ORIGINAL RESEARCH

Dairy Consumption and Risk of Stroke: A Systematic Review and Updated Dose–Response Meta-Analysis of Prospective Cohort Studies

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Background—A higher milk consumption may be associated with a lower stroke risk. We conducted a comprehensive systematic review and dose–response meta-analysis of milk and other dairy products in relation to stroke risk.

Methods and Results—Through a systematic literature search, prospective cohort studies of dairy foods and incident stroke in stroke-free adults were identified. Random-effects meta-analyses with summarized dose–response data were performed, taking into account sources of heterogeneity, and spline models were used to systematically investigate nonlinearity of the associations. We included 18 studies with 8 to 26 years of follow-up that included 762 414 individuals and 29 943 stroke events. An increment of 200 g of daily milk intake was associated with a 7% lower risk of stroke (relative risk 0.93; 95% CI 0.88–0.98; P=0.004; I^2=86%). Relative risks were 0.82 (95% CI 0.75–0.90) in East Asian and 0.98 (95% CI 0.95–1.01) in Western countries (median intakes 38 and 266 g/day, respectively) with less but still considerable heterogeneity within the continents. Cheese intake was marginally inversely associated with stroke risk (relative risk 0.97; 95% CI 0.94–1.01 per 40 g/day). Risk reductions were maximal around 125 g/day for milk and from 25 g/day onwards for cheese. Based on a limited number of studies, high-fat milk was directly associated with stroke risk. No associations were found for yogurt, butter, or total dairy.

Conclusions—Milk and cheese consumption were inversely associated with stroke risk. Results should be placed in the context of the observed heterogeneity. Future epidemiological studies should provide more details about dairy types, including fat content. In addition, the role of dairy in Asian populations deserves further attention. **(*J Am Heart Assoc*. 2016;5:e002787 doi: 10.1161/JAHA.115.002787)**

Key Words: dairy products • meta-analysis • prospective cohort study • stroke • systematic review

Stroke is the second-leading global cause of death, accounting for 11% of total deaths worldwide,[1] and a major cause of long-term disability.[2] East Asian countries such as Japan and China have greater mortality and morbidity from stroke than from coronary heart disease, whereas it is the opposite in Western countries.[3] A healthy diet is important for the primary prevention of stroke.[4,5] In Western as well as Asian countries, dairy consumption is recommended as part of a healthy diet.[6–9] For example, in the United States, 3 daily servings of dairy, mainly low-fat or fat-free, is recommended.[7] The Chinese and Japanese recommendations are 300 mL of daily dairy[8] and 2 daily servings of milk and dairy products, respectively.[9]

In 2011, we observed a nonsignificant inverse association of milk with stroke risk with a relative risk (RR) of 0.87 (95% CI: 0.72–1.07) per 200 mL of daily intake in a meta-analysis.[10] This meta-analysis was, however, based on only 6 cohort studies and showed large heterogeneity, partly due to a strong inverse association in a Japanese cohort.[11] In a more recent meta-analysis of dairy consumption and stroke risk, the pooled RR was 0.91 (95% CI 0.82–1.01) for high versus low milk intake with large heterogeneity, based on 9 studies,[12] including 1 study in children.[13] Based on 6 studies, the association was nonlinear.[12]

Several new prospective cohort studies[14–17] have become available on the association between dairy consumption and stroke risk, amounting to a total of 18

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An accompanying Data S1 is available at http://jaha.ahajournals.org/content/5/5/e002787/DC1/embed/inline-supplementary-material-1.pdf

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studies. Most evidence of dairy in relation to stroke risk relates to milk consumption. However, a considerable amount of heterogeneity was present in 2 previous meta-analyses in relation to the results of milk.[10,12] Previous investigations on heterogeneity were limited based on the number of available studies[10] or were limited to the analysis of total dairy only.[12] We conducted a comprehensive dose–response meta-analysis, taking into account potential nonlinear associations and sources of heterogeneity (such as continent, type of stroke, and fat content), for which additional or unpublished data were obtained from investigators.

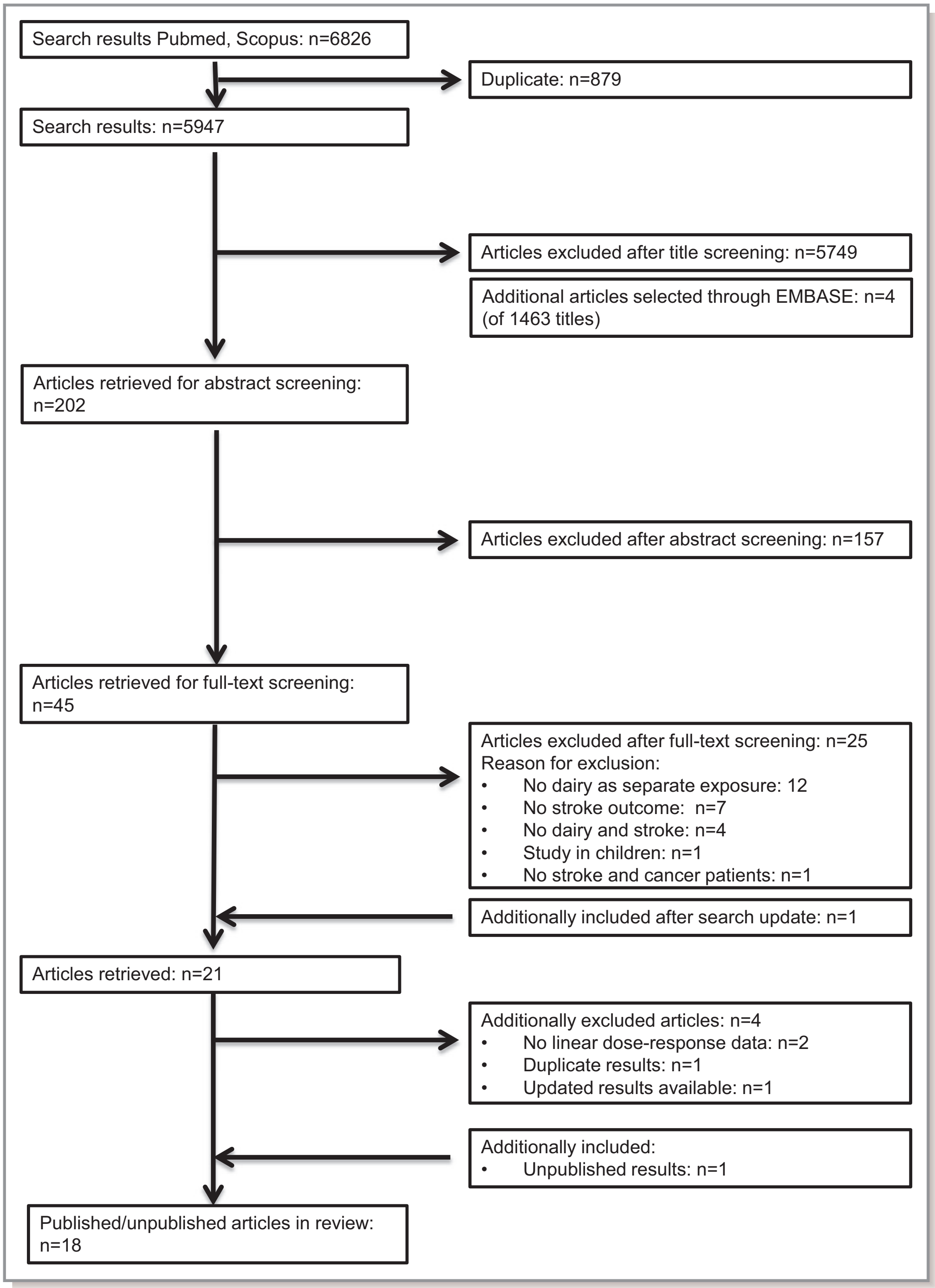

Figure 1. Flow chart of literature search for meta-analysis on dairy intake and incident stroke.

Table 1. Characteristics of 18 Prospective Cohort Studies on Dairy Consumption and Stroke Risk

