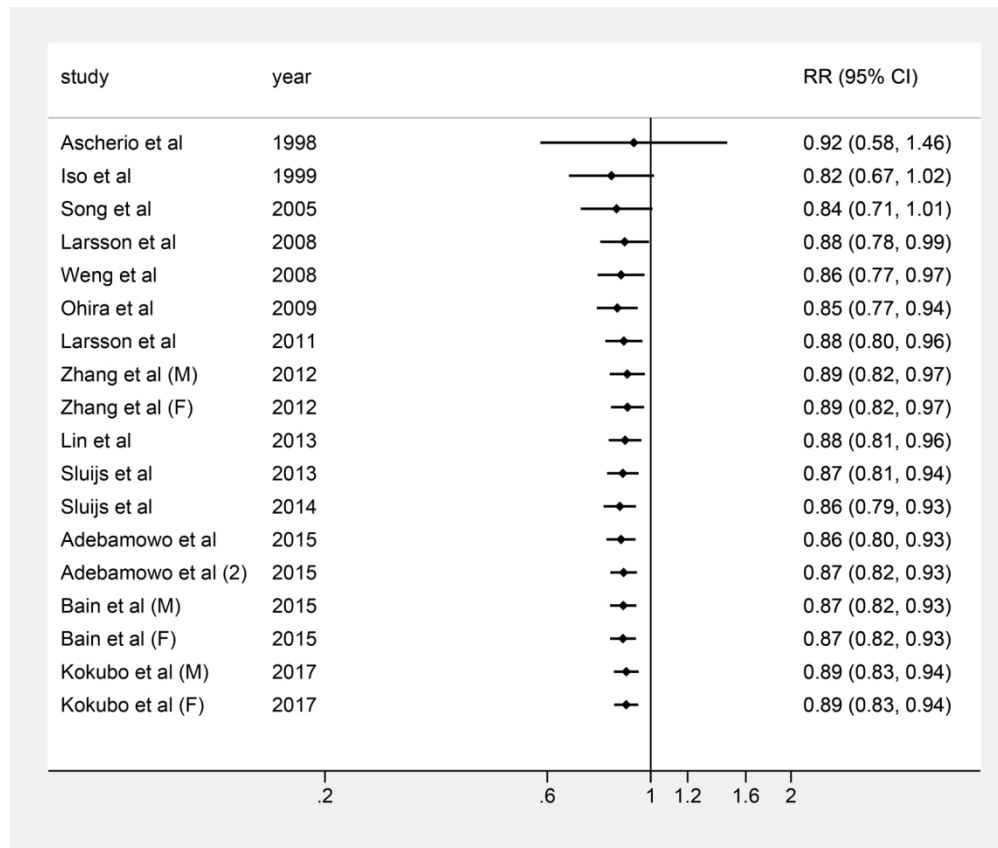
Meta-regression

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			

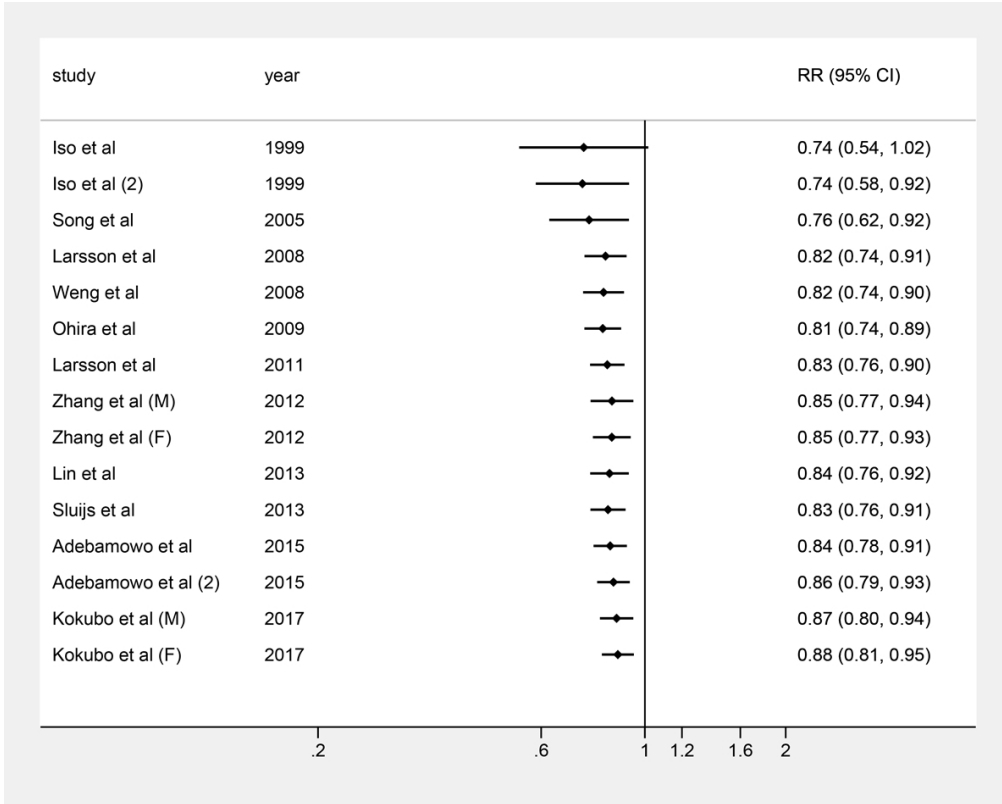
logrr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
dietaryassessmentnew1	.0642559	.1426454	0.45	0.644	-.2044051 .3319134
_cons	-.112665	.1133825	-0.99	0.349	-.2741255 .1487955

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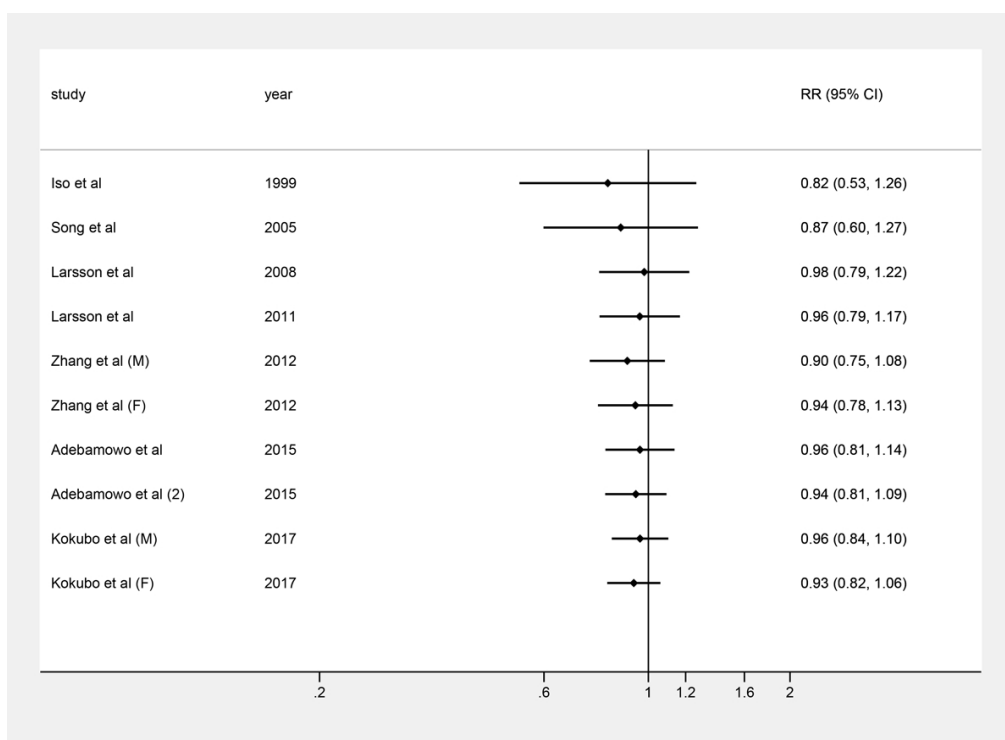




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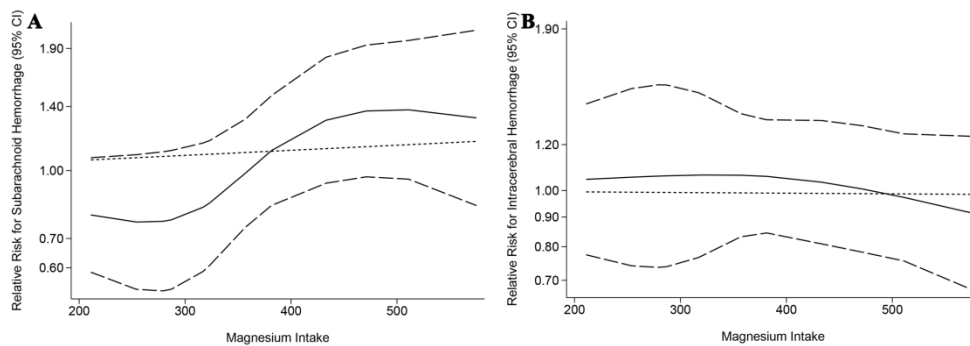




Table S1 PRISMA 2009 Checklist

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:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-032240.R2
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Date Submitted by the Author:	09-Feb-2020
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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Diabetes and endocrinology, Epidemiology, Evidence based practice, Neurology, Cardiovascular medicine
Keywords:	Magnesium Intake, Type 2 Diabetes, Stroke < NEUROLOGY, Meta-Analysis

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3
4 **1 The association of magnesium intake with type 2 diabetes and total stroke: an**
5
6 **2 updated systematic review and meta-analysis**
7
8

9 Binghao Zhao^{1,2}; Lianli Zeng^{3,4}; Jiani Zhao^{3,4}; Qian Wu^{3,4}; Yifei Dong³; Fang Zou⁵;
10
11 Li Gan⁶; Yiping Wei¹; Wenxiong Zhang¹.
12
13

14 **Affiliations**
15

16 ¹Department of Cardio-Thoracic Surgery, The Second Affiliated Hospital of
17
18 Nanchang University, Nanchang, China, 330006.
19

20 ²Departments of Neurosurgery, Peking Union Medical College Hospital, Chinese
21
22 Academy of Medical Sciences and Peking Union Medical College, Beijing, China,
23
24
25 100000.
26

27 ³Department of Cardiovascular Medicine, The Second Affiliated Hospital of
28
29 Nanchang University, Nanchang, China, 330006.
30

31 ⁴Jiangxi medical college, Nanchang University, 330006, Nanchang, China
32
33

34 ⁵Department of Endocrinology, The Second Affiliated Hospital of Nanchang
35
36 University, Nanchang, China, 330006.
37

38 ⁶Department of Neurology, The Second Affiliated Hospital of Nanchang University,
39
40 China, 330006.
41
42

43
44 **18 Corresponding Author:** Wenxiong Zhang, MD, Department of Cardio-Thoracic
45
46 Surgery, The Second Affiliated Hospital of Nanchang University, 1 Minde Road,
47
48 Nanchang, China, 330006; E-mail: zwx123dr@126.com; Phone: +8618720909414;
49
50
51 Fax: 0791-86133161.
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54 **22 Short running head:** Magnesium Intake Reduces Diabetes and Total Stroke.
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56
57 **23 Word count:** 5071.
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1
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4 24 **Abstract**

5
6 25 **Objective:** The detailed associations between type 2 diabetes (T2D) and total stroke
7
8
9 26 and magnesium intake as well as the dose-response trend should be updated in a
10
11
12 27 timely manner.

13
14 28 **Design:** Systematic review and meta-analyses.

15
16
17 29 **Data sources:** PubMed, EMBASE, Cochrane Library, Web of Science and
18
19
20 30 ClinicalTrials.gov were rigorously searched from inception to March 15, 2019.

21
22 31 **Eligibility criteria:** Prospective cohort studies investigating these two diseases were
23
24
25 32 included.

26
27 33 **Data synthesis:** Relative risk (RR) and 95% confidence intervals (95% CI) in random
28
29
30 34 effects models as well as absolute risk (AR) were pooled to calculate the risk of T2D
31
32
33 35 and stroke. Methodological quality was assessed by the Newcastle-Ottawa Scale.

34
35 36 **Results:** Forty-one studies involving 53 cohorts were included. The magnitude of the
36
37
38 37 risk was significantly reduced by 22% for T2D (RR, 0.78 [95% CI, 0.75-0.81]; $P <$
39
40
41 38 0.001; AR reduction, 0.120%), 11% for total stroke (RR, 0.89 [95% CI, 0.83-0.94];
42
43
44 39 $P <$ 0.001; AR reduction, 0.281%), and 12% for ischemic stroke (RR, 0.88 [95% CI,
45
46
47 40 0.81-0.95]; $P =$ 0.001; AR reduction, 0.246%) when comparing the highest
48
49
50 41 magnesium intake to the lowest. The inverse association still existed when studies on
51
52
53 42 T2D were adjusted for cereal fiber (RR, 0.79; $P <$ 0.001) and those on total stroke
54
55
56 43 were adjusted for calcium (RR, 0.89; $P =$ 0.040). Subgroup analyses suggested that
57
58
59 44 the risk for total and ischemic stroke was significantly decreased in females,
60
45 participants with ≥ 25 mg/m² body mass index, and those with ≥ 12 y follow-up; the

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4 46 reduced risk in Asians was not as notable as that in North American and European
5
6
7 47 populations.
8

9 48 **Conclusions:** Magnesium intake has significantly inverse associations with T2D and
10
11
12 49 total stroke in a dose-dependent manner. Feasible magnesium-rich dietary patterns
13
14
15 50 may be highly beneficial for specific populations and could be highlighted in the
16
17 51 primary T2D and total stroke prevention strategies disseminated to the public.
18

19 52 PROSPERO registration number CRD42018092690
20
21

22 53
23

24 54 **Strengths and limitations of this study**

25
26
27 55 1. In this study, we performed an updated comprehensive quantitative analysis
28
29 56 focusing on the dietary effect of magnesium intake.

30
31 57 2. The study identified an inverse association between magnesium intake and T2D
32
33 58 and stroke.

34
35 59 3. A quite number of prospective cohort studies were employed to guarantee the
36
37 60 robust evidence.

38
39 61 4. There was imperfect of not including randomized controlled trails to prove the
40
41 62 causality.

42
43 63 5. Cases ascertainment are limited by FFQ or self-reports.
44
45

46 64
47

48 65 **Keywords:** Magnesium Intake; Type 2 Diabetes; Stroke; Meta-Analysis.
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66 **Introduction**

67 Diabetes is a global burden with an alarming increasing rate throughout the world^{1,2}.

68 Stroke is an independent disorder and a typical macrovascular complication of type 2
69 diabetes (T2D), and it is regarded as the second leading cause of death after ischemic
70 heart disease^{3,4}. These pandemic health problems necessitate better primary
71 prevention strategies.

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

78 Notably, many adults in developed countries do not consume the recommended
79 daily amount of magnesium-rich foods such as whole grains, nuts, and green leafy
80 vegetables, and magnesium is less mentioned in dietary guidelines and in studies on
81 T2D or stroke prevention^{9,10}. Thus, we chose T2D and stroke as our outcome of
82 interest (cardiovascular disease (CVD) was not evaluated because there is already a
83 wealth of research relating to CVD, and the definitions of CVD vary greatly among
84 studies, which would increase the heterogeneity in the pooled process and impair our
85 interpretation of the final conclusions). Emerging studies¹¹⁻⁵¹ on this topic are limited,
86 and the results remain mixed. For example, most studies have indicated that
87 magnesium intake has an inverse association with T2D or total stroke incidence;

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3
4 88 however, several others have revealed that there is an inverse trend but not a
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7 89 significant association, which is possibly due to limitations related to small sample
8
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10 90 sizes and differences in the intervention duration, study design, and participant
11
12 91 characteristics. Moreover, consecutive meta-analyses^{52,53} have used less rigorous
13
14 92 inclusion; the results were not comprehensive, and they did not completely address
15
16
17 93 the influence of other confounders (i.e., body mass index (BMI), cereal fiber, calcium,
18
19
20 94 potassium) on the relationship. Accordingly, we performed a meta-analysis to (1)
21
22 95 establish a comprehensive estimate and update the epidemiological evidence for
23
24
25 96 clinical practice; (2) discuss the results of stroke subtype and the impact of several
26
27
28 97 statistical and epidemiology confounders on the investigated association; and (3)
29
30 98 highlight the details of the dose-response pattern observed among the participants
31
32
33 99 analyzed in the studies.
34

100

101 **Methods**

102 This study was reported according to the Preferred Reporting Items for Systematic
103 Reviews and Meta-Analyses (PRISMA) guidelines (**Table S1**) and the Meta-analysis
104 of Observational Studies in Epidemiology (MOOSE) Guidelines Checklist (**Table S2**)
105 (Registration information: PROSPERO CRD42018092690).
106

107

107 **Search Strategy**

108 PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were
109 systematically reviewed through inception to March 15, 2019, for studies on
110

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2
3
4 110 magnesium intake and T2D or stroke without language restrictions. The following key
5
6 111 words were used: “Magnesium”, “Type 2 Diabetes Mellitus”, “Type 2 Diabetes”,
7
8
9 112 “Stroke”, “Cerebrovascular Stroke”, “Cohort Studies”, and “Prospective Studies”. We
10
11
12 113 also manually searched the reference lists of the retrieved literature (including
13
14 114 meta-analyses and brief reports), bibliographies and gray literature (including
15
16
17 115 presentations and unpublished literature) for further eligible articles. The search
18
19
20 116 strategy can be found in **Table S3**.

21
22 117

23 24 25 118 **Selection Criteria**

26
27 119 (1) Eligible populations must be composed of individuals with plausible
28
29
30 120 dietary/energy intake who had no history of diabetes and/or insulin treatment for T2D
31
32
33 121 analysis and no current stroke for stroke analysis. (2) Their apparent life expectancy
34
35
36 122 was long enough for proper follow-up. (3) We included only prospective cohort
37
38
39 123 studies that reported magnesium intake and T2D and/or various types of stroke. (4)
40
41
42 124 The follow-up duration of eligible studies was at least one year if they provided
43
44
45 125 follow-up data. Notably, magnesium intake consisted of both dietary magnesium
46
47
48 126 intake and total magnesium intake (dietary and supplementary magnesium).

49
50
51 127 Only studies containing the most comprehensive information on the population
52
53
54 128 or endpoints were included to avoid duplication. We excluded reviews, basic science
55
56
57 129 studies, meta-analyses, studies on gestational diabetes mellitus (GDM) and studies
58
59
60 130 that focused only on magnesium supplementation.

131

132 **Data Extraction and Quality Assessments**

133 Two researchers independently extracted the following information: the first author,
134 publication year, period of cohort studies, duration of persistent exposure, basic
135 characteristics of the enrolled participants (weight, age, region, BMI, drinking and
136 smoking habits (previous plus current), etc.), median magnesium intake for each
137 quantile (tertile, quartile, or quintile), diabetes and total stroke cases, subtypes of total
138 stroke, dietary and case assessments, adjusted confounding covariates. Importantly,
139 total stroke is classified as clinical ischemic stroke (87%), hemorrhagic stroke (13%)
140 and undetermined stroke⁵⁴. Hemorrhagic stroke is classified as subarachnoid
141 hemorrhage and intracerebral hemorrhage according to anatomical site or presumed
142 etiology⁵⁵. In cases of continuing disagreement, a final decision was reached after
143 discussion with a third member of the panel.

144 Methodological quality was described by the Newcastle-Ottawa Scale (NOS),
145 which was validated for assessment of the quality of nonrandomized controlled trials
146 in meta-analyses⁵⁶. For the 0-10 scale, each study was categorized as low (0-5),
147 medium (6-7), or high (8-10) quality.

149 **Statistical Analysis**

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

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4 154 T2D, total stroke and other wanted outcomes, particularly for the highest vs. the
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7 155 lowest categories of magnesium intake, were estimated by the DerSimonian-Laird
8
9 156 random effects model because the assumptions involved account for the presence of
10
11 157 within-study and between-study variability. Statistical heterogeneity was determined
12
13
14 158 with the Cochran Q chi-square test and the I^2 . An $I^2 > 50\%$ or a P -value for the Q test
15
16
17 159 < 0.1 was considered to indicate significant heterogeneity⁵⁷. We performed sensitivity
18
19
20 160 analyses to test the robustness and post-subgroup analyses to detect the source of
21
22 161 heterogeneity. In addition, a random effects meta-regression analysis on BMI, sex,
23
24
25 162 participant region, and dietary assessments with RR for each trial was performed to
26
27 163 obtain an understanding of the reasons for heterogeneity. RR and 95% CI might begin
28
29
30 164 to significantly change as publication years increased in T2D and total stroke, etc.,
31
32
33 165 which would be validated by cumulative meta-analyses.

34
35 166 The dose-response analyses for all outcomes were proposed by Greenland and
36
37
38 167 Longnecker⁵⁸ and Orsini⁵⁹ et al. The categories of magnesium intake, distributions of
39
40
41 168 cases and person-year, RR and 95 CI were extracted. If the number of cases and/or
42
43
44 169 person-years was not available, variance-weighted least squares regression was used
45
46
47 170 to pool the risk estimate. For most studies, the median intake for each quantile (tertile,
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49
50 171 quartile or quintile) of magnesium intake was assigned as the representative dose. For
51
52
53 172 continuous intake, which was reported as categorical data (range) in some studies, we
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56 173 assigned the midpoint category of the lower and upper bounds to the RR in these
57
58
59 174 studies; when the highest category was open ended, we assumed the length of the
60
175 open-ended interval to be 1.5 times the adjacent interval; when the lowest category

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4 176 was open, we assigned the adjacent interval of the category to be 1.5 times the length
5
6 177 of the open-ended interval. We employed generalized least squares regression models
7
8
9 178 to calculate study-specific RR estimates per 50 mg/day, 100 mg/day, and 150 mg/day
10
11
12 179 magnesium intake increment if there was evidence of a linear relationship. Nonlinear
13
14 180 relationships between magnesium intake and all outcomes were evaluated using
15
16
17 181 restricted cubic splines with four knots located at the 5th, 35th, 65th, and 95th
18
19 182 percentiles of the distribution. The *P*-value for curve linearity or nonlinearity was
20
21
22 183 calculated by testing the null hypothesis that the coefficient of the second spline is
23
24
25 184 equal to zero. All results were presented using two-stage dose-response model plots
26
27
28 185 (including linear and nonlinear relationships). Some results were demonstrated as
29
30 186 forest plots for intake increments of < 50 mg/day, ≥ 50 and < 100 mg/day, ≥ 100 and
31
32 187 < 150 mg/day, and ≥ 150 mg/day.

34
35 188 Publication bias was assessed graphically by Begg's adjusted rank correlation
36
37 189 funnel plots⁶⁰ and Egger's linear regression tests⁶¹. All analyses were performed using
38
39
40 190 Stata version 14.0 (StataCorp, College Station, TX, USA); two-sided *P* < 0.05 was
41
42
43 191 considered statistically significant except where otherwise specified.

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46 192

47 48 193 **Patient and Public Involvement**

49
50 194 No patients were involved in developing the research question or the outcome
51
52
53 195 measures, and no patients were involved in planning the design or implementation of
54
55
56 196 the study. Furthermore, no patients were asked to advise on the interpretation or
57
58
59 197 writeup of the results. Since this study used aggregated data from previous
60

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4 198 publications, it is not easy to disseminate the results of the research to study
5
6 199 participants directly.
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9 200

11 201 **Results**

14 202 **Study Characteristics and Quality Assessment**

17 203 Of the 8713 studies, 107 studies were considered for eligibility after screening the
18
19 204 titles and abstracts (**Figure 1**). A total of 41¹¹⁻⁵¹ prospective cohort studies comprising
20
21
22 205 53 cohorts, 1 912 634 participants and 76 678 cases were eligible for inclusion in the
23
24 206 systematic review and meta-analysis (**Table S4**). Hodge et al¹⁸ recorded only 500
25
26 207 mg/day increments of magnesium for further pooled analyses; 2 studies^{33,51} failed to
27
28 208 clearly distinguish the diabetes type, but the vast majority of cases had T2D. We
29
30
31 209 computed the subtype data in three studies^{14,27,36} after the extraction of total stroke,
32
33
34 210 and we regarded ischemic stroke in three other studies^{28,30,42} as total stroke given that
35
36
37 211 ischemic stroke accounted for nearly 87% of total stroke. Participants were
38
39 212 predominately middle-aged at baseline, with a mean magnesium intake of 370 mg/day
40
41
42 213 for the highest category and 232 mg/day for the lowest category. The mean duration
43
44 214 of all eligible studies was 10.7 years. Nineteen studies were conducted in North
45
46
47 215 America (America); 5 studies were conducted in Europe (Sweden, the Netherlands
48
49 216 and Britain); 13 studies were conducted in Asia (China and Japan and Taipei); and 4
50
51
52 217 studies enrolled individuals in multiple nations. Most of the included studies used
53
54 218 food frequency questionnaires (FFQs) or semiquantitative FFQs (SFFQs) to assess
55
56
57 219 individual dietary intake. Eighteen studies used dietary magnesium intake, and 21
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4 220 studies recorded total magnesium intake (dietary and supplementary magnesium
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6
7 221 intake). Of note, supplementary magnesium intake was assessed by the use of
8
9
10 222 magnesium or multivitamin supplements; nevertheless, dietary magnesium accounted
11
12 223 for the majority of magnesium intake. Adjusted confounders were mostly similar;
13
14 224 however, adjusted dietary confounders such as cereal fiber, potassium, and calcium
15
16
17 225 still varied across individual studies. It was unclear whether the included studies had
18
19
20 226 adjusted for sodium because they did not provide this information. All the studies
21
22 227 were written in English.

23
24
25 228 After the quality assessments of the studies according to NOS, the average score
26
27 229 was 8.85 (**Table S5**), and all studies were of high quality (NOS score 8-10).