Study, Country	Men (%); Mean Age (Range)	Follow-Up Time (Years) (Range)	No. Events (Cohort Size)	Dairy Types	Dietary Method, Years	Outcome; Source	Adjustments
Bernstein 2012,[23] Health Professionals Follow-up Study	100; (30–55)	19.3	1397 (43 150)	Low-fat dairy High-fat dairy	1986, 131 item FFQ with updated information in 1990, 1994, 1998, 2002, 2006.	Total stroke; Registries and medical records	Stratified on age, time period, adjusted for BMI, cigarette smoking, PA, parental history of early MI, multivitamin use, vitamin E supplement use, aspirin use, intake of total energy, cereal fiber, alcohol, trans fat, fruits and vegetables, other protein sources
Bernstein 2012,[23] Nurses' Health Study	0; (30–55)	24.3	2633 (84 010)	Low-fat dairy High-fat dairy	1980, 61 item FFQ with updated and extended information in 1986, 1990, 1994, 1998, 2002.	Total stroke; Registries and medical records	Stratified on age, time period, adjusted for BMI, cigarette smoking, PA, parental history of early MI, menopausal state, multivitamin use, vitamin E supplement use, aspirin use, intake of total energy, cereal fiber, alcohol, trans fat, fruits and vegetables, other protein sources
Dalmeijer 2013,[22] EPIC-NL, The Netherlands	26; 49	13.1	531 (33 625)	Total dairy Low-fat dairy High-fat dairy milk products Fermented dairy Cheese	1993–1997, 178-item FFQ	Total stroke; Registries	Sex, age, total energy, PA, smoking, education, BMI, intake of ethanol, coffee, fruit, vegetables, fish, meat, bread
Elwood 2004,[32] Caerphilly, UK	100; 52 (45–59)	22* (20–24)	185 (2403)	Milk	1979–1983, FFQ	Total stroke; GP and hospital records	Age, total energy, smoking, social class, BMI, SBP, consumption of alcohol, fat, prior vascular disease
Goldbohm 2011,[29] Netherlands Cohort Study, The Netherlands Men Women	100; 0; (55–69)	10*	 657 (12 912) 397 (7870)	Low-fat dairy milk products Low-fat milk (nonfermented) High-fat milk (nonfermented) fermented dairy[†] Cheese Butter	1986, 150-item FFQ	Fatal stroke; National registries	Age, education, smoking (cigarette, cigar, pipe), nonoccupational PA, occupational PA, BMI, multivitamin use, alcohol, total energy, MUFA, PUFA, vegetables, fruits
Iso 1999,[28] Nurses' Health Study, USA	0; 46	13.6	347 (85 764)	Milk Low-fat milk High-fat milk Yogurt Cheese	1980, 61-item FFQ	Ischemic stroke; Medical records, national registries, relatives, death certificates	Age, smoking, time period, BMI, alcohol, menopausal status (including hormone replacement therapy), PA, multivitamin use, vitamin E supplementation, history of hypertension, DM, and hypercholesterolemia
Kinjo 1999,[11] Six prefectures, Japan	46[‡]; (40–69)	15*	Total stroke: 11 030; Ischemic stroke: 4084 (223 170)	Milk	1965, 1-page questionnaire	Fatal total, ischemic, and hemorrhagic stroke; Death registry (ICD-7)	Sex, age, follow-up interval, prefecture, alcohol drinking, smoking, occupation

Continued

Table 1. Continued

Study, Country	Men (%); Mean Age (Range)	Follow-Up Time (Years) (Range)	No. Events (Cohort Size)	Dairy Types	Dietary Method, Years	Outcome; Source	Adjustments
Kondo, 2013,[19] NIPPON, Japan Men Women	 100 0 50.3 (>30)	24*	 217 (4045) 200 (5198)	Milk and dairy products§	1980, weighed diet records during 3 consecutive weekdays	Fatal stroke; death registry (ICD-9; 430–438)	Age, BMI, smoking, alcohol drinking habit, history of DM, use of antihypertensives, work category, total energy intake
Larsson 2009[20] ATBC, Finland	100; 57.6 (50–69)	13.6	3365 (26 556)	Total dairy Milk Low-fat milk High-fat milk Yogurt Cheese Butter	1985–1988, 276-item FFQ	Total, ischemic, and hemorrhagic stroke; national registries (ICD8: 430–434, 436 or ICD9 or ICD10)	Age, supplementation group, education, cigarettes, BMI, serum total cholesterol, serum HDL-cholesterol, history of DM and heart disease, leisure-time PA, total energy, alcohol, caffeine, sugar, red meat, poultry, fish, fruit, fruit juices, vegetables, potatoes, whole grains, refined grains
Larsson 2012,[21] Swedish Mammography Cohort, Cohort of Swedish Men, Sweden	54; 60.3 (45–83)	10.2	4089 (74 961)	Total dairy Low-fat dairy High-fat dairy Milk Fermented dairy† Cheese	1997, 96-item FFQ	Total, ischemic, or hemorrhagic stroke; Swedish national hospital discharge registry (ICD10: I60, I61, I63, I64)	Age, sex, smoking status, smoking pack years, education, BMI, PA, aspirin use, history of hypertension, DM, family history of MI, total energy, alcohol, coffee, fresh red meat, processed meat, fish, fruits, vegetables, mutually adjusted for other dairy types
Lin 2013,[24] CVDFACTS, China	23; 45.8	10.5* (9–12)	123 (2061)	Total dairy§	1990–1993, 49-item FFQ	Total stroke; self-report confirmed by medical records, death certificate (ICD9: 430–438)	Sex, age, urinary sodium/creatinine, smoking status, drinking status, PA, BMI, SBP change, DBP change, hypertension medication
Louie 2013,[33] BMES, Australia	44; 65.4	15*	158 (2662)	Total dairy Low-fat dairy High-fat dairy	1992–1994, 145-item FFQ	Fatal stroke; National death registry (ICD9 and ICD10; I60–I69)	Age, sex, total energy, BMI, weight change, PA, previous MI, previous stroke, smoking, stage II hypertension, type 2 DM, use of antihypertensive medication, use of statins, change in dairy intake
Misirli 2012,[16] EPIC Greece, Greece	41; NR	10.6	395 (23 601)	Total dairy	1994–1999, 150-item FFQ, validated, but no information on validation provided	Total stroke, fatal stroke; I60 to I69, G45, G46; Self-report verified by pathology reports, medical records, discharge diagnosis, or death certificates.	Sex, age, education, smoking, BMI, PA, hypertension, DM, total energy intake
Ness 2001[30] Collaborative Study, Scotland	100; 48.3 (35–64)	25*	196 (5765)	Milk	1970–1973, FFQ validated, 1 question on usual milk intake	Fatal stroke; Death registry	Age, smoking, DBP, cholesterol, BMI, adjusted forced expiratory volume, social class, father's social class, education, deprivation category, siblings, car user, angina, electrocardiogram ischemia, bronchitis, and alcohol consumption

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Table 1. Continued

Study, Country	Men (%); Mean Age (Range)	Follow-Up Time (Years) (Range)	No. Events (Cohort Size)	Dairy Types	Dietary Method, Years	Outcome; Source	Adjustments
Pan, Singapore Chinese Cohort Study, Singapore (unpublished data)	45; 60* (45–74)	14.7	1098 (total stroke) 579 (ischemic stroke) (57 078)	Total dairy Milk	1993–1998, 165-item FFQ	Fatal total, ischemic, and hemorrhagic stroke; Registry linkage	Age, sex, dialect, year of interview, educational level, BMI, PA, smoking status, alcohol use, baseline history of self-reported DM, hypertension, and total energy intake, dietary intakes of red meat, poultry, fish, vegetables, fruit, all grains, tea and coffee
Praagman 2015[15] Rotterdam Study, The Netherlands	38; 66.9 (>55)	17.3	182 (4235)	Total dairy Low-fat dairy High-fat dairy Milk Fermented dairy Cheese Yogurt	1990–1993, validated 170-item FFQ	Total stroke, fatal stroke; Medical records, validated by a specialist and (incident stroke) by linkage with GP and medical specialists (ICD10: I60–I69)	Sex, age, total energy intake, BMI, smoking, education, alcohol, vegetables, fruit, meat, bread, fish, coffee, tea
Sauvaget 2003[31] Life-span study, Japan	38; 56	15.5* (15–16)	1094 (31 831)[‖]	Milk	1979–1981, 22-item FFQ, validated for animal products	Fatal stroke; National registration (ICD9) and death certificates	Stratified on sex, birth cohort, adjusted for city, radiation dose, self-reported BMI, smoking status, alcohol habits, education level, history of DM or hypertension
Sonestedt 2011[25] Malmö, diet and cancer cohort, Sweden	38; 57.3 (44–74)	12	1176 (26 445)	Total dairy Milk Fermented dairy[†] Low-fat milk High-fat milk Cheese Butter	1991–1996, modified diet history method (7 days) and 168-item questionnaire	Total stroke; Hospital discharge register and cause-of-death register, local stroke register of Malmö (ICD9; 430, 431, 434, 436)	Age, sex, season, method, energy intake, BMI, smoking, alcohol consumption, leisure-time PA, education
Yaemsiri 2012[17] WHI-OS, USA	0; 63.5	7.6 (7–11)	1049 (87 025)	Total dairy	1994–1998, 120-item FFQ at baseline and after 3 years	Incident ischemic stroke	Age, race, education, family income, smoking years, hormone replacement therapy, metabolic equivalent task hours per week, alcohol intake, history of coronary heart disease, atrial fibrillation, DM, use of aspirin, antihypertensive medication, cholesterol-lowering medication, BMI, SBP, total energy intake

BMI indicates body mass index; DBP, diastolic blood pressure; DM, diabetes mellitus; FFQ, food frequency questionnaire; GP, general practitioner; ICD, International Classification of Diseases; MI, myocardial infarction; MUFA, monounsaturated fatty acids; NR, not reported; PA, physical activity; PUFA, polyunsaturated fatty acids; SBP, systolic blood pressure; WHI-OS, Women's Health Initiative Observational Study.

*Midpoint of range.

†Fermented dairy comprised yogurt and sour milk,[25] fermented sour cream and yogurt,[21] or fermented low-fat milk,[29] which were the largest contributors to total fermented dairy in these studies.

‡Retrieved from other publications of this cohort.

§According to the authors, total dairy is mainly milk: 93% of total dairy[19] or almost all dairy (personal communication Dr Lin) comprised milk and is therefore included in milk analysis.

‖Based on milk as exposure.