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30 230

31 32 231 **Magnesium Intake and T2D Incidence**

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34
35 232 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
36
37
38 233 participants and 56 540 T2D cases) reported that the magnitude of T2D risk was
39
40
41 234 reduced by 22% (RR, 0.78 [95% CI, 0.75-0.81]; $P < 0.001$; AR reduction, 0.120%),
42
43 235 comparing the highest category of magnesium intake to the lowest, with little
44
45
46 236 evidence of heterogeneity ($I^2 = 35.6\%$; $P = 0.021$). The dose category-specific
47
48
49 237 analysis suggested that for the < 50 mg/day magnesium increment, the risk of T2D
50
51
52 238 was reduced by 10% (RR, 0.90 [95% CI, 0.88-0.93]; $P < 0.001$); for the ≥ 50 and $<$
53
54
55 239 100 mg/day increments, the risk was decreased by 16% (RR, 0.84 [95% CI,
56
57
58 240 0.82-0.87]; $P < 0.001$); for ≥ 100 and < 150 mg/day increments, the risk was reduced
59
60 241 by 22% (RR, 0.78 [95% CI, 0.74-0.83]; $P < 0.001$); and for the ≥ 150 mg/day

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4 242 increment, the risk was reduced by 21% (RR, 0.79 [95% CI, 0.74-0.84]; $P < 0.001$)
5
6 243 (**Figure 2**). Little evidence of publication bias was found (Egger's test: $P = 0.088$)
7
8
9 244 (**Figure S1A**).
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12 245

14 246 **Magnesium Intake and Stroke Incidence**

16
17 247 Eighteen cohorts from 15 publications^{13,14,21,27,28,30,36,38,40,42,44-47,50} (692 998
18
19 248 participants and 20 138 total stroke cases) reported that the magnitude of the risk of
20
21
22 249 total stroke was decreased by 11% (RR, 0.89 [95% CI, 0.83-0.94]; $P < 0.001$; AR
23
24 250 reduction, 0.281%), comparing the highest category of magnesium intake with the
25
26
27 251 lowest, with no heterogeneity ($I^2 = 0\%$; $P = 0.529$). The dose category-specific
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29
30 252 analysis revealed no significant association with the < 50 mg/day, ≥ 50 and < 100
31
32 253 mg/day increments or the ≥ 100 and < 150 mg/day increments. For the ≥ 150 mg/day
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34
35 254 increment, the risk of total stroke was decreased by 15% (RR, 0.85 [95% CI,
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37 255 0.79-0.91]; $P < 0.001$) (**Figure S2**). Publication bias was evaluated for stroke
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39
40 256 subtypes.

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42
43 257 Fifteen cohorts from 12 publications^{14,21,27,28,30,36,38,40,42,45,46,50} reported ischemic
44
45 258 stroke. The magnitude of the risk of ischemic stroke was reduced by 12% (RR, 0.88
46
47
48 259 [95% CI, 0.81-0.95]; $P = 0.001$; AR reduction, 0.246%) with no significant
49
50
51 260 heterogeneity ($I^2 = 16.9\%$; $P = 0.265$). The dose category-specific analysis identified
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53
54 261 no significant association with the < 50 mg/day, ≥ 50 and < 100 mg/day, or ≥ 100 and
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56 262 < 150 mg/day increments. A decreasing trend existed but remained nonsignificant.
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58
59 263 The original risk was reduced by 16% in the analysis of the ≥ 150 mg/day increment
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4 264 (RR, 0.84 [95% CI, 0.78-0.91]; $P < 0.001$) (**Figure S3**). No publication bias was
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6
7 265 observed in terms of ischemic stroke (Egger's test: $P = 0.937$) (**Figure S1B**).

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9 266 Ten cohorts from 8 studies^{14,21,27,36,38,45,46,50} reported that hemorrhagic stroke was
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11
12 267 not significantly associated with magnesium intake (RR, 0.93 [95% CI, 0.82-1.06]; P
13
14 268 = 0.282). The dose category-specific analysis identified no significant association
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16
17 269 (**Figure S4**). No significant heterogeneity or publication bias was observed in terms of
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20 270 hemorrhagic stroke (Egger's test: $P = 0.809$) (**Figure S1C**).

21
22 271 Three publications involving 3 cohorts^{14,27,36} showed that high magnesium intake
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25 272 had no significant effect on reducing the risk of subarachnoid hemorrhage (RR, 0.99
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27 273 [95% CI, 0.71-1.39]; $P = 0.963$). The dose category-specific analysis revealed no
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29
30 274 significant association (**Figure S5**).

31
32 275 With respect to intracerebral hemorrhage, the pooled results from 3 cohorts^{14,27,36}
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34
35 276 in 3 publications revealed no significant advantages of intracerebral hemorrhage (RR,
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37 277 0.92 [95% CI, 0.71-1.20]; $P = 0.540$). The dose category-specific analysis revealed no
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40 278 significant association (**Figure S6**).

41 42 43 44 45 280 **Meta-Regression and Cumulative Meta-Analysis**

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48 281 According to the meta-regression results, there was no evidence of BMI, sex,
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51 282 participant region or dietary assessment for each individual trial bias in terms of T2D
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53 283 (**Figure S7**), total stroke (**Figure S8**), ischemic stroke (**Figure S9**) and hemorrhagic
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56 284 stroke events (**Figure S10**). The male subgroup ($P = 0.041$) in the sex category might
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59 285 lead to slight heterogeneity in terms of total stroke; however, sex ($P = 0.112$) showed
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4 286 no association with total stroke incidence.
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6 287 Analyses of T2D (**Figure S11**), total stroke (**Figure S12**) and ischemic stroke
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9 288 demonstrated that the RRs of the final results became robust within a narrow range
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12 289 and remained significant as publication years increased and more recent high-quality
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15 290 studies were included. After inclusion of the Iso et al¹⁴ study, the RR and 95% CI for
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17 291 ischemic stroke decreased to less than 1 and then became stable (**Figure S13**).
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20 292 Although there was no significant reduction in the risk of hemorrhagic stroke, the
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22 293 evidence clearly showed that the confidence interval was becoming narrow, which
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25 294 trended toward significance (**Figure S14**). Thus, the risk for hemorrhagic stroke might
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27 295 be reduced; additional studies are warranted.
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33 297 **Sensitivity Analysis**

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35 298 When three²⁴⁻²⁶ studies were excluded from the T2D analysis, the summary RR
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38 299 changed from 0.78 ([95% CI, 0.75-0.81]) to 0.78 ([95% CI, 0.75-0.82]), with the
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41 300 heterogeneity declining from ($I^2 = 35.6\%$; $P = 0.021$) to ($I^2 = 24.0\%$; $P = 0.112$).
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43 301 Among T2D analyses, eight studies^{19,22,23,26,33,39,48,49} adjusted for cereal fiber intake
44
45 302 yielded an RR of 0.79 ([95% CI, 0.73-0.85]; $P < 0.001$), and two studies^{15,35} adjusted
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47
48 303 for calcium yielded an RR of 0.87 ([95% CI, 0.73-1.04]; $P = 0.128$). Among the total
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51 304 stroke analysis, the summary RR was 0.92 ([95% CI, 0.82-1.02]; $P = 0.097$) in five
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53
54 305 studies^{13,44-46,50} adjusted for potassium intake and was 0.89 ([95% CI, 0.80-0.99]; $P =$
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56 306 0.040) in five studies^{14,44-46,50} adjusted for calcium. Only one study¹⁵ adjusted for
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58
59 307 potassium intake in T2D, and one study³⁶ adjusted for cereal fiber in total stroke.
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309 **Subgroup Analysis**

310 Stratified analyses by characteristics of the population and study design were
311 conducted on T2D (**Table 1**), total stroke, ischemic stroke and hemorrhagic stroke
312 (**Table 2**). The inverse association with T2D remained robust across all subgroups
313 with little evidence of heterogeneity. For stroke incidence, a decreased risk of total
314 stroke and ischemic stroke was found in female participants (RR, 0.91 [95% CI,
315 0.83-0.99] for total stroke; 0.89 [95% CI, 0.79-1.00] for ischemic stroke) and
316 individuals with ≥ 25 kg/m² mean BMI (RR, 0.89 [95% CI, 0.82-0.96] for total stroke;
317 0.88 [95% CI, 0.81-0.96] for ischemic stroke). When restricted to a ≥ 12 y follow-up,
318 the risk of total stroke and ischemic stroke was significantly reduced (RR, 0.89 [95%
319 CI, 0.83-0.95] for total stroke; 0.88 [95% CI, 0.81-0.95] for ischemic stroke). These
320 risks were more reduced in North American and European individuals than in Asians.
321 Cardiovascular events (CV events, coronary heart disease, heart failure, atrial
322 fibrillation, self-reported heart disease, etc. other than stroke), hypercholesterolemia
323 and diabetes would blunt the effect of magnesium on total and ischemic stroke.
324 However, magnesium intake could still, or at least, demonstrate the trend to decrease
325 total and ischemic stroke in individuals even with those risk factors. Similarly, CV
326 events, hypercholesterolemia and family diabetes history had no substantial impact on
327 the inverse association between T2D incidence and magnesium intake. We did not
328 find a significantly reduced risk of hemorrhagic stroke in the subgroup analyses.

329

330 **Dose-Response Analysis**

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

336 Specifically, we calculated the RR for the magnesium increments if a linear
337 relationship was found. The calculated RR was 0.94 ([95% CI, 0.93-0.95]) for the 100
338 mg/day increment for T2D. For total stroke, the summary RR was 0.98 ([95% CI,
339 0.97-0.99]) related to a 100 mg/day increment in magnesium intake, and the RR for
340 ischemic stroke was 0.98 ([95% CI, 0.97-0.99]) related to a 100 mg/day increment in
341 magnesium intake. There was no RR cut-off point at which the decreasing trend
342 reversed, but the RR decreased slightly rapidly with any slight decreases at
343 approximately 260 mg/day for T2D and 350 mg/day for total/ischemic stroke.
344 However, there was substantial uncertainty in the lower range of this distribution
345 (**Figure 3A, 3B, 3C**).

347 **Discussion**

348 **Main findings**

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

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4 352 total stroke and ischemic stroke at the highest level vs. the lowest. No significant
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6 353 association for hemorrhagic stroke, subarachnoid hemorrhage or intracerebral
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9 354 hemorrhage was detected. Female obese participants (mean BMI \geq 25 kg/m²) with a
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11 355 longer follow-up period (\geq 12 y) might obtain greater benefit from magnesium intake
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14 356 with a lower risk of total and ischemic stroke incidence. In subgroup analyses, the RR
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17 357 of stroke risk was highly decreased among North American and European individuals.
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19 358 Significant risk was reduced by 6%, 2%, and 2% for T2D, total stroke and ischemic
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22 359 stroke, respectively, per 100 mg/day increment in magnesium intake level. Overall,
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25 360 our study supports the guidelines to address the role of magnesium intake in early
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27 361 prevention strategies to combat T2D and stroke. However, additional randomized
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30 362 controlled trials (RCTs) are needed in the future to validate the causality.
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364 **Clinical implications**

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

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4 374 health educators and policymakers. Third, to date, no related paper has discussed such
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6 375 detailed stratified analyses; thus, this work helps physicians amplify dietary benefits
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9 376 through individualized strategies. Interestingly, North American and European
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11 377 participants seemed to receive more benefits from magnesium intake than Asians.
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14 378 Fourth, to the best of our knowledge, this is the first study in which a cumulative
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17 379 meta-analysis was performed to predict changes in the tendency of main risk
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19 380 estimates. Based on past and current cutting edge evidence about nutrition and T2D
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22 381 prevention, the US Diabetes Prevention Program (DPP) conducted a study and
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24 382 demonstrated that proper lifestyle modification (exercise and Mediterranean diet)
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26 383 significantly reduced T2D risk irrespective of population baselines, and this benefit
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29 384 was enhanced with increased follow-up⁶⁴. The UK National Health Service (UK
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32 385 NHS) will launch an intervention program including weight loss, nutrition,
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35 386 monitoring and peer support targeting up to 10 000 people prone to develop T2D⁶⁵.

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38 387 The 2018 American Diabetes Association (ADA) guidelines⁶⁶ recommend that
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40 388 the intake of nuts, berries, yogurt, coffee and tea be increased in individuals who are
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43 389 at high risk of diabetes. The latest guidelines by the American Heart Association
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45 390 (AHA)/American Stroke Association (ASA)⁹ also validate the considerable status of
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48 391 early management of stroke (ischemic stroke). In fact, magnesium is a cofactor in
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51 392 enzyme systems that regulate diverse biomedical reactions, including protein
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53 393 synthesis, muscle and nerve transmission, neuromuscular conduction, signal
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56 394 transduction blood glucose control and blood pressure management⁶⁷. Magnesium
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58 395 also plays a role in transporting calcium and potassium ions across the cell membrane
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4 396 and is crucial for the structural function of proteins, nucleic acids or mitochondria⁶⁸.
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6 397 In diabetes, magnesium is involved in glucose and insulin metabolism by regulating
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9 398 the tyrosine kinase activity of the insulin receptor. Magnesium also influences
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11 399 phosphorylase B kinase activity by releasing glucose-1-phosphate from glycogen and
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14 400 regulates glucose translocation into the cell⁶⁹. In stroke, higher magnesium levels lead
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17 401 to the deregulation of glutamate and calcium cation influx by reducing NMDA
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19 402 receptor activity and blocking voltage-gated calcium channels, eliminating calcium
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22 403 cation cytotoxicity. Additionally, the vasodilatory effects of magnesium may benefit
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24 404 ischemic stroke patients⁷⁰. Indeed, a poor outcome of hemorrhagic stroke was
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27 405 observed in an RCT; however, high serum magnesium might be better for the
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30 406 prognosis of intracerebral hemorrhage⁷¹.

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32 407 Most specific nutrients, especially macronutrients, are correlated with total
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34 408 energy intake. In the included free-living human studies, the variation in total energy
35
36 409 intake originated from differences in physical activity levels, body size, and energy
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38 410 efficiency⁷². Thus, total energy intake can weaken the investigated association with
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40 411 considerable nutrient intake if this covariable is not properly removed.
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43 412 Epidemiologists should assess the reproducibility and validity of energy-adjusted
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45 413 nutrients as well as absolute nutrient intake. For micronutrients such as magnesium,
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48 414 an inverse association with T2D, total stroke and ischemic stroke outcomes could be
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51 415 still found after total energy intake adjustment. In terms of other nutrients, potassium
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54 416 intake is proposed to lower blood pressure (BP) and improve vascular outcomes
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57 417 (including stroke); dietary potassium may also be influential in glucose control and
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4 418 limiting the risk of diabetes⁷³. Vitamin D and calcium may negatively influence
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6 419 glycemia, but the evidence is limited and mostly based on cross-sectional
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9 420 observational studies⁷⁴. Calcium may be inversely associated with stroke in
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11 421 populations with low to moderate calcium intakes, but no significant association was
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14 422 found between calcium and CVD⁷⁵. Altogether, the results indicate that
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16 423 magnesium-rich food such as nuts (151-567 mg/100 g edibles), fruits (132-448
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18 424 mg/100 g edibles), vegetables (132-1257 mg/100 g edibles), legumes (138-243
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20 425 mg/100 g edibles), fish (143-303 mg/100 g edibles) and total grain (134-306 mg/100 g
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22 426 edibles) should be recommended to populations with insufficient magnesium intake.
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30 428 **Comparisons with other similar studies**

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32 429 This analysis has several differences from previous studies. Dong et al⁵² found that
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34 430 magnesium intake had an inverse association with T2D incidence (RR, 0.78 [95% CI,
35
36 431 0.73-0.84]), and with an intake of 100 mg/day magnesium, the risk was reduced by
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38 432 14%. However, they failed to include adequate studies, and standard quality
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40 433 assessments of eligible studies were absent. Individuals from multiple nations were
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42 434 included in some studies^{18,25,26,32} but were incorrectly assigned to Asia or the U.S. in
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44 435 the subgroups; other minor issues also existed in the selection criteria, making it
45
46 436 unclear whether they excluded participants with subclinical diabetes. BMI was not a
47
48 437 potential modifier for T2D in our study due to the inclusion of more evidence with a
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50 438 longer follow-up period. Fang et al⁷⁶ revealed that dietary magnesium was
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52 439 significantly associated with a reduced risk of T2D (RR, 0.74 [95% CI, 0.69-0.80])
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4 440 and stroke (RR, 0.88 [95% CI, 0.82-0.95]). The results were comparable, but they
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6 441 focused only on dietary magnesium intake rather than overall magnesium intake (total
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8
9 442 or dietary), and subtypes of total stroke were missing. To the best of our knowledge,
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11 443 BMI, follow-up, family diabetes history, etc. are crucial confounders for evaluating
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13
14 444 the association, and these factors were not addressed in their study. Moreover, other
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16
17 445 researchers have better investigated the likelihood of a linear association in the
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19 446 dose-response pattern (using methods by Greenland and Orsini et al.). For example,
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22 447 Fang et al⁷⁷ found that the 100 mg/day intake of dietary magnesium was associated
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24 448 with an 8-13% reduction in T2D risk, and while a nonlinear relationship did not exist,
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26
27 449 a minor publication bias was present. Twenty-five studies were eligible; however,
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30 450 some of them focused not on dietary intake but rather on total magnesium intake.
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32 451 Moreover, there were two included studies focusing on red meat intake instead of
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34
35 452 magnesium intake. After excluding ineligible studies, we found no evidence of
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38 453 publication bias. Additionally, both linear and nonlinear relationships existed for T2D
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40
41 454 because the RRs of the highest category of magnesium intake vs. the lowest in our
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43 455 pooled study were still used. A study by Larsson et al⁵³ including 7 studies supported
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45
46 456 a modest but statistically significant inverse association between dietary magnesium
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48 457 intake and stroke. However, the sample size was quite small, and there was no useful
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51 458 information on stroke subtypes (e.g., ischemic stroke, hemorrhagic stroke) in the main
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54 459 analysis. In our opinion, a well-designed subgroup analysis is compulsory, and a
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56 460 pooled stroke result restricted by potassium and calcium adjustment is recommended.
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59 461 The current study found that magnesium intake was strongly inversely associated with
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4 462 total stroke and ischemic stroke, which still existed in the dose-response pattern.
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9 464 **Directions for future research**

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11 465 Future studies are needed to address some remaining questions. At first, no significant
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14 466 association was found for hemorrhagic stroke; however, a beneficial trend was
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17 467 observed in the cumulative meta-analysis, which highlights the need for more updated
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20 468 prospective studies and RCTs. Second, there is a key question regarding the optimal
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23 469 time to start prevention and methods to screen severe complications. Cardiovascular
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25 470 events occur in more than 50% of patients with diabetes, and diabetic kidney disease
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27 471 occurs in 20-40%. Additionally, cardiovascular events increase the risk of death three-
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30 472 to fourfold compared with patients without such complications. A sustained period of
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33 473 intensive glucose control early in T2D has been confirmed to reduce complication
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35 474 rates⁷⁸. Most importantly, for the public, educators and policymakers, promoting
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38 475 magnesium-rich food consumption can translate into considerable benefit in
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40 476 preventing T2D and total stroke, especially for high-risk populations.
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45 478 **Limitations**

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48 479 This work has several limitations that deserve further discussion. First, this
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51 480 group-level meta-analysis is insufficient. Although strong inverse associations for
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54 481 T2D and total stroke were reported, individual-level studies having more detection
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56 482 power are required. Second, several variations cannot be totally understood; for
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59 483 example, we cannot exclude the possibility that other nutrients and/or dietary
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4 484 components correlated with dietary magnesium may have been responsible, either
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6 485 partially or entirely, for the observed associations. Based on eligible studies, we could
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9 486 not quantify the impact of supplementary magnesium (not combined with dietary
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11 487 intake) on T2D and stroke incidence. The real effect of some dietary supplements on
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14 488 T2D or cardiovascular disease has proven very interesting to a number of medical
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17 489 experts, clinicians and nutrition educators. Third, FFQs/validated FFQs mostly used
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20 490 in primary studies could not characterize all the nutrients, which misclarified plausible
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22 491 associations. It was suggested that magnesium-specific food questionnaires and/or
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25 492 food records should be reasonably used for accurate magnesium intake estimation.
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28 493 Finally, additional RCT are needed, as observational studies might only reach one
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30 494 conclusion (i.e., magnesium intake is inversely associated with T2D incidence) and
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32
33 495 cannot prove causality.

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37 497 **Conclusion**

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40 498 Magnesium intake has a substantial inverse association with T2D and total stroke.
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43 499 Among these populations, magnesium consumption can be recommended as an
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46 500 optimization for T2D, total stroke and ischemic stroke primary prevention or early
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49 501 management. In particular, the greater the magnesium intake is, the greater the
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52 502 reduction in risk. As patients, physicians, policy makers and legislators debate these
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55 503 issues, such a cost-effective alternative is needed to inform policy decisions and aid in
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58 504 reforming nutritional health care worldwide.

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10
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18
19 512 None declared
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32 517 **Data availability statement**

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35 518 All data relevant to the study are included in the article or uploaded as supplementary
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37 519 information.
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43 521 **Patient consent for publication**

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45 522 Not required.
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7
8 530 manuscript and takes responsibility for the integrity of the data and the accuracy of
9
10 531 the data analysis.

11 532 Concept and design: All authors.

12
13 533 Acquisition, analysis, or interpretation of data: All authors.

14 534 Drafting of the manuscript: Binghao Zhao and Wenxiong Zhang.

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16 535 Critical revision of the manuscript for important intellectual content: Binghao Zhao,

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19
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22 538 Supervision: Wenxiong Zhang and Yiping Wei

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768 **Table 1** Subgroup Analysis relating to Magnesium Intake and Type 2 Diabetes (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/m²)	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	

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

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

773 ^b, Male and female participants were in independent cohorts;

774 ^c, Two studies reported total magnesium and dietary magnesium intake outcome;

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

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

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

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

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781 **Table 2.** Subgroup Analyses Relating to Magnesium Intake and Total Stroke, Ischemic Stroke, Hemorrhagic stroke.
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Group	Total Stroke				Ischemic Stroke				Hemorrhagic stroke			
	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}	No.of studies	RR (95% CI)	I ² (%)	P _{interaction}
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/m²)	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	

1	intake	7	(0.81-0.96)		6	(0.77-1.03)		3		
2	Total energy adjustment	15		0.888	12		0.689	8		0.538
3			0.87			0.86				
4	Yes	5	(0.77-0.99)	27.00	2	(0.78-0.94)	0.00	2	0.93 (0.82-1.06)	0.00
5	No	10	0.89	0.00	10	0.88	26.60	6	0.90 (0.76-1.07)	11.40
6	Difference between top and bottom intake (mg/day)^d		(0.83-0.96)			(0.79-0.99)				
7		15		0.107	12		0.180	8		0.244
8										
9	≥ 180	7	0.83	0.00	5	0.83	0.00	6	1.07 (0.83-1.37)	0.00
10			(0.76-0.91)			(0.76-0.91)				
11	< 180	8	0.93	0.00	7	0.92	26.20	2	0.89 (0.76-1.03)	0.00
12			(0.86-1.00)			(0.81-1.03)				
13	Current CV events status^e			0.074	12		0.393	8		NA
14	Yes	12	0.90	0.00	11	0.88	18.20	8	0.93 (0.82-1.06)	0.00
15			(0.85-0.96)			(0.81-0.96)				
16	Unknown	3	0.75	0.00	1	0.76	NA	0	NA	NA
17			(0.63-0.90)			(0.57-1.01)				
18	Hypercholesterolemia status^f			0.480	12		0.565	8		0.651
19	Yes	7	0.91	0.00	6	0.90	6.90	5	0.90 (0.76-1.08)	0.00
20			(0.83-0.99)			(0.80-1.01)				
21	Unknown	8	0.86	13.10	6	0.86	32.40	3	0.94 (0.72-1.22)	40.30
22			(0.79-0.95)			(0.77-0.97)				
23	Current diabetes status^g			0.039	12		0.159	8		NA
24	Yes	10	0.91	0.00	10	0.89	13.50	8	0.93 (0.82-1.06)	0.00
25			(0.82-0.97)			(0.82-0.97)				
26	Unknown	5	0.75	0.00	2	0.72	0.00	0	NA	NA
27			(0.64-0.88)			(0.56-0.92)				

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.

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2
3 783 **Figure Legends**
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5 784 **Figure 1.** Flow Chart for the Literature Search and Screening Process
6

7 785 **Figure 2.** Forest Plots for the Risk of Type 2 Diabetes (T2D) for Magnesium Intake
8 (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D)
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10 786
11
12 787 and ≥ 150 mg/day Increments (E).
13

14 788 **Figure 3.** Two-Stage Dose-Response Effect on the Relationships between Magnesium
15 Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and
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17 789 Hemorrhagic Stroke (D).
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3 791 **Supplementary material online:**
4

5 792 **Table S1.** PRISMA 2009 Checklist
6

7 793 **Table S2.** MOOSE Checklist
8

9 794 **Table S3.** Complete Search Terms for PubMed
10

11 795 **Table S4.** Summary of Baseline Characteristics of the Included Studies
12

13 796 **Table S5.** Methodological Quality Assessments of the Included Studies with
14
15
16
17 797 Newcastle-Ottawa Scales

18 798 **Figure S1.** Funnel Plots for Magnesium Intake and Type 2 Diabetes (A), Ischemic
19
20
21 799 Stroke (B) and Hemorrhagic Stroke (C).
22

23 800 **Figure S2.** Forest Plots for the Risk of Total Stroke for Magnesium Intake (A) and for
24
25
26 801 < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and ≥ 150
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28 802 mg/day Increments (E).
29

30 803 **Figure S3.** Forest Plots for the Risk of Ischemic Stroke for Magnesium Intake (A) and
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33 804 for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and \geq
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35 805 150 mg/day Increments (E).
36

37 806 **Figure S4.** Forest Plots for the Risk of Hemorrhagic Stroke for Magnesium Intake (A)
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39
40 807 and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150 mg/day (D) and
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42 808 ≥ 150 mg/day Increments (E).
43

44 809 **Figure S5.** Forest Plots for the Risk of Subarachnoid Hemorrhage for Magnesium
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47 810 Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150
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49 811 mg/day (D) and ≥ 150 mg/day Increments (E)
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51 812 **Figure S6.** Forest Plots for the Risk of Intracerebral Hemorrhage for Magnesium
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54 813 Intake (A) and for < 50 mg/day (B), ≥ 50 and < 100 mg/day (C), ≥ 100 and <150
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56 814 mg/day (D) and ≥ 150 mg/day Increments (E)
57

58 815 **Figure S7.** Meta-Regression of the Relative Risk for Type 2 Diabetes According to
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3 816 Body Mass Index (A, $P = 0.716$), Sex (B, $P = 0.284$), Participant Region (C, $P =$
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5 817 0.904) and Dietary Assessment (D, $P = 0.521$).