Table 2. Results of Linear and Nonlinear Dose–Response Meta-Analyses

Dairy Type (Increment g/day)	Studies	No Studies (Results)	RR (95% CI), *P* Value	Heterogeneity I^2 (%), *P* Value	No Events; Total n	Median Intake (g/day),* Range	Knot, *P* Nonlinearity RR (95% CI) at Knot
Milk (200)	[11,15,19–22,24,25,28–32]	14 (16)	0.93 (0.88–0.98), 0.004	86.0; <0.001	25 269; 603 920	147, 0 to 1051	125 g/day, <0.001 0.86 (0.82–0.89)
	Western countries[15,20–22,25,28–30,32]	9 (10)	0.98 (0.95–1.01), 0.18	47.2; 0.048	11 507; 280 536	266, 0 to 1051	
	East Asian countries[11,19,24,31]	5 (6)	0.82 (0.75–0.90), <0.0001	46.4; 0.10	13 762; 323 384	38, 0 to 232	165 g/day, <0.0001 0.79 (0.75–0.84)
	Ischemic stroke[11,20,21,28]	5	0.95 (0.89–1.01), 0.09	83.6; <0.001	10 871; 467 529	115, 0 to 1051	115 g/day, 0.03 0.90 (0.85–0.96)
	Hemorrhagic stroke[11,20,21]	4	0.90 (0.74–1.09), 0.29	94.4; <0.001	1237; 158 595	197, 0 to 1051	125 g/day, <0.0001 0.76 (0.70–0.82)
	Fatal stroke[11,15,19,29–31]	7 (9)	0.88 (0.81–0.96), 0.002	65.1; 0.003	15 071; 352 105	66, 0 to 757	150 g/day, <0.0001 0.81 (0.77–0.85)
Low-fat milk (200)	[20,25,28,29]	4 (5)	0.96 (0.90–1.03), 0.26	68.2; 0.01	5942; 159 547	150, 0 to 783	†
High-fat milk (200)	[20,25,28,29]	4 (5)	1.04 (1.02–1.06), 0.001	0.0; 0.65	5942; 159 547	102, 0 to 850	†
Cheese (40)	[15,20–22,25,28,29]	7 (8)	0.97 (0.94–1.01), 0.12	31.2; 0.18	11 126; 272 368	26, 0 to 112	25 g/day, 0.002 0.91 (0.86–0.96)
Yogurt (100)	[15,20,28]	3	1.02 (0.90–1.17), 0.73	47.8; 0.15	4276; 116 555	22, 0 to 214	†
Fermented dairy (200)	[15,21,22,25,29]	5 (6)	0.91 (0.82–1.01), 0.08	64.5; 0.02	7414; 160 048	110, 0 to 436	
Total dairy (200)	[15–17,20–22,25,33]	9	0.99 (0.96–1.02); 0.42	65.6; 0.003	12 425; 336 118	305, 0 to 2078	
	Ischemic stroke[20,21]	3	1.00 (0.96–1.04); 0.95	67.6; 0.046	6440; 158 595	347, 2 to 1296	
	Hemorrhagic stroke[20,21]	3	1.02 (0.98–1.06); 0.41	0; 0.37	1237; 158 595	347, 2 to 1296	
	Fatal stroke[15,16,33]	4	0.97 (0.85–1.11); 0.65	65.3; 0.04	1652; 87 576	99, 2 to 571	
Low-fat dairy (200)	[15,21–23,29,33]	7 (8)	0.97 (0.95–0.99); 0.005	0.0; 0.65	9372; 242 643	179, 0 to 632	75 g/day, 0.01 0.94 (0.89–1.004)
High-fat dairy (200)	[15,21–23,33]	6	0.96 (0.93–0.99); 0.02	0.0; 0.84	9372; 262 643	163, 18 to 497	55 g/day, 0.01 0.94 (0.89–1.004)
Butter (10)	[20,25,29]	3 (4)	1.00 (0.99–1.01), 0.66	0.0; 0.70	2230; 47 227	11, 0 to 79	†

RR indicates relative risk.
*Weighted according to study size.
†Not investigated because the number of available studies was ≤3.

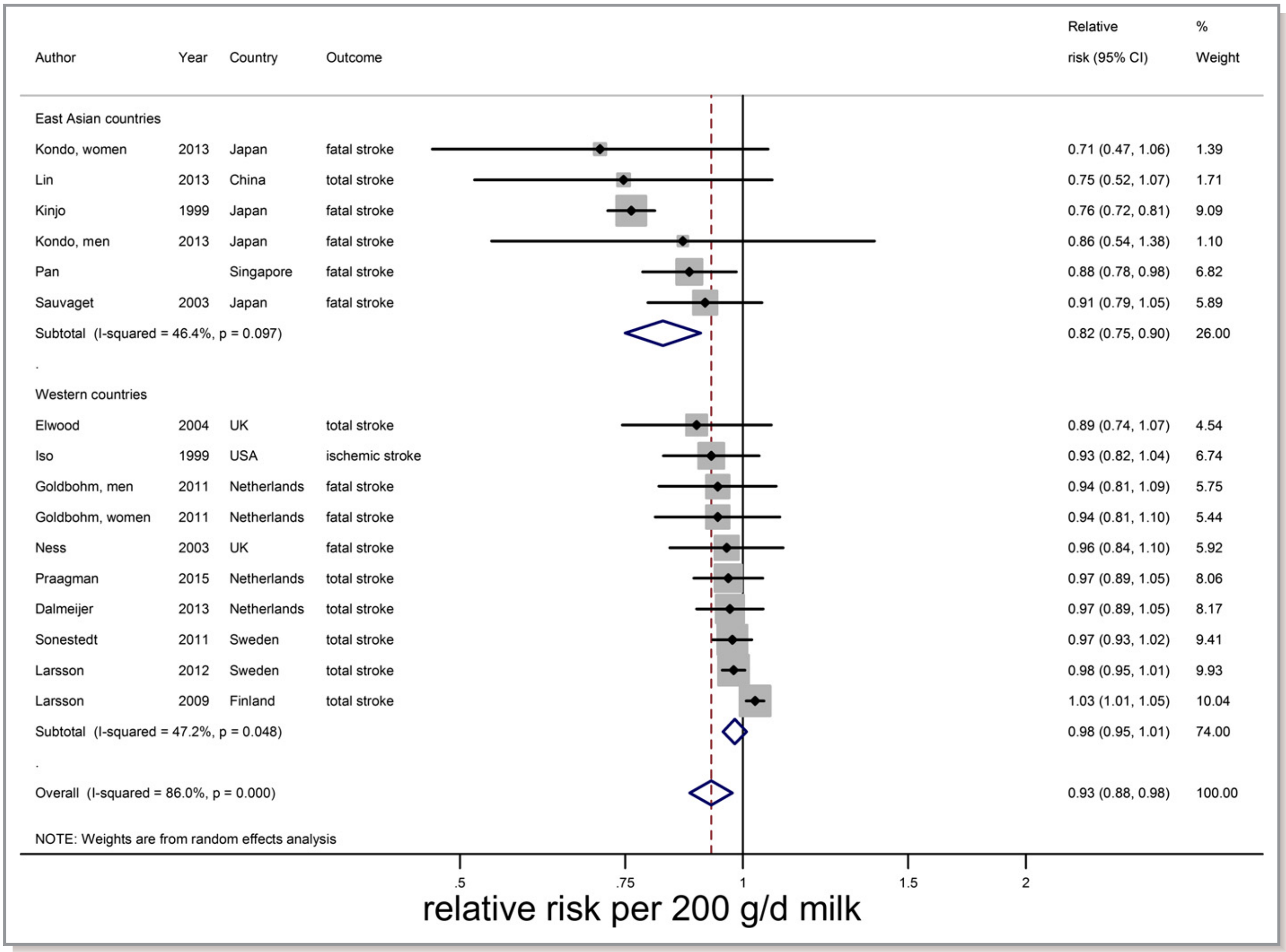

Figure 2. Relative risks of total stroke for an increment of 200 g of daily milk intake, by continent. Squares represent relative risks and square sizes study-specific statistical weight; horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

Methods

Literature Search and Selection

This review was conducted in accordance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines.[18] Published articles, without language restrictions, up to October 2015 were retrieved from PubMed, EMBASE, and SCOPUS (search strategy and MOOSE checklist are shown in Data S1), complemented by hand searches of reference lists and correspondence with researchers in the field. Based on titles and abstract, we excluded studies on animals, children aged <18 years, and patient populations. Eligible studies were selected using predefined criteria (ie, prospective design and reported data on dairy consumption in relation to incident fatal or total stroke). For 21 eligible articles, the full text was retrieved. Several authors provided additional information upon request.[14,15,19–25] One of the authors (A.P.) additionally provided unpublished data from the Singapore Chinese Health Study, a population-based cohort of 63 257 Chinese adults (A.P., unpublished results, 2015).

Two articles were excluded because the available data did not allow dose–response calculations.[15,18] In case of duplicate results,[26,27] we included the most updated[23] or comprehensive[27] results. For the Nurses' Health Study we used 2 articles: 1 on low-fat and high-fat dairy[23] and 1 on other types of dairy.[28] One article provided results for 2 studies (Nurses' Health Study and the Health Professionals Follow up Study)[23] and 2 presented results for men and women separately,[19,29] resulting in 18 studies (see flow chart in Figure 1).[11,14–17,19–25,28–33]

Data Extraction

The selection and data extraction process was conducted by the first author (J.G.) and checked by a coauthor (S.S.S.-M.)