7
8 818 **Figure S8.** Meta-Regression of the Relative Risk for Total Stroke According to Body
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10 819 Mass Index (A, $P = 0.606$), Sex (B, $P = 0.112$), Participant region (C, $P = 0.891$) and
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12 820 Dietary Assessment (D, $P = 0.891$).

14
15 821 **Figure S9.** Meta-Regression of the Relative Risk for Ischemic Stroke According to
16
17 822 Body Mass Index (A, $P = 0.631$), Sex (B, $P = 0.134$), Participant Region (C, $P =$
18
19 823 0.584) and Dietary Assessment (D, no regression P -value due to limited data).

21
22 824 **Figure S10.** Meta-Regression of the Relative Risk for Hemorrhagic Stroke According
23
24 825 to Body Mass Index (A, $P = 0.418$), Sex (B, $P = 0.872$), Participant Region (C, $P =$
25
26 826 0.872) and Dietary Assessment (D, no regression P -value due to limited data).

28
29 827 **Figure S11.** Cumulative Meta-Analysis Related to Magnesium Intake and Type 2
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31 828 Diabetes (T2D)

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34 829 **Figure S12.** Cumulative Meta-Analysis Related to Magnesium Intake and Total
35
36 830 Stroke

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38 831 **Figure S13.** Cumulative Meta-Analysis Related to Magnesium Intake and Ischemic
39
40 832 Stroke

42
43 833 **Figure S14.** Cumulative Meta-Analysis Related to Magnesium Intake and
44
45 834 Hemorrhagic Stroke

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47 835 **Figure S15.** Dose-Response Effect on the Relationships between Magnesium Intake
48
49 836 and Subarachnoid Hemorrhage (A) and Intracerebral Hemorrhage (B).

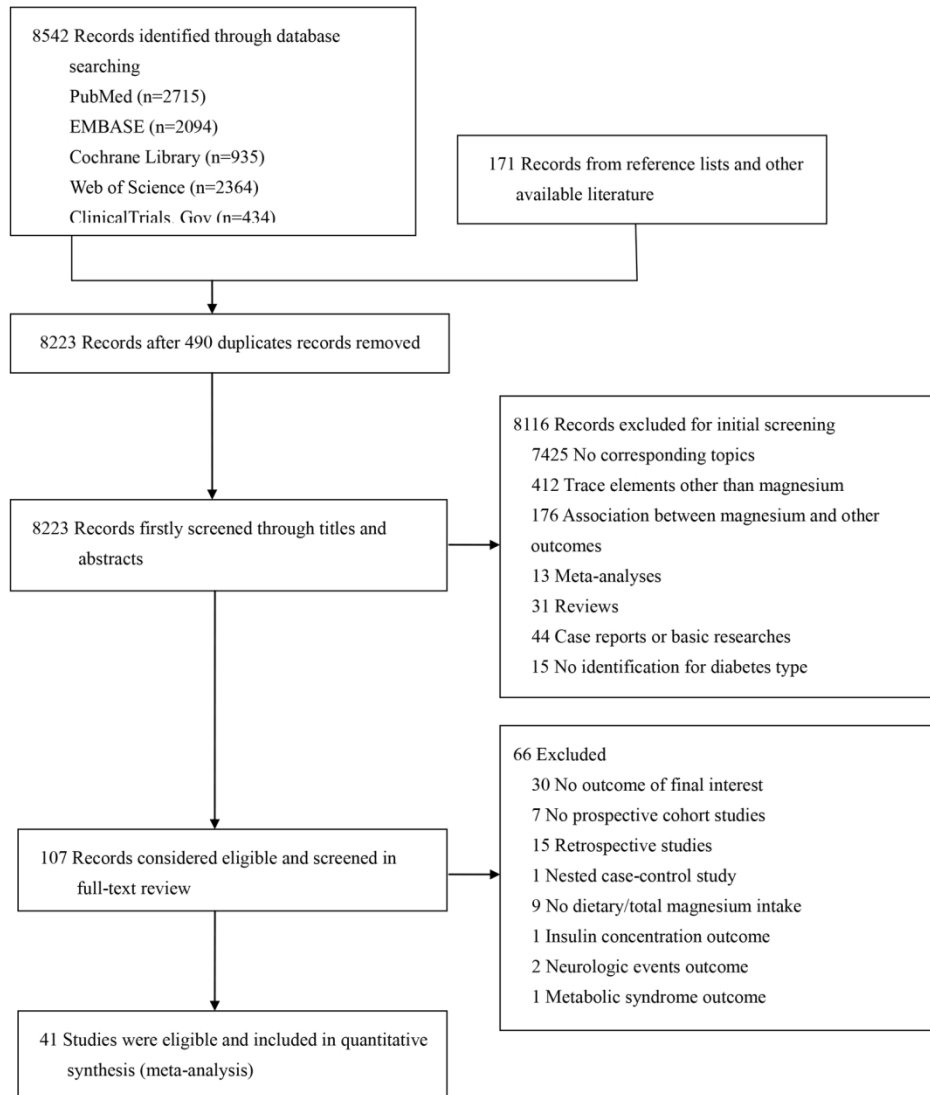


Figure 1. Flow Chart for the Literature Search and Screening Process

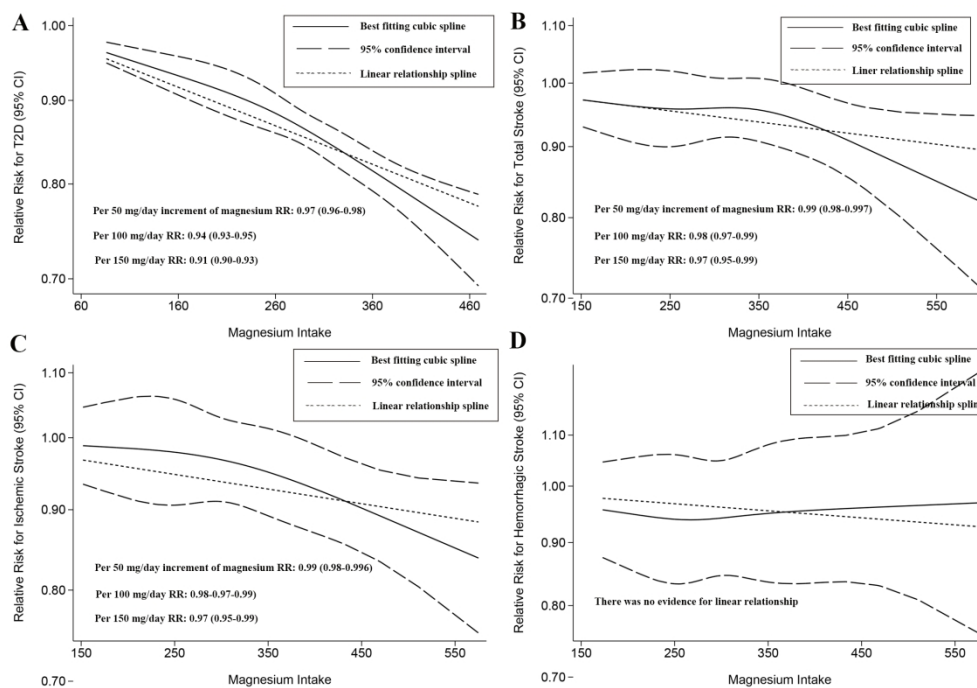


Figure 3. Two-Stage Dose-Response Effect on the Relationships between Magnesium Intake and Type 2 Diabetes (T2D) (A), Total Stroke (B), Ischemic Stroke (C) and Hemorrhagic Stroke (D).



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

Page 1 of 2

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.

Page 2 of 2

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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))
Schulze 2007 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))

1	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))
2	Nanri 2010 ³⁵	Japan	1990-1995	M; 40-65 y	NA	validated FFQ	self-reported questionnaire	634 T2D (25872)	348 VS. 213 (0.86 (0.63-1.16))
3				F; 40-65 y				480 T2D (33919)	333 VS. 213 (0.92 (0.66-1.28))
4	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))
5	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))
6				M; 40-79 y				22.7	634 stroke (23083)
7	Zhang 2012 ³⁸	Japan	1988-2006/	F; 40-79 y	22.9	validated FFQ	follow-up examination	620 stroke (35533)	274 VS. 175 (0.90 (0.69-1.16))
8				M/F; 40-79 y				22.9	417 T2D (1999)
9	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))
10	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))
11				M; 40-69 y				23.6	690 T2D (27769)
12	Oba 2013 ⁴¹	Japan	1990-2000	F; 40-69 y	23.5	validated FFQ	self-reported questionnaire	500 T2D (36864)	356 VS. 211 (0.69 (0.54-0.88))
13				M/F; 21-70 y				NA	FFQ
14	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))
15	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))
16	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))
17	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))
18				F; 30-55 y				26.4	3237 stroke (86149)
19	Adebamowo 2015(2) ⁴⁶	USA	1976-2006	F; 25-42 y	25.7	validated FFQ	self-reported questionnaire	543 stroke (94715)	411 VS. 233 (0.93 (0.79-1.08))
20				M; 40-75 y				26.5	364 stroke (2000)
21	Bain 2015 ⁴⁷	Britain	2002-2008	F; 40-75 y	26.2	7-day diary recall	follow-up examination	511 stroke (2445)	374 VS. 456 (0.82 (0.54-1.24))
22				M/F; ≥65 y				NA	24 h dietary recall and SFFQ
23	Huang 2015 ⁴⁸	Taipei	2000-2008	F; 30-55 y	24.8			7620 T2D (69176)	390 VS. 229 (0.80 (0.73-0.88))
24				M; mean 53.5 y				24.8	3430 T2D (42096)
25	Hruby 2017 ⁴⁹	USA	1991-2013	F; 25-42 y	24.6	validated SFFQ	self-reported questionnaire	6080 T2D (91471)	424 VS. 249 (0.89 (0.81-0.99))
26				M; 40-69 y				23.6	2576 stroke (39505)
27	Kokubo 2017 ^{50b}	Japan	1990-2009	F; 40-69 y	23.6	FFQ	follow-up examination	1846 stroke (45788)	333 VS. 213 (0.88 (0.67-1.14))
28				M; ≥35 y				22.6	266 T2D (5885)
29	Konishi 2017 ⁵¹	Japan	1992-2002	F; ≥35 y	22.1	validated FFQ	self-reported questionnaire	172 T2D (7640)	432 VS. 285 (0.50 (0.30-0.84))
30									

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

39 ^a, different ethnicities of participants are in multiple nations cohort;

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

41 ^c the range of enrolled participants age is not mentioned.

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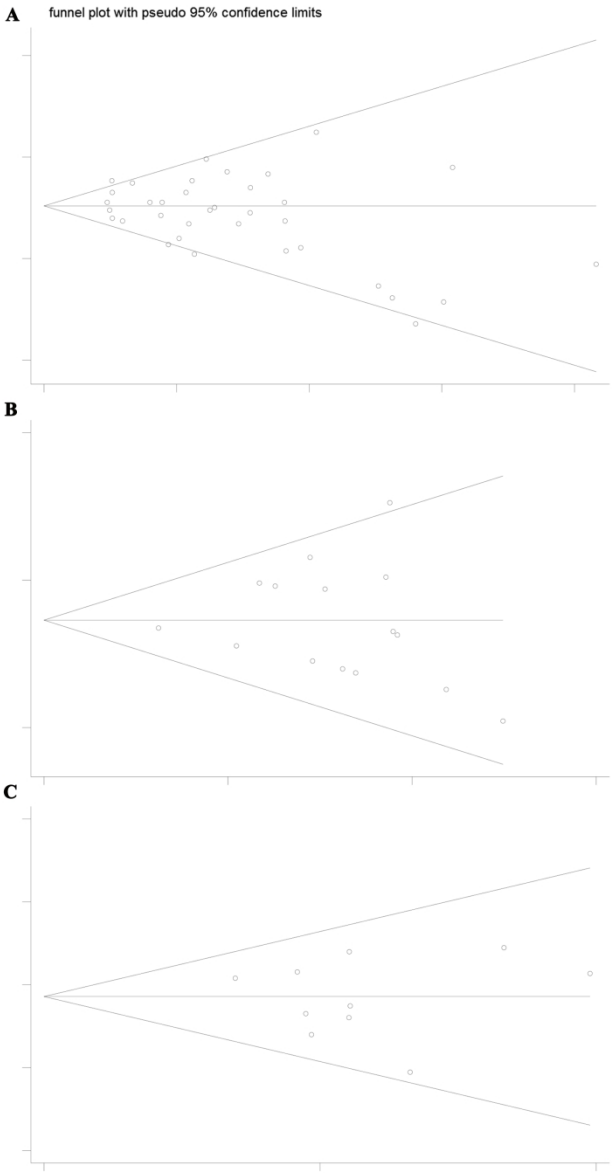
For peer review only

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

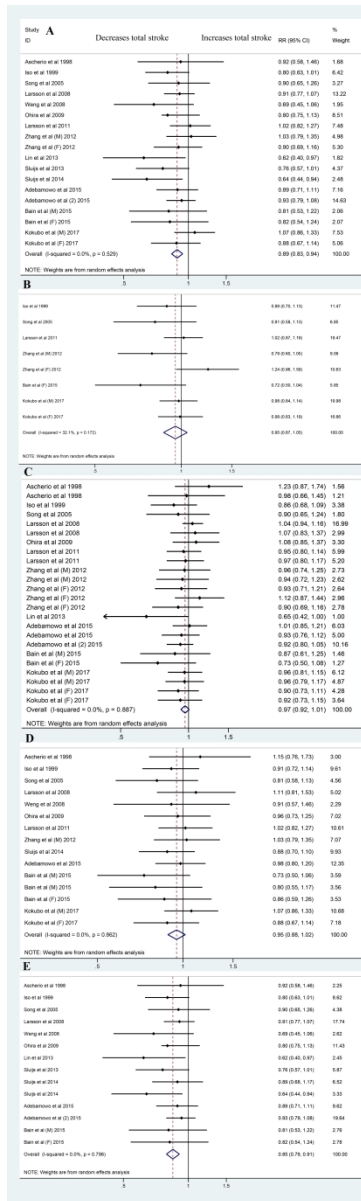
	Study	Selection				Comparability	Outcome			Total score
		Exposed cohort	Nonexposed cohort	Ascertainment of exposure	Outcome of interest		Assessment of outcome	Length of follow-up	Adequacy of follow-up	
1										
2										
3										
4										
5										
6										
7	1997	Salmeron et al, ¹¹	*	*	*	*	**	*	*	9
8	1997	Salmeron et al (2), ¹²	*	*	*	*	**	*	*	9
9	1998	Ascherio et al, ¹³	*	*	*	*	**	*	*	9
10	1999	Iso et al, ¹⁴	*	*	*	*	**	*	*	9
11	1999	Kao et al, ¹⁵	*	*	*	*	**	*	*	9
12	1999	Kao et al, ¹⁵	*	*	*	*	**	*	*	9
13	2000	Liu et al, ¹⁶	*	*	*	*	**	*	*	9
14	2000	Meyer et al, ¹⁷	*	*	*	*	**	*	*	9
15	2000	Meyer et al, ¹⁷	*	*	*	*	**	*	*	9
16	2004	Hodge et al, ¹⁸	*	*	*	*	*	*	*	7
17	2004	Hodge et al, ¹⁸	*	*	*	*	*	*	*	7
18	2004	Lopez et al, ¹⁹	*	*	*	*	**	*	*	9
19	2004	Lopez et al, ¹⁹	*	*	*	*	**	*	*	9
20	2004	Song et al, ²⁰	*	*	*	*	**	*	*	9
21	2004	Song et al, ²⁰	*	*	*	*	**	*	*	9
22	2005	Song et al, ²¹	*	*	*	*	**	*	*	9
23	2005	Song et al, ²¹	*	*	*	*	**	*	*	9
24	2006	Liu et al, ²²	*	*	*	*	**	*	*	9
25	2006	Liu et al, ²²	*	*	*	*	**	*	*	9
26	2006	Pereira et al, ²³	*	*	*	*	**	*	*	9
27	2006	Pereira et al, ²³	*	*	*	*	**	*	*	9
28	2006	Pittas et al, ²⁴	*	*	*	*	**	*	*	9
29	2006	Pittas et al, ²⁴	*	*	*	*	**	*	*	9
30	2006	Van et al, ²⁵	*	*	*	*	**	*	*	9
31	2006	Van et al, ²⁵	*	*	*	*	**	*	*	9
32	2007	Schulze et al, ²⁶	*	*	*	*	**	*	*	9
33	2007	Schulze et al, ²⁶	*	*	*	*	**	*	*	9
34	2008	Larsson et al, ²⁷	*	*	*	*	**	*	*	9
35	2008	Larsson et al, ²⁷	*	*	*	*	**	*	*	9
36	2008	Weng et al, ²⁸	*	*	*	*	**	*	*	9
37	2008	Weng et al, ²⁸	*	*	*	*	**	*	*	9
38	2009	Kirii et al, ²⁹	*	*	*	*	**	*	*	9
39	2009	Kirii et al, ²⁹	*	*	*	*	**	*	*	9
40	2009	Ohira et al, ³⁰	*	*	*	*	**	*	*	9
41	2009	Ohira et al, ³⁰	*	*	*	*	**	*	*	9
42	2009	Villegas et al, ³¹	*	*	*	*	**	*	*	9
43	2009	Villegas et al, ³¹	*	*	*	*	**	*	*	9
44	2010	Hopping et al, ³²	*	*	*	*	**	*	*	9
45	2010	Hopping et al, ³²	*	*	*	*	**	*	*	9
46	2010	Kim et al, ³³	*	*	*	*	**	*	*	8
47	2010	Kim et al, ³³	*	*	*	*	**	*	*	8
48	2010	Kirii et al, ³⁴	*	*	*	*	**	*	*	9
49	2010	Kirii et al, ³⁴	*	*	*	*	**	*	*	9
50	2010	Nanri et al, ³⁵	*	*	*	*	**	*	*	9
51	2010	Nanri et al, ³⁵	*	*	*	*	**	*	*	9
52	2011	Larsson et al, ³⁶	*	*	*	*	**	*	*	9
53	2011	Larsson et al, ³⁶	*	*	*	*	**	*	*	9
54	2012	Weng et al, ³⁷	*	*	*	*	**	*	*	8
55	2012	Weng et al, ³⁷	*	*	*	*	**	*	*	8

1	2012	Zhang et al, ³⁸	*	*	*	*	**	*	*	*	9
2	2013	Hata et al, ³⁹	*	*	*	*	**	*	*	*	9
3	2013	Lin et al, ⁴⁰	*	*	*	*	**	*	*	*	9
4	2013	Oba et al, ⁴¹	*	*	*	*	**	*	*	*	9
5	2013	Sluijs et al, ⁴²	*	*	*	*	**		*	*	8
6	2014	Hruby et al, ⁴³	*	*	*	*	**	*	*	*	9
7	2014	Sluijs et al, ⁴⁴	*	*	*	*	**	*	*	*	9
8	2015	Adebamowo et al, ⁴⁵	*	*	*	*	**	*	*	*	9
9	2015	Adebamowo et al (2), ⁴⁶	*	*	*	*	**	*	*	*	9
10	2015	Bain et al, ⁴⁷	*	*	*	*	**	*	*	*	9
11	2015	Huang et al, ⁴⁸	*	*	*	*	**	*	*	*	8
12	2017	Hruby et al, ⁴⁹	*	*	*	*	**	*	*	*	9
13	2017	Kokubo et al, ⁵⁰	*	*	*	*	**	*	*	*	9
14	2017	Konishi et al, ⁵¹	*	*	*	*	*	*	*	*	9

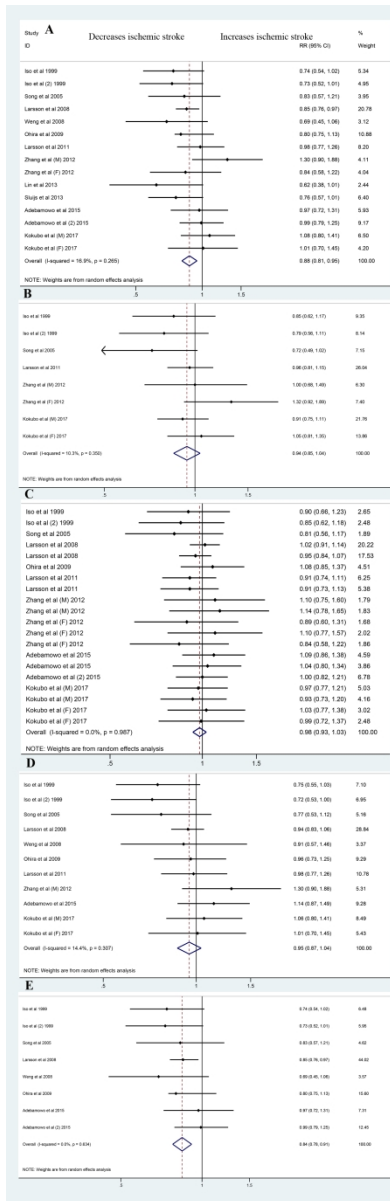
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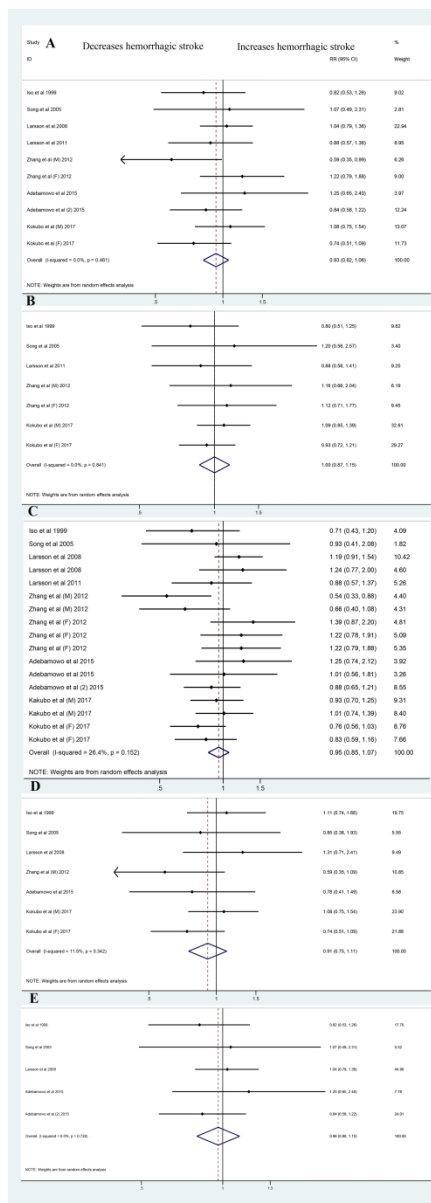
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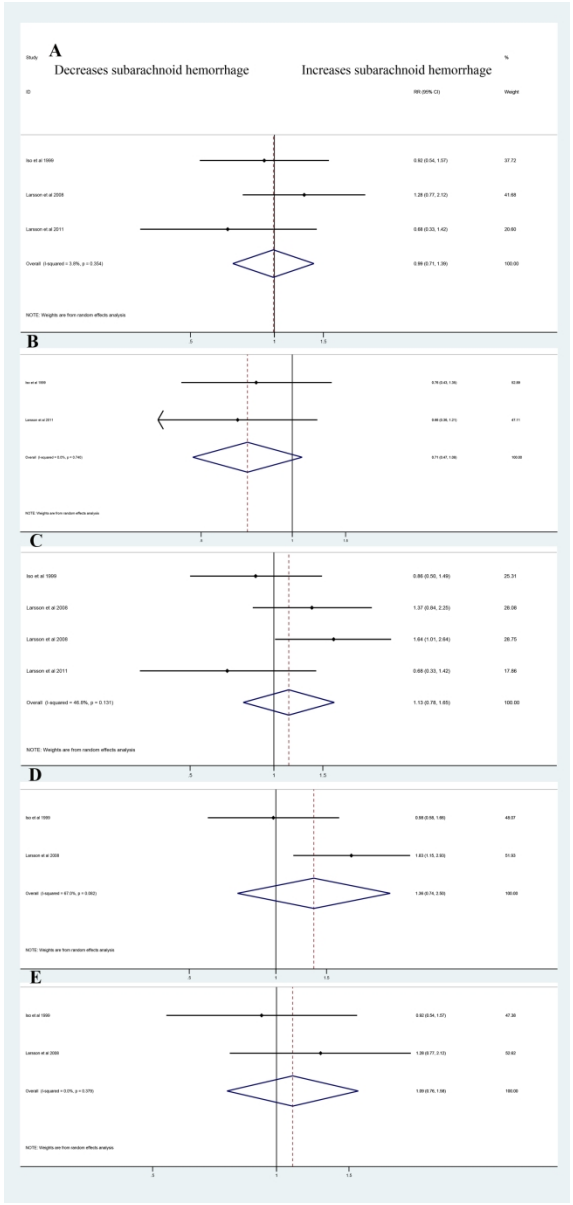
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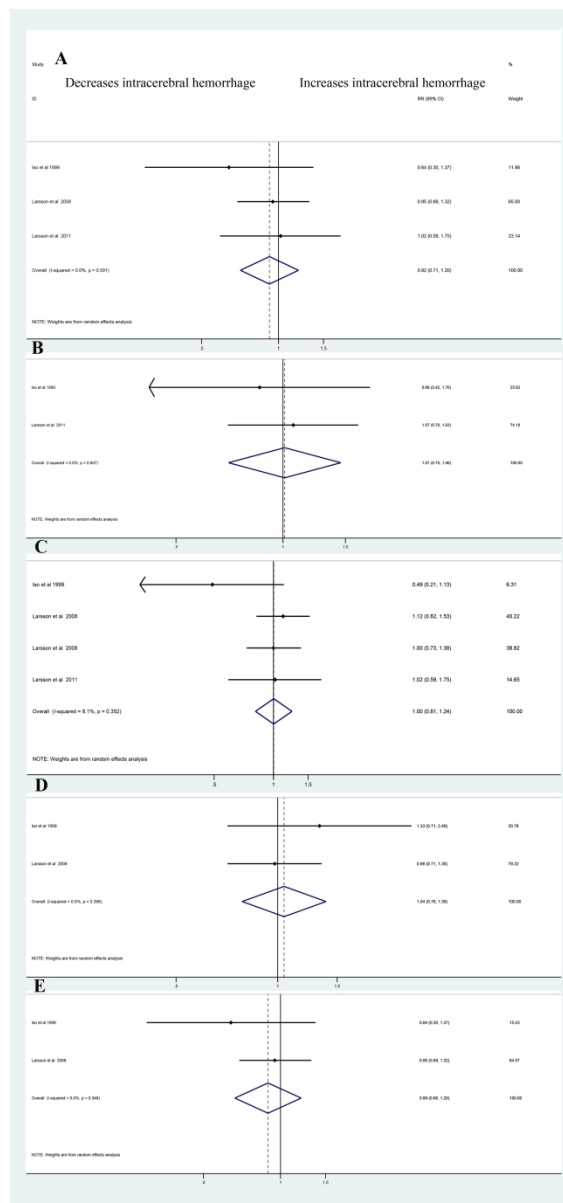
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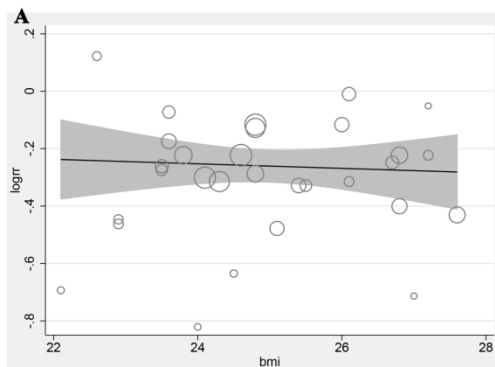