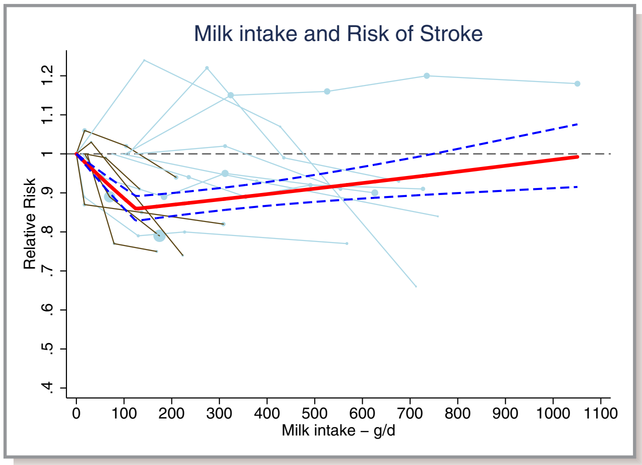

Figure 3. Ding's spaghetti plot for the nonlinear association between milk intake and total stroke (n=13). Light blue lines represent Western and brown lines East Asian studies. Circles are placed at study-specific relative risks related to the corresponding quantity of intake. Circle areas are proportional to the study-specific statistical weight. The solid red line represents the pooled RR at each quantity of intake and the 2 dashed dark blue lines the corresponding 95% CI.

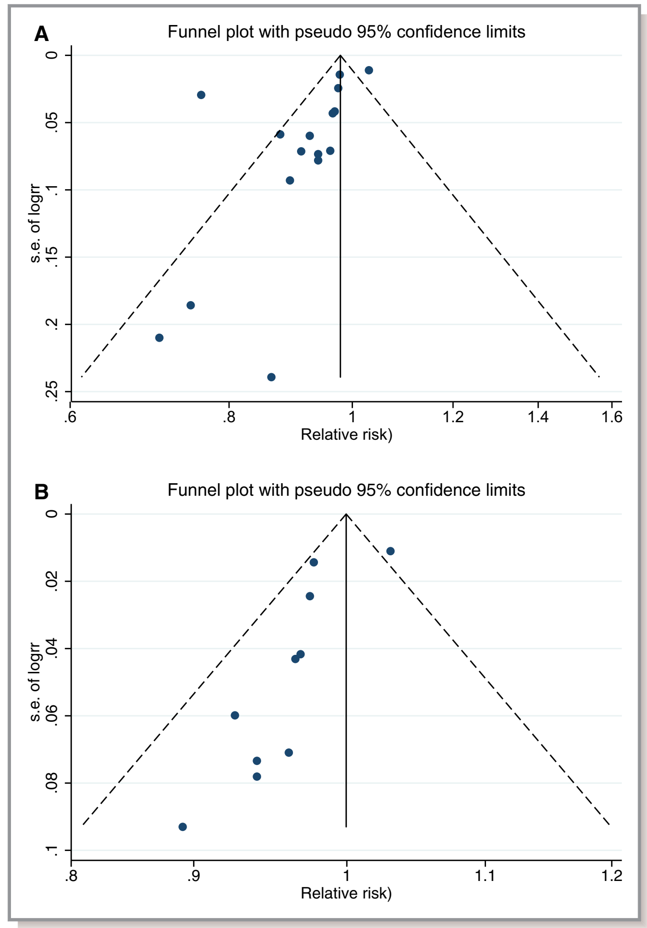

Figure 4. Funnel plots for studies of the association between milk intake and stroke risk based on dose–response slopes; Egger's test, P=0.06 (A) and funnel plot for studies in Western countries of the association between milk intake and stroke risk (B) based on dose–response slopes; Egger's test, P=0.02.

using a structured extraction form. We extracted descriptive study data as well as ranges of intake, medians or midpoints, numbers of subjects and stroke events, person-years at risk, and RRs with the corresponding 95% CIs for each category of dairy intake (ie, total dairy, low-fat dairy, high-fat dairy, fermented dairy, milk, low-fat milk, high-fat milk, cheese, yogurt, and butter).

If dairy intake was only reported in portions,[11,23,28,31,33] we used portion sizes of 177 g for total, low-fat, and high-fat dairy; 244 g for total, low-fat, and high-fat milk; 244 g for yogurt; and 43 g for cheese to estimate grams per day[34,35] or we used previously reported serving sizes of the same cohort.[23,28] For open-ended upper limits of intake, we applied the same width as the adjacent category, whereas for open-ended lowest categories a zero was assigned.

Categorization of dairy types was primarily based on the categorization in the original studies (see Data S1). For the meta-analysis on fermented dairy we included studies that combined at least 2 of the products cheese, yogurt, and sour milk. If results on total stroke (primary outcome) were not available, we used ischemic stroke.[17,28] Two reviewers (J.G. and S.S.S.-M.) independently evaluated the quality of the studies by using the Newcastle-Ottawa quality assessment scale (Data S1).[36] The rating system scores studies from 0 (highest degree of bias) to 9 (lowest degree of bias).

Statistical Analysis

We performed meta-analyses for dairy types reported upon by 3 or more studies. If studies presented several statistical models, we included the model that included most confounders. Median intakes for each dairy type were estimated as the average of medians, midpoints, or means per study, weighted by study size. For 4 or more studies, linearity of associations was investigated using spline analysis and dose–response meta-regression (Generalized Least-Square Trend). Three studies could not be used for nonlinear analyses, because they only provided linear results.[16,17,29]

Splined variables were created using MKSPLINE in STATA in order to select the most appropriate knot points of nonlinear associations based on goodness-of-fit tests and χ^2 statistics. Linear and nonlinear associations were further analyzed using dose–response (Generalized Least-Square Trend) meta-regression analysis. Random-effects meta-regression trend estimation of summarized dose–response data[37] was used to derive the incremental dose–response RRs.

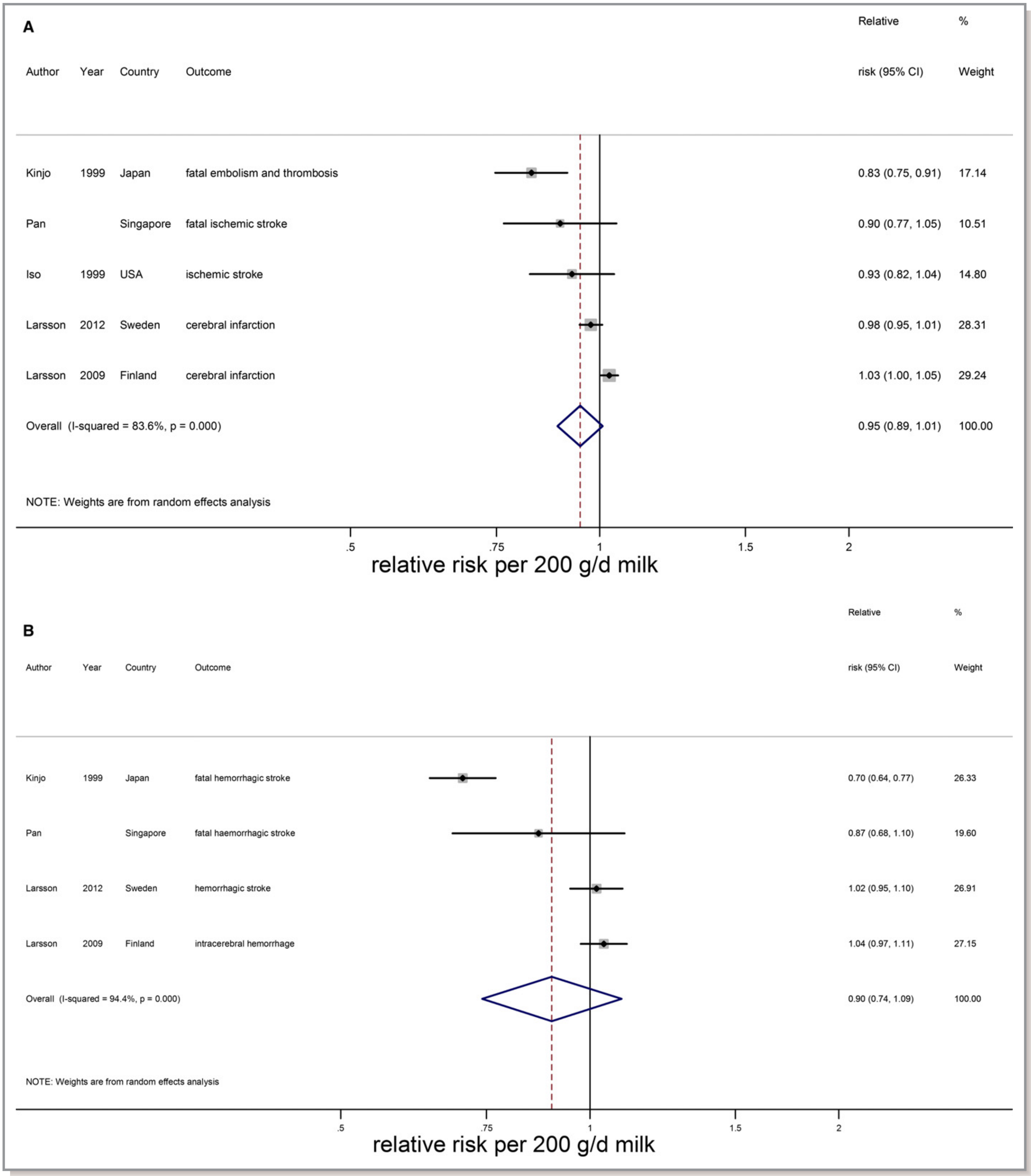

Figure 5. Relative risks of ischemic stroke (A), hemorrhagic stroke (B), and fatal stroke stratified by continent (C) for an increment of 200 g/day in milk intake. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