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B
. tabulate sex, generate ( sexnew )

      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
RMSE 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    | -1.1314075  .0857798   -1.53  0.135   -1.3061323   -.0433174
sexnew2    | -.0630804   .0541113   -1.17  0.252   -1.733016   -.0471407
      _cons | -1.956565   .0461514   -4.24  0.000   -2.096637   -1.1016492
    
```

```

C
. tabulate participantregion, generate ( participantregionnew )

      participantregion | Freq.  Percent   Cum.
-----+-----
on                    |    35    100.00
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 participantregionnew1 participantregionnew2 participantregionnew3, wsse (selogrr) knapphartung reml
note: participantregionnew3 dropped because of collinearity

Meta-regression              Number of obs =   35
RMSE estimate of between-study variance      tau2 = .004698
% residual variation due to heterogeneity     I-squared_res = 35.22%
Proportion of between-study variance explained  Adj R-squared = -30.80%
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]
-----+-----
participantregionnew2 | .0027567  .0731865   0.04  0.970   -1.63193   .1518327
participantregionnew1 | -.001657  .0599158  -0.34  0.739   -1.422102   .1018788
      _cons | -2.392399  .0510872  -4.68  0.000   -2.483012   -1.351766
    
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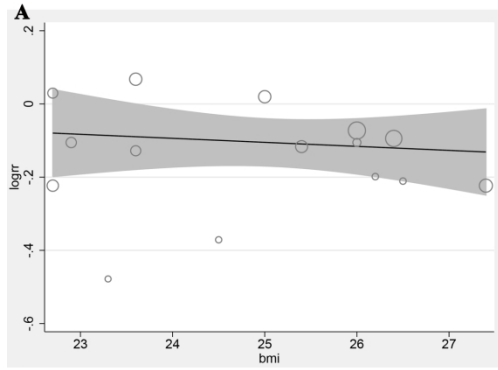
D
. tabulate dietaryassessment, generate ( dietaryassessmentnew )

      dietaryassessment | Freq.  Percent   Cum.
-----+-----
24h dietary recall and FFQ |     1     2.86   2.86
FFQ                       |     4    11.43  14.29
SPFQ                      |     1     2.86  17.14
validated DRQ             |     1     2.86  20.00
validated FFQ             |    17    48.57  68.57
validated SPFQ            |    15    42.86  100.00
-----+-----
Total                      |    35    100.00

. metareg logrr dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3 dietaryassessmentnew4 dietaryassessmentnew5 dietaryassessmentnew6 dietaryassessmentnew7 dietaryassessmentnew8 dietaryassessmentnew9 dietaryassessmentnew10 dietaryassessmentnew11 dietaryassessmentnew12 dietaryassessmentnew13 dietaryassessmentnew14 dietaryassessmentnew15 dietaryassessmentnew16 dietaryassessmentnew17 dietaryassessmentnew18 dietaryassessmentnew19 dietaryassessmentnew20 dietaryassessmentnew21 dietaryassessmentnew22 dietaryassessmentnew23 dietaryassessmentnew24 dietaryassessmentnew25 dietaryassessmentnew26 dietaryassessmentnew27 dietaryassessmentnew28 dietaryassessmentnew29 dietaryassessmentnew30 dietaryassessmentnew31 dietaryassessmentnew32 dietaryassessmentnew33 dietaryassessmentnew34 dietaryassessmentnew35 dietaryassessmentnew36 dietaryassessmentnew37 dietaryassessmentnew38 dietaryassessmentnew39 dietaryassessmentnew40 dietaryassessmentnew41 dietaryassessmentnew42 dietaryassessmentnew43 dietaryassessmentnew44 dietaryassessmentnew45 dietaryassessmentnew46 dietaryassessmentnew47 dietaryassessmentnew48 dietaryassessmentnew49 dietaryassessmentnew50 dietaryassessmentnew51 dietaryassessmentnew52 dietaryassessmentnew53 dietaryassessmentnew54 dietaryassessmentnew55 dietaryassessmentnew56 dietaryassessmentnew57 dietaryassessmentnew58 dietaryassessmentnew59 dietaryassessmentnew60 dietaryassessmentnew61 dietaryassessmentnew62 dietaryassessmentnew63 dietaryassessmentnew64 dietaryassessmentnew65 dietaryassessmentnew66 dietaryassessmentnew67 dietaryassessmentnew68 dietaryassessmentnew69 dietaryassessmentnew70 dietaryassessmentnew71 dietaryassessmentnew72 dietaryassessmentnew73 dietaryassessmentnew74 dietaryassessmentnew75 dietaryassessmentnew76 dietaryassessmentnew77 dietaryassessmentnew78 dietaryassessmentnew79 dietaryassessmentnew80 dietaryassessmentnew81 dietaryassessmentnew82 dietaryassessmentnew83 dietaryassessmentnew84 dietaryassessmentnew85 dietaryassessmentnew86 dietaryassessmentnew87 dietaryassessmentnew88 dietaryassessmentnew89 dietaryassessmentnew90 dietaryassessmentnew91 dietaryassessmentnew92 dietaryassessmentnew93 dietaryassessmentnew94 dietaryassessmentnew95 dietaryassessmentnew96 dietaryassessmentnew97 dietaryassessmentnew98 dietaryassessmentnew99 dietaryassessmentnew100, wsse (selogrr) knapphartung reml
note: dietaryassessmentnew2 through dietaryassessmentnew100 dropped because of collinearity

Meta-regression              Number of obs =   35
RMSE 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(15,29) = 0.16
With Knapp-Hartung modification              Prob > F = 0.5210

      logrr | Coef.  Std. Err.   t   P>|t|   [95% Conf. Interval]
-----+-----
dietaryassessmentnew1 | .1072405  .5101822   0.20  0.841   -1.07096   1.339455
dietaryassessmentnew2 | .0470373  .294068   1.58  0.124   -1.394023   1.073557
dietaryassessmentnew3 | -.5104405 .311752   -1.64  0.107   -1.152599   1.155949
dietaryassessmentnew4 | .3690754 .2813794   1.30  0.205   -1.204983   .4659589
dietaryassessmentnew5 | .3948872  .2812421   1.40  0.171   -1.057583   .4697238
dietaryassessmentnew6 | -.6388793 .279225   -2.27  0.031   -1.205958   -.071790
    
```

```

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, wase (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
    
```

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C . tabulate participantregion, generate (participantregionnew)

participantregion      Freq.      Percent      Cum.
-----+-----
asia                   6      33.33      33.33
Europe                 4      22.22      55.56
North America         4      22.22      77.78
-----+-----
Total                  18      100.00

. metareg logrr participantregionnew1 participantregionnew2 participantregionnew3, wase (selogrr) knapphartung reml random
note: participantregionnew3 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]
-----+-----
participantregionnew1     .056278     .0743754      0.74      0.470     -.1061605     .1196149
participantregionnew2    -1028959     .8725841     -1.18      0.249     -1.518134     .1574053
      _cons     -1378955     .8476362     -1.63      0.112     -2.387575     -.3694336
    
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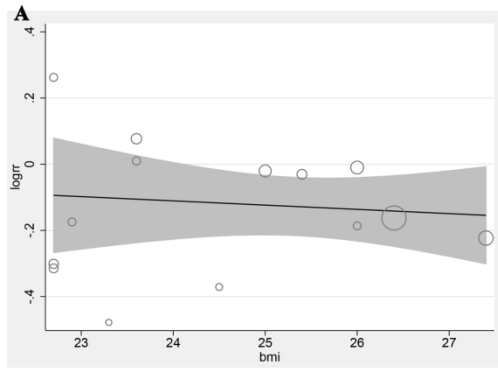
D . tabulate dietaryassessment, generate (dietaryassessmentnew)

dietaryassessment      Freq.      Percent      Cum.
-----+-----
1-day diary recall      2      11.11      11.11
FFQ                     4      22.22      33.33
validated FFQ           9      50.00      83.33
validated SPQ           3      16.67      100.00
-----+-----
Total                   18      100.00

. metareg logrr dietaryassessmentnew1 dietaryassessmentnew2 dietaryassessmentnew3, wase (selogrr) knapphartung
> reml
note: dietaryassessmentnew3 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 = 0.20%
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 = 0.9811

      logrr      Coef.      Std. Err.      t      P>|t|      [95% Conf. Interval]
-----+-----
dietaryassessmentnew1    -0596066     .167476     -3.56      0.002     -.0945537     -.0086595
dietaryassessmentnew2    -1046332     .1615368     -6.48      0.000     -1.061318     -.9853465
dietaryassessmentnew3    -1211845     .291513     -4.16      0.000     -1.540595     -.6831355
      _cons     -12845481     .1547379    -83.81      0.000     -1.5407374     -1.014813
    
```



```

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, wase (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   -0.4770662   .0004339
sexnew2      -.0739192   .0940187   -0.79   0.447   -0.2787683   .1309299
      _cons      -.0480002   .0681983   -0.70   0.495   -0.1965933   .1005894
    
```

```

C . tabulate participantregion, generate ( participantregionnew )
      participantregion
      region      Freq.   Percent   Cum.
-----+-----
Asia              4     40.00    40.00
Europe            3     30.00    70.00
North America     8     80.00   100.00
-----+-----
Total             10    100.00

. metareg logrr participantregionnew1 participantregionnew2, wase (selogrr) knapphartung reml
note: participantregionnew3 dropped because of collinearity

Meta-regression              Number of obs =    15
REML estimate of between-study variance      tau2 = .0014
% residual variation due to heterogeneity     I-squared_res = 21.74%
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]
-----+-----
participantregionnew1      -.1089353   .1083661   1.01   0.335   -0.1271992   .3450197
participantregionnew2      .0517202   .0911749   0.53   0.598   -0.1849328   .1030732
      _cons      -.1429514   .0453255   -3.15   0.008   -0.2052493   -.0806492
    
```

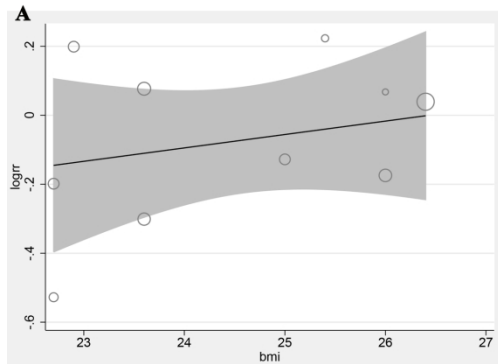
```

D . tabulate dietaryassessment, generate ( dietaryassessmentnew )
      dietaryassessment
      assessment      Freq.   Percent   Cum.
-----+-----
FFQ                  6     40.00    40.00
validated FFQ        9     60.00   100.00
-----+-----
Total                 15    100.00

. metareg logrr dietaryassessmentnew1 dietaryassessmentnew2, wase (selogrr) knapphartung reml
note: dietaryassessmentnew3 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   -0.1508236   .2445382
      _cons      -.1429514   .0453255   -3.15   0.008   -0.2052493   -.0806492
    
```



C

```
. tabulate participantregion, generate ( participantregionew )
```

participantregion	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 participantregionew1 participantregionew2 participantregionew3, wsize (selogrr) knapphartung reml
note: participantregionew3 dropped because of collinearity
```

Meta-regression

REML estimate of between-study variance	tau2	=	-.608835
% 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 # (2,3)	=	0.14
With Knapp-Hartung modification	Prob > F	=	0.8726

logrr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
participantregionew1	-.010555	.1797495	-0.06	0.954	-.4356955 .4143845
participantregionew2	.0796745	.1944402	0.41	0.694	-.3801034 .5394524
_cons	-.9943218	.1371043	-6.49	0.514	-.4195164 .228930

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, wsize (selogrr) knapphartung reml
note: sexnew2 dropped because of collinearity
```

Meta-regression

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

D

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

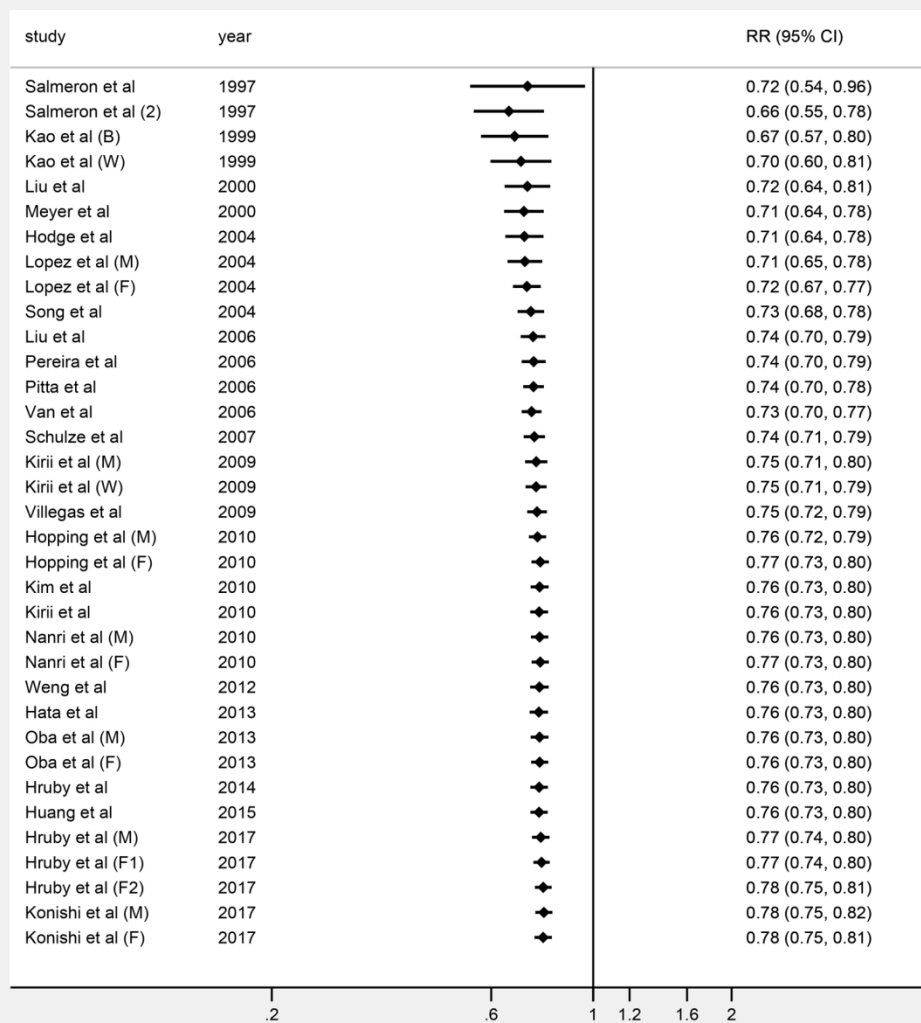
dietaryassessment	Freq.	Percent	Cum.
FFQ	4	40.00	40.00
validated FFQ	6	60.00	100.00
Total	10	100.00	

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

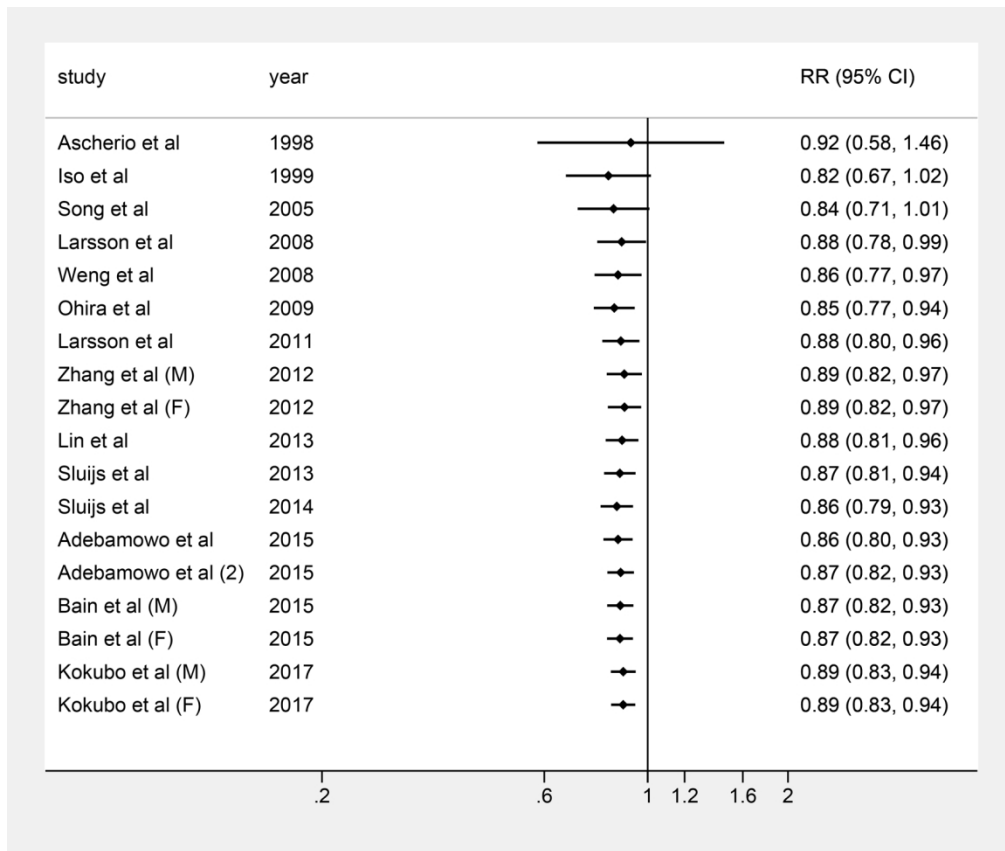
Meta-regression

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			

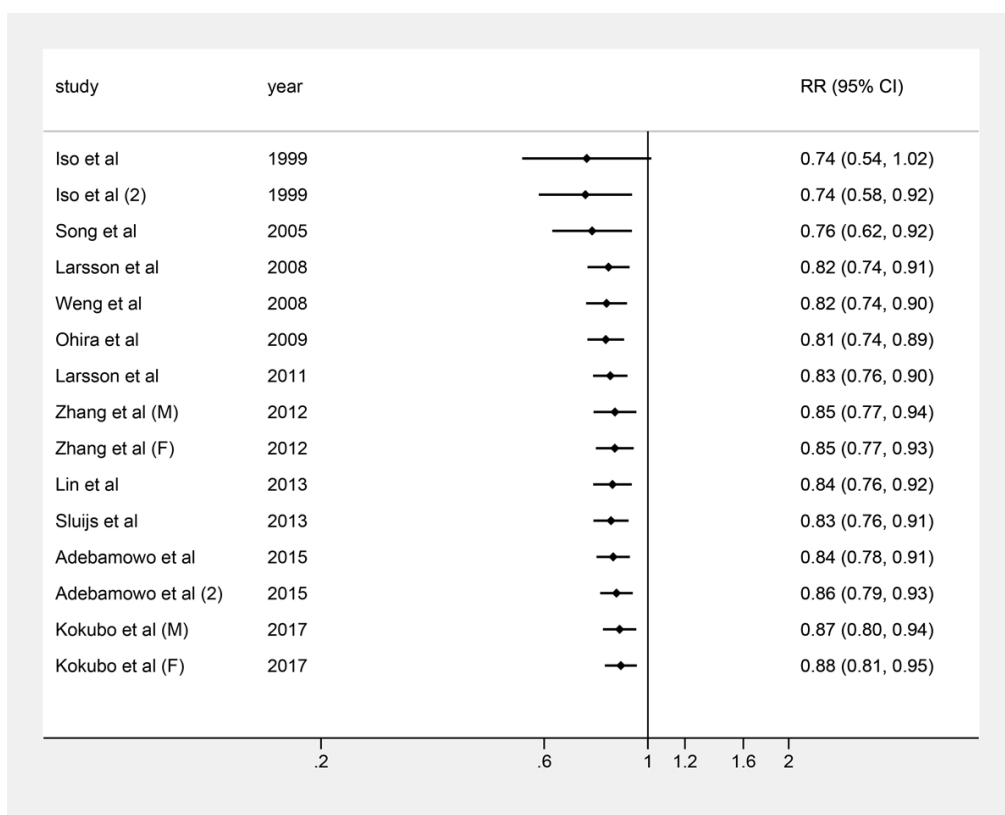
logrr	Coef.	Std. Err.	t	P> t	[95% Conf. Interval]
dietaryassessmentnew1	.0642559	.1426454	0.45	0.644	-.2648051 .3911941
_cons	-.112665	.1133825	-0.99	0.349	-.2741295 .1487955



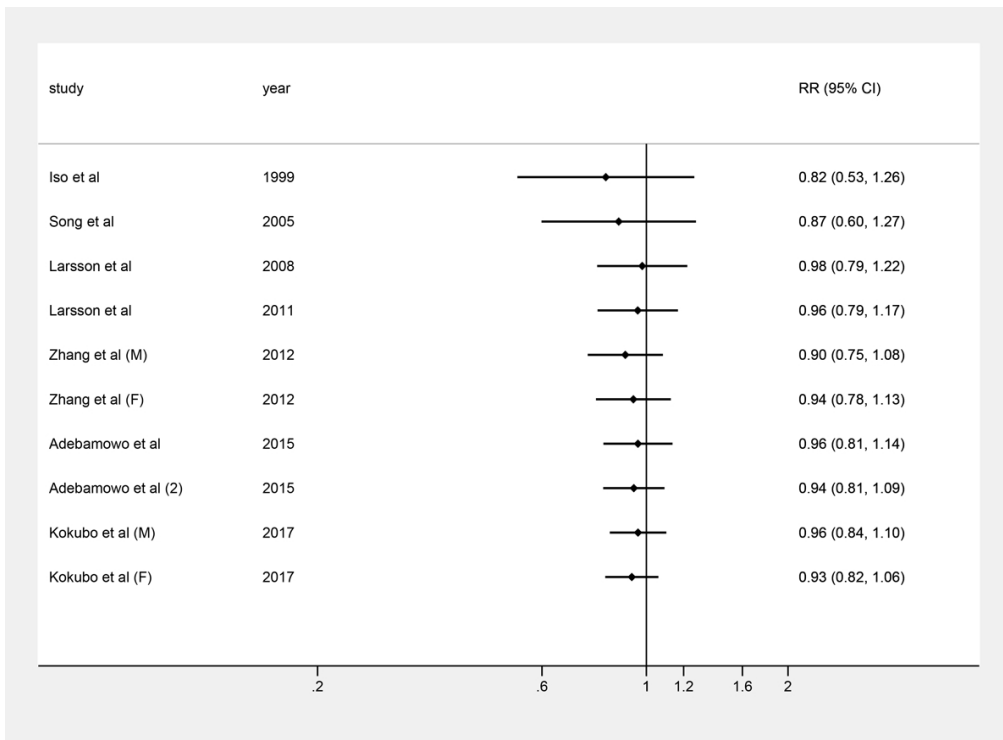
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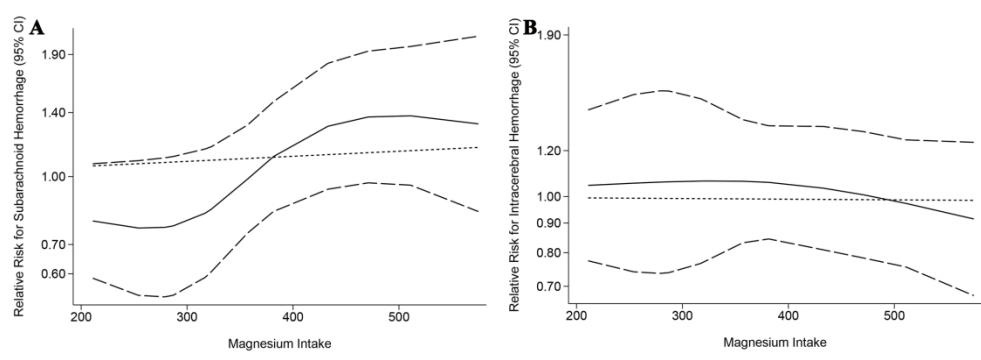




Table S1 PRISMA 2009 Checklist

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

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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