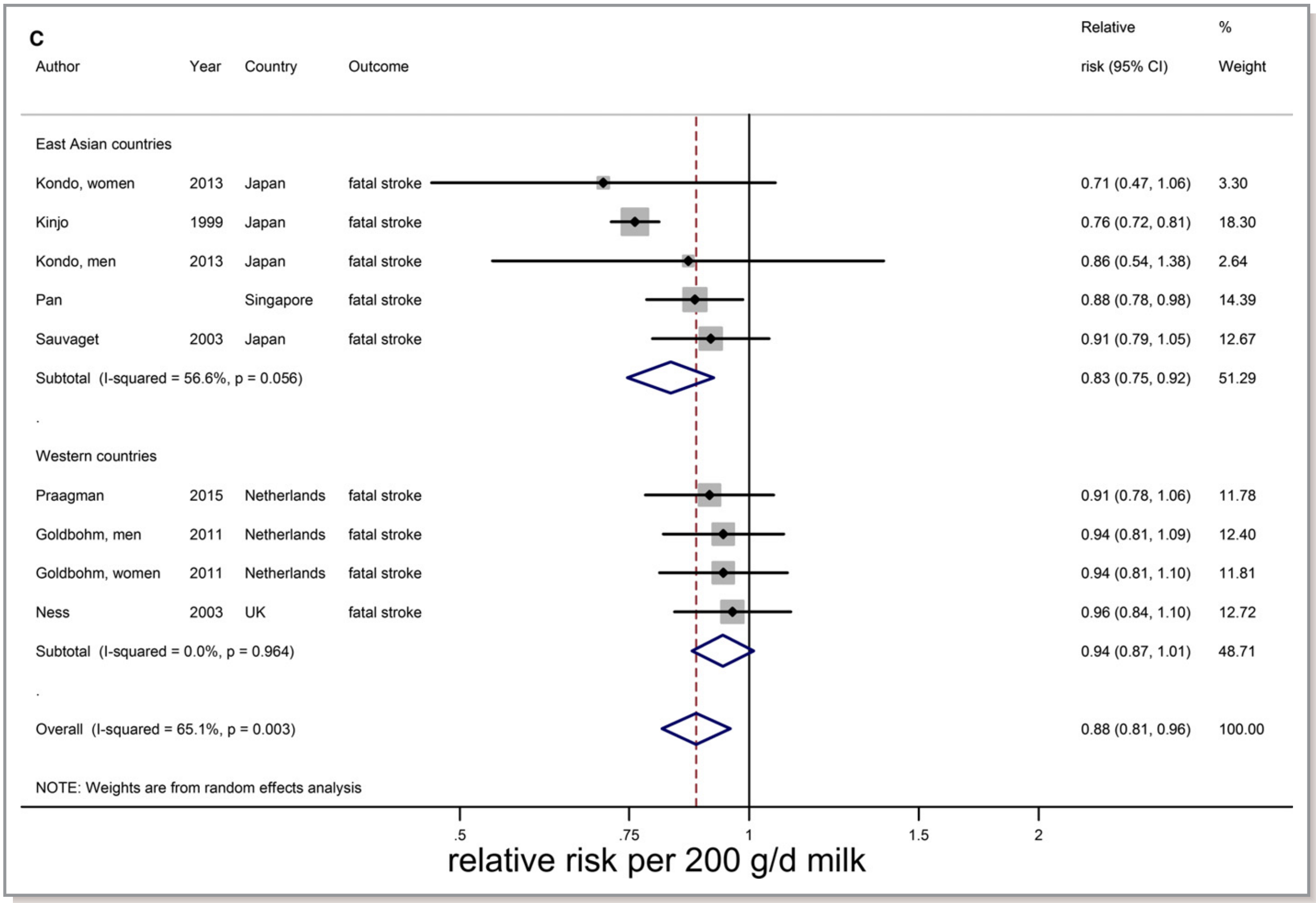

Figure 5. Continued.

Forest plots were created to visualize linear dose–response slopes and corresponding 95% CIs across studies with increments of 200 g/day for total, low-fat, and high-fat dairy, fermented dairy, total milk, low-fat and high-fat milk, per 100 g/day for yogurt, 40 g/day for cheese, and 10 g/day for butter. The shape of the associations within individual studies was visualized by means of Ding's spaghetti plots, as described previously.[38]

To explore between-study heterogeneity, the Cochrane Q test was conducted and the I^2 statistic was calculated.[39] Meta-regression and subgroup analyses to explore sources of heterogeneity based on the linear analyses were performed for percentage of men, the Newcastle-Ottawa Quality score (<7 versus ≥7), continent (East Asian versus Western including Australia), outcome (fatal versus total incident stroke), stroke subtype (ischemic and hemorrhagic) versus total stroke, follow-up time (≥15 years versus <15 years), and whether analyses were adjusted for age, sex, body mass index, smoking, total energy intake, physical activity, and dietary factors. Potential publication bias was assessed by the Eggers test and symmetry of the funnel plot[40] if at least 10 studies were available. Statistical analyses were performed using STATA version 11.0 (StataCorp, College Station, TX).

Results

Table 1 shows the characteristics of the 18 prospective cohort studies[11,15–17,19–25,28–33] including 1 case-cohort study,[29] which comprised 762 414 participants and 29 943 stroke events. Two studies presented sex-specific results,[19,29] 2 comprised only women,[17,28] and 3 only men.[20,30,32] Eight studies were from Europe,[15,16,20–22,29,30,32] 5 were from east Asia (China and Japan),[11,19,24,31] 3 were from the United States,[17,23,28] and 1 was from Australia.[33] The Asian populations mainly consumed milk. The sample size of the studies ranged from 2061 to 223 170 and the duration of follow-up from 8 to 26 years. Six studies reported fatal stroke,[11,19,29,30,33] 10 total stroke,[16,17,20,22–25,28,32] and 1 both outcomes.[15] All studies adjusted for age, sex, and smoking. Eight studies additionally adjusted for body mass index, physical activity, total energy intake, and other dietary factors.[15,20,22,23,25,29] Five studies scored <7 points for study quality.[11,16,24,30,31]

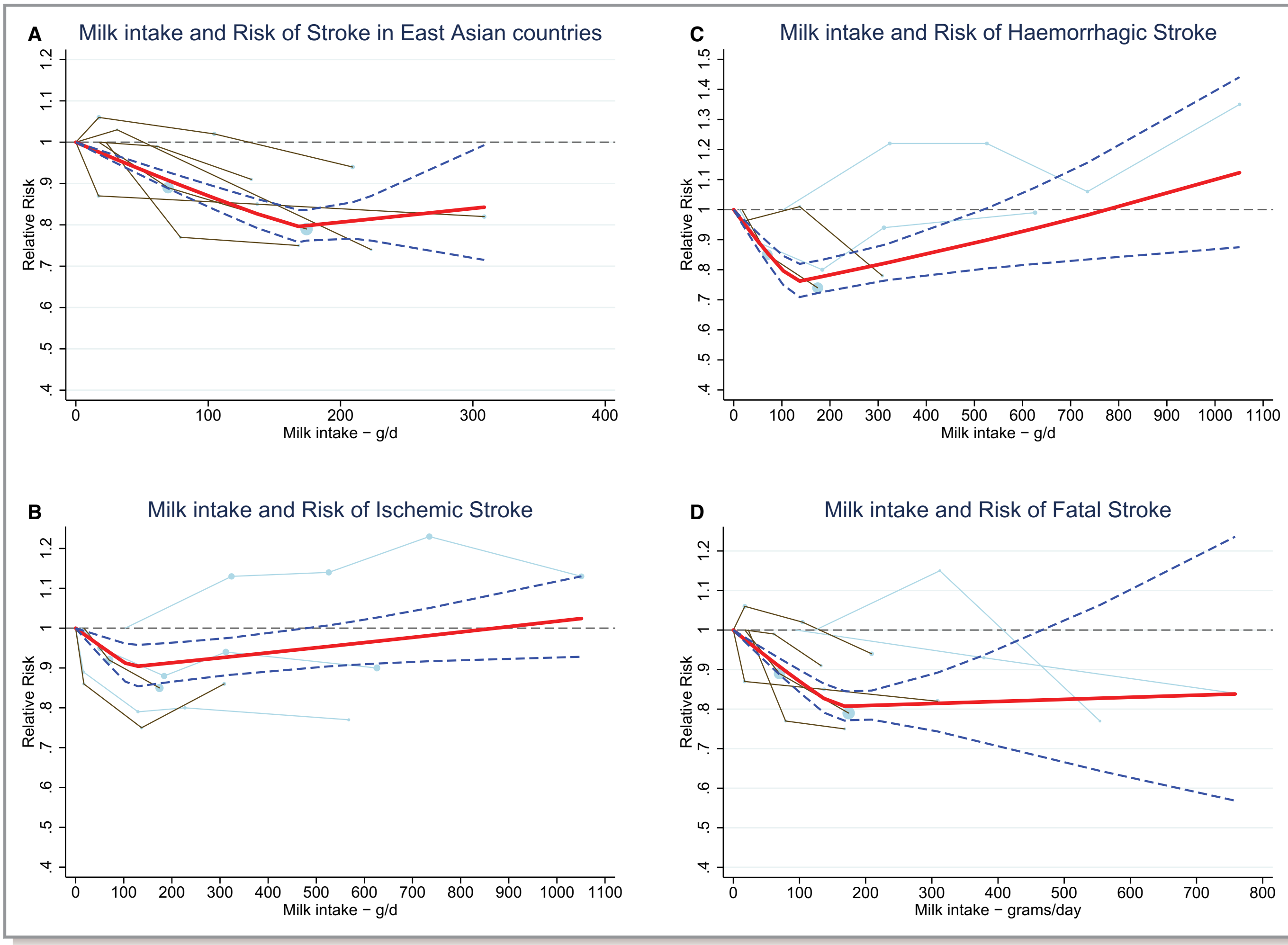

Figure 6. Ding's spaghetti plots for (A) the nonlinear association (*P* for nonlinearity=0.01, knot at 165 g/day) between milk intake and total stroke in East Asian countries (n=5). B, For the nonlinear association (*P* for nonlinearity=0.03; knot at 115 g/day) between milk intake and ischemic stroke (n=5). C, For the nonlinear association (*P* for nonlinearity <0.0001; knot at 125 g/day) between milk intake and hemorrhagic stroke (n=4). D, For the nonlinear association (*P* for nonlinearity <0.0001; knot at 150 g/day) between milk intake and fatal stroke (n=6). Light blue lines represent Western studies and brown lines represent East Asian studies. The circles are placed at the study-specific relative risks that are related to the corresponding quantity of intake. The area of the circles is proportional to the study-specific statistical weight. The solid red line represents the pooled relative risks at each quantity of intake and the 2 dashed dark blue lines the corresponding 95% CI.

Milk

An increment of 200 g of daily milk intake was associated with a 7% lower risk of stroke (RR 0.93; 95% CI 0.88–0.98; n=14)* including 603 920 participants and 25 269 stroke events (Table 2 and Figure 2). The median milk intake was 147 g/day (range 0–1051 g/day). Considerable heterogeneity was present (I^2=86%, P<0.001), which could be partly attributed to continent. The RR per 200 g/day milk was 0.82 (95% CI 0.75–0.90, n=5) in Asian populations (median intake 38 g/day) and 0.98 (95% CI 0.95–1.01; n=9) in Western populations (median intake 266 g/day). Based on multivariable meta-regression, degree of adjustment, study quality, and outcome event also explained some heterogeneity, but not significantly in addition to the continent variable. The association of milk with total stroke was nonlinear, with the strongest inverse association around 125 g/day (RR 0.86; 95% CI 0.82–0.89; n=13; Figure 3). For milk intake in the range of 125 to 750 g/day the inverse association remained significant, but was attenuated.

There were indications of publication bias (small study effect) based on asymmetry of the funnel plot, especially in Western countries (Eggers test, P=0.06 for all studies and 0.02 for Western studies; Figure 4). However, removal of 2 small studies[19,24] did not change the results. For ischemic stroke, hemorrhagic stroke, and fatal stroke RRs were 0.95 (95% CI 0.89–1.01; n=5), 0.90 (0.74–1.09; n=4), and 0.88

*References 11,15,19,20,22,24,25,28–32.

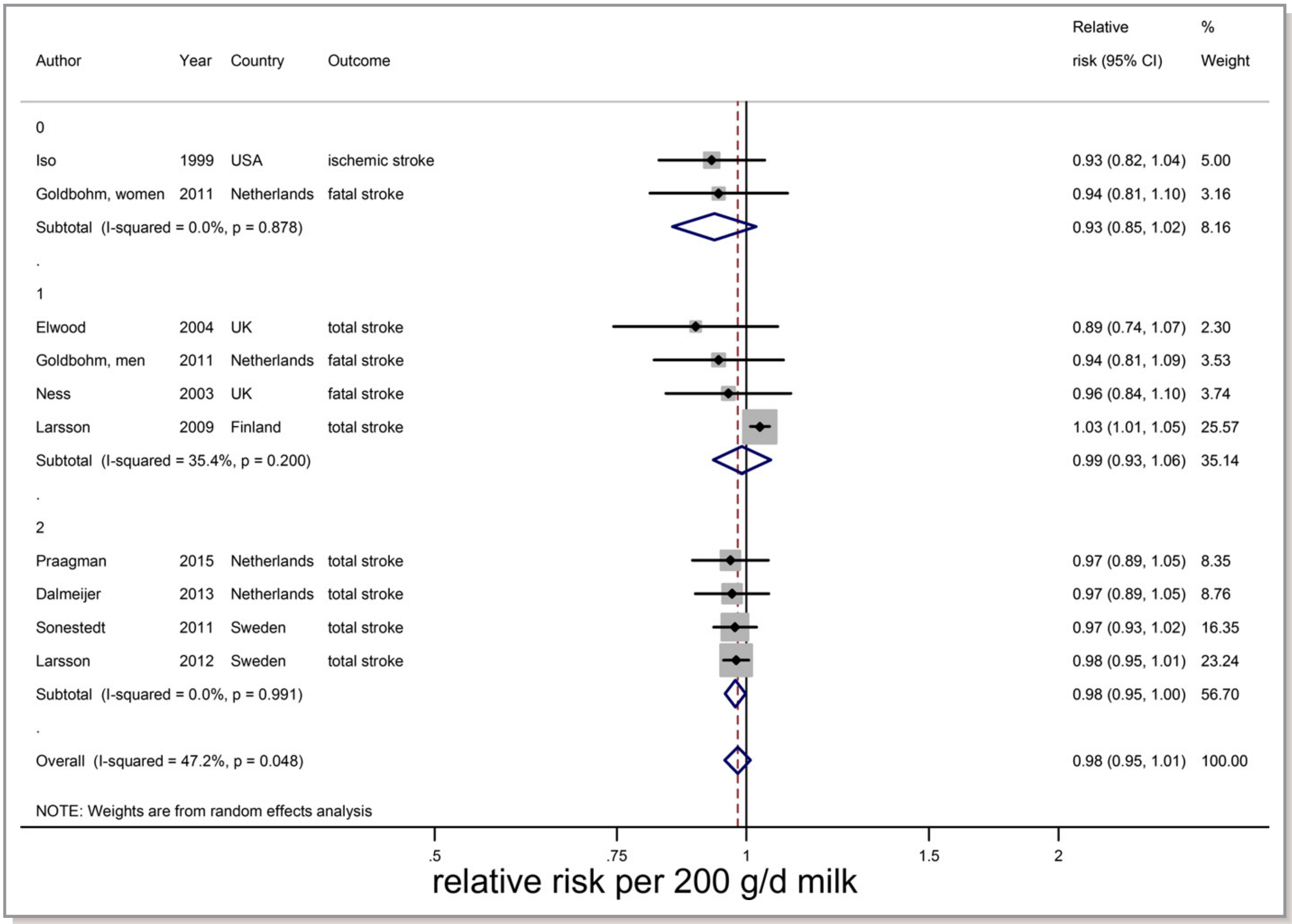

Figure 7. Relative risks of total stroke for an increment of 200 g/day in milk intake in Western countries, stratified for sex. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs (0=women, 1=men, 2=mixed).

(95% CI 0.81–0.96; n=7), respectively, with considerable heterogeneity for each end point (Figure 5). Nonlinear associations were observed for total stroke in Asian countries, ischemic stroke, hemorrhagic stroke, and fatal stroke, with the strongest inverse associations until 165, 115, 125, and 155 g/day, respectively (Figure 6). Within Western countries, the percentage of men predicted the effect size of milk in relation to stroke risk (P=0.02). However, the results were dominated by 1 large Finnish cohort[20] (Figure 7).

The RR of low-fat milk consumption (4 Western studies, median intake: 150 g/day)[20,25,28,29] was 0.96 (95% CI 0.90–1.03) per 200 g/day (Figure 8A) with considerable heterogeneity (I^2=68%, P=0.01), which was explained by sex (meta-regression: P=0.04). Based on the same studies, high-fat milk (median intake 102 g/day) was significantly associated with a higher risk of stroke (RR 1.04; 95% CI 1.02–1.06) per 200 g/day with no heterogeneity (Figure 8B).

Cheese, Yogurt, and Total Fermented Dairy

Cheese intake (weighted median intake 26 g/day) was marginally associated with a lower stroke risk, with a RR of 0.97 (95% CI 0.94–1.01) per 40 g/day with low heterogeneity (I^2=31%, P=0.18; n=7; Figure 9).[15,20–22,25,28,29] The inverse association was nonlinear and most pronounced above 25 g/day (RR 0.91; 95% CI 0.86–0.96; P for nonlinearity<0.002; Figure 10). Yogurt intake (n=3) was not associated with stroke risk (RR: 1.02; 95% CI 0.90–1.17 per 100 g/day; Figure 11).[15,20,28] Total fermented dairy intake was borderline significantly associated with a 9% (RR of 0.91; 95% CI 0.82–1.01, n=5) lower risk of stroke per 200 g/day, with no indications of a nonlinear association (Figure 12A).[15,20,22,25,29] The considerable heterogeneity (I^2=65%, P=0.02) was absent for the subset of 3 studies with results on fatal stroke (RR: 0.80; 95% CI: 0.67–0.95; Figure 12B).

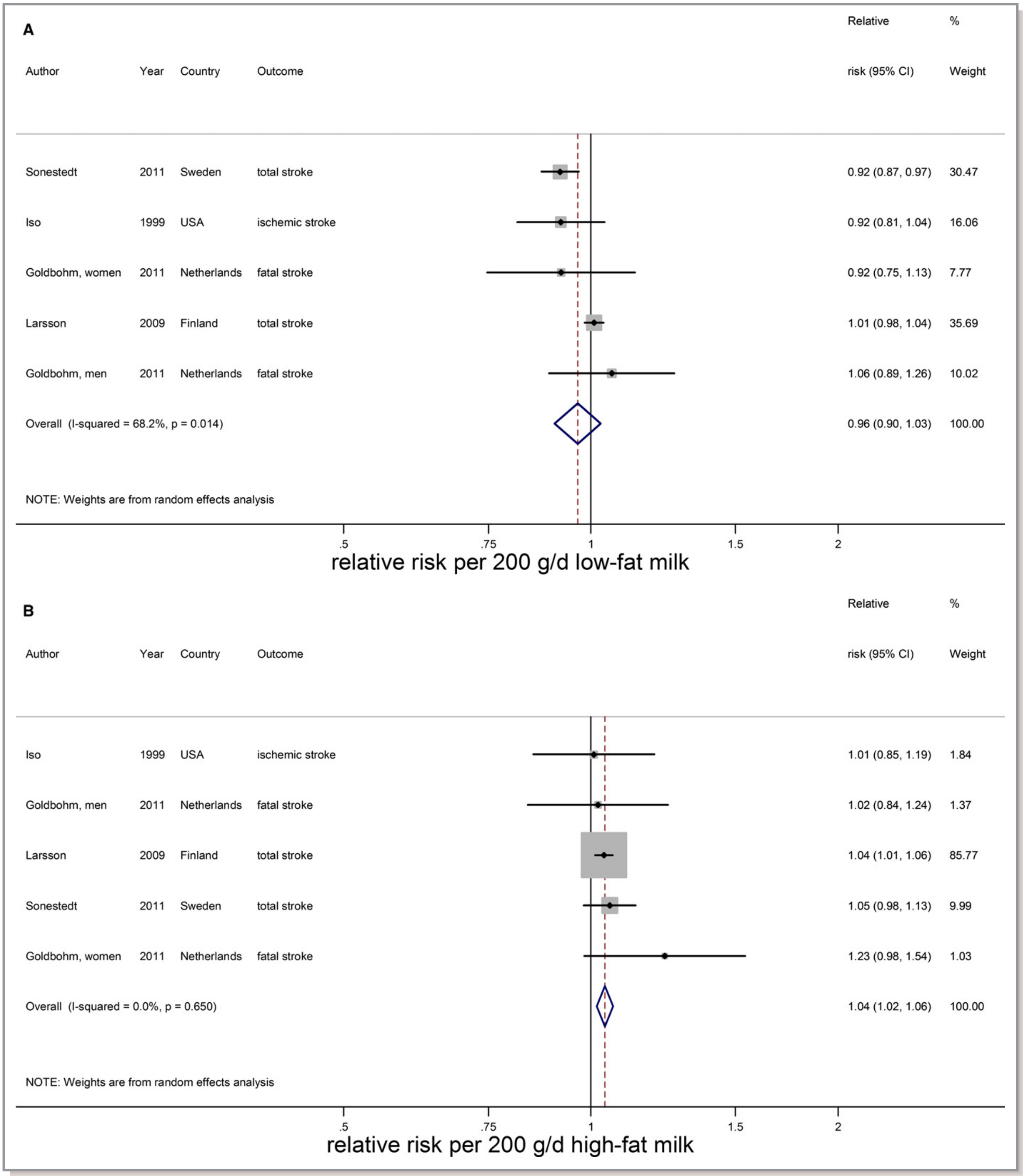

Figure 8. Relative risks of total stroke for an increment of 200 g/day in low-fat milk intake (A) and high-fat milk intake (B). Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

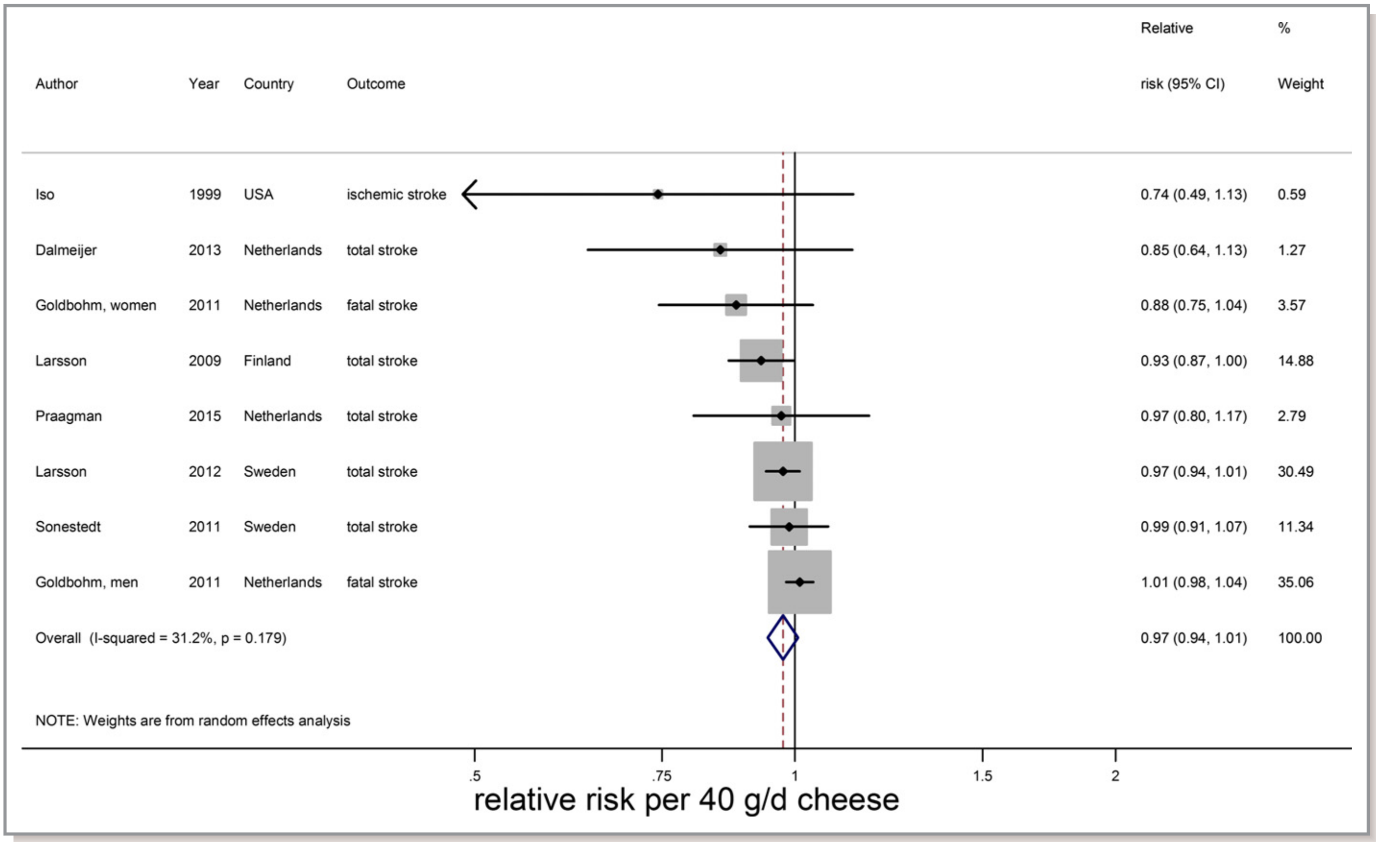

Figure 9. Relative risks of total stroke for an increment of 40 g/day in cheese intake. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

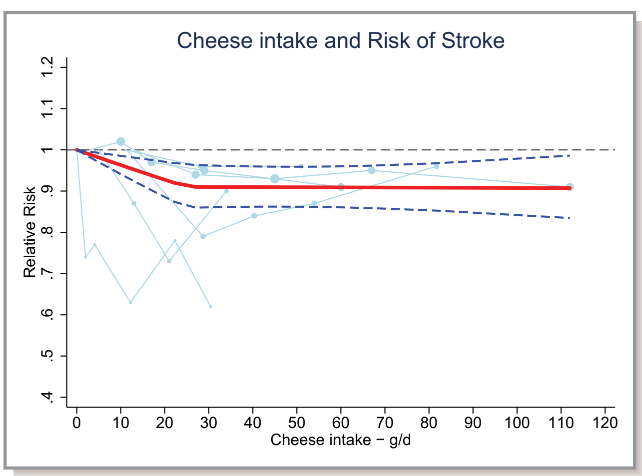

Figure 10. Ding's spaghetti plot for the nonlinear association between cheese intake and total stroke (n=6). Circles are placed at the study-specific relative risks related to the corresponding quantity of intake. The area of the circles is proportional to the study-specific statistical weight. The solid red line represents the pooled RR at each quantity of intake and the 2 dashed dark blue lines the corresponding 95% CI.

Total Dairy, Low-Fat Dairy, High-Fat Dairy, and Butter

Total dairy was not associated with stroke risk (RR 0.99; 95% CI 0.96–1.02 per 200 g/day; n=9) with no evidence for a nonlinear association (Figure 13A).[15–17,20–22,25,33] The considerable heterogeneity (I^2=66%, P<0.005) could not be explained by end point, study quality, degree of adjustment, and duration of follow-up. The percentage of males influenced the RR (P=0.049), but this was driven by 1 large Finnish cohort study with only men.[20] Total dairy was also not associated with ischemic stroke (n=3), hemorrhagic stroke (n=3), and fatal stroke (n=4), with considerable heterogeneity for ischemic and fatal stroke (Figure 13B through 13D). Nonlinear associations could not be investigated. Both low-fat[15,21–23,29,33] and high-fat dairy[15,21–23,33] were significantly associated with a lower stroke risk per 200 g/day. RRs (95% CI) were 0.97 (0.95–0.99) for low-fat dairy and 0.96 (0.93–0.99) for high-fat dairy with no heterogeneity (Figure 14). Both associations were nonlinear with stronger inverse associations above 75 g/day for low-fat dairy and 55 g/day for high-fat dairy (Figure 15). Butter intake[20,25,29] was not associated with

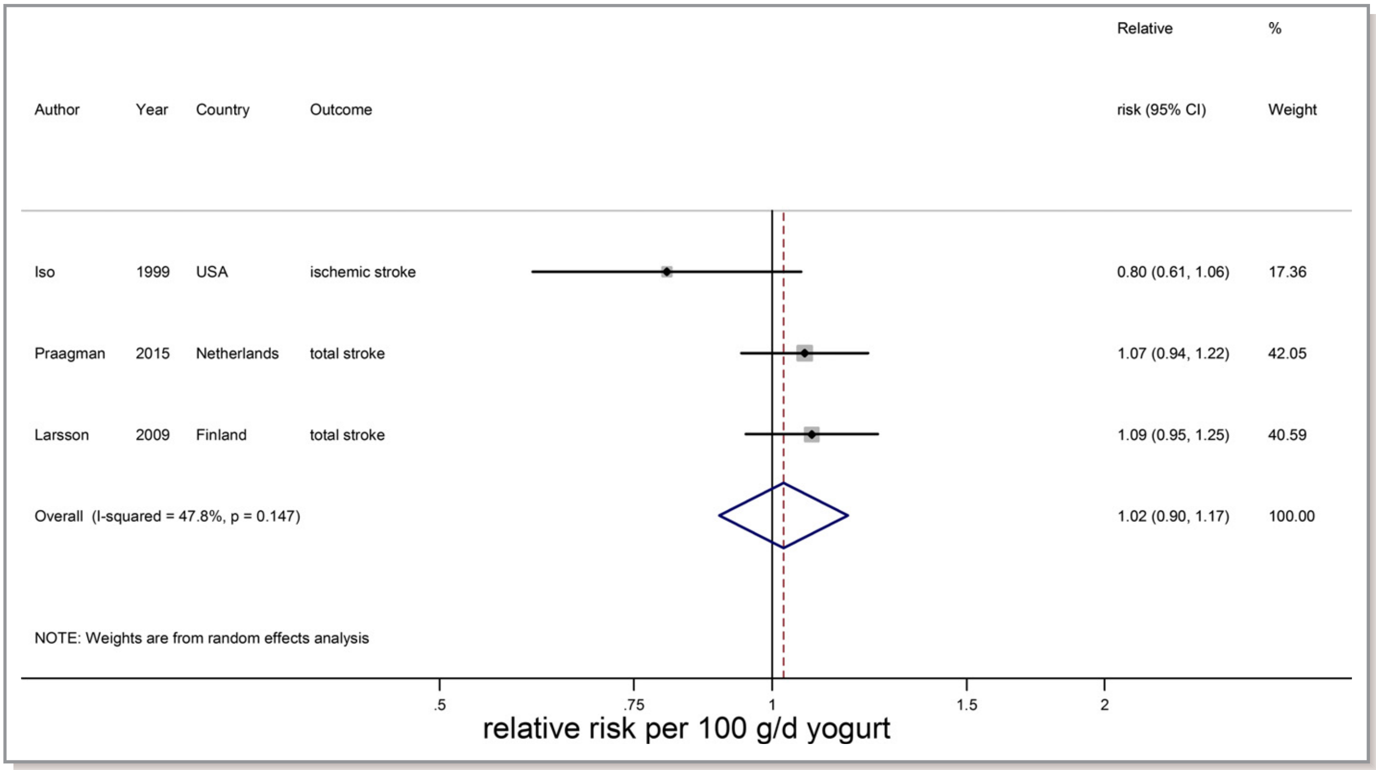

Figure 11. Relative risks of total stroke for an increment of 100 g/day in yogurt intake. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

stroke risk (RR: 1.00; 95% CI 0.99–1.01 per 10 g/day; Figure 16).

Discussion

This meta-analysis showed an inverse association of milk consumption with risk of stroke, with a maximal reduction around 125 g/day. The high amount of heterogeneity was partly explained, but not completely absent, after stratifying for continent. Based on a limited number of studies, high-fat milk was directly associated with stroke risk. Cheese intake was marginally inversely associated with stroke risk, with a maximal risk reduction from 25 g/day onwards for cheese. For yogurt, butter, and total dairy no associations were observed. The role of fat content of dairy products is not yet clear.

Dairy is a heterogeneous food group of (semi) solid and liquid fermented or nonfermented foods, differing in nutrients such as fat and sodium. We therefore separately analyzed specific dairy types. Based on 14 studies, we found a significant 7% lower risk of stroke per 200 g/day of milk, which was smaller than the 13% (based on 6 studies) that we showed in our previous meta-analysis.[10] Our findings are in line with the meta-analysis by Hu et al,[12] who reported a 9% lower risk for a high versus a low milk intake. The association in our study was nonlinear, with the lowest risk observed at 125 g/day. Heterogeneity was partly attributable to continent, with milk being inversely associated with stroke in East Asia, but not in Europe. Hu et al[12] studied heterogeneity for total dairy in relation to stroke risk, and also observed stronger associations in Asian studies.[12] It should be noted that some Asian studies were based on multivariable models that contained only a few covariates.[11,24,31] However, the results provided by A.P., which were adjusted for many potential confounders, supported the lower risk of stroke with increasing milk intake making residual confounding unlikely as an explanation for the difference between continents. The difference in results between continents may reflect differences in types of stroke as in Asia hemorrhagic stroke is more common than in Western countries.[41] Our results on hemorrhagic stroke, however, did not provide an explanation for the observed heterogeneity.

Cheese consumption was inversely associated with stroke risk, with a 3% lower risk of stroke per 40 g/day of cheese and a maximum reduction above 25 g/day. Our results regarding cheese were in agreement with Hu et al[12] and Qin et al,[42] who also reported inverse associations for a high versus a low cheese consumption. They did not investigate whether the association was nonlinear. Yogurt was not

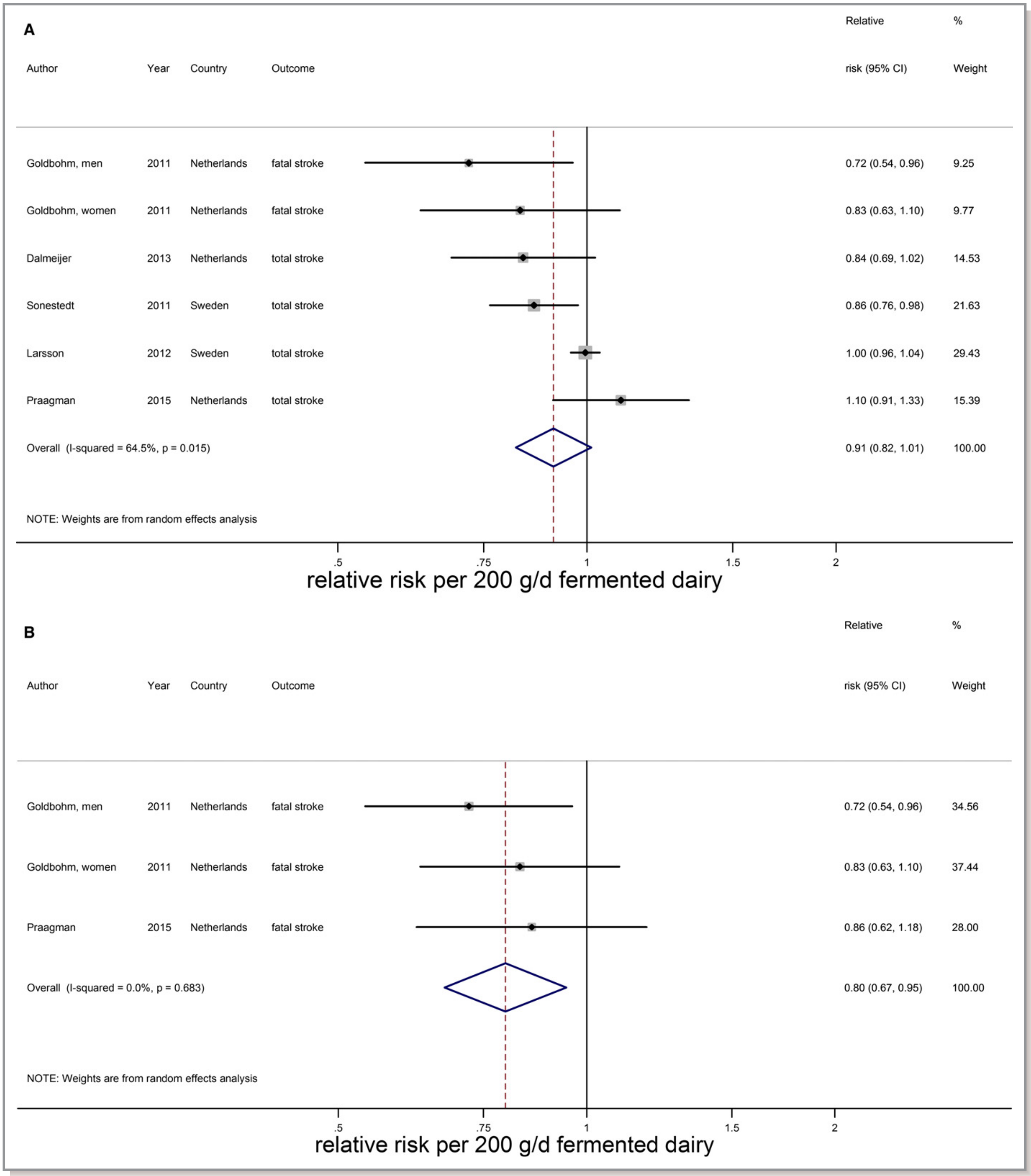

Figure 12. Relative risks of total stroke for an increment of 200 g/day in fermented dairy intake (A) and fatal stroke for an increment of 200 g/day in fermented dairy intake (B). Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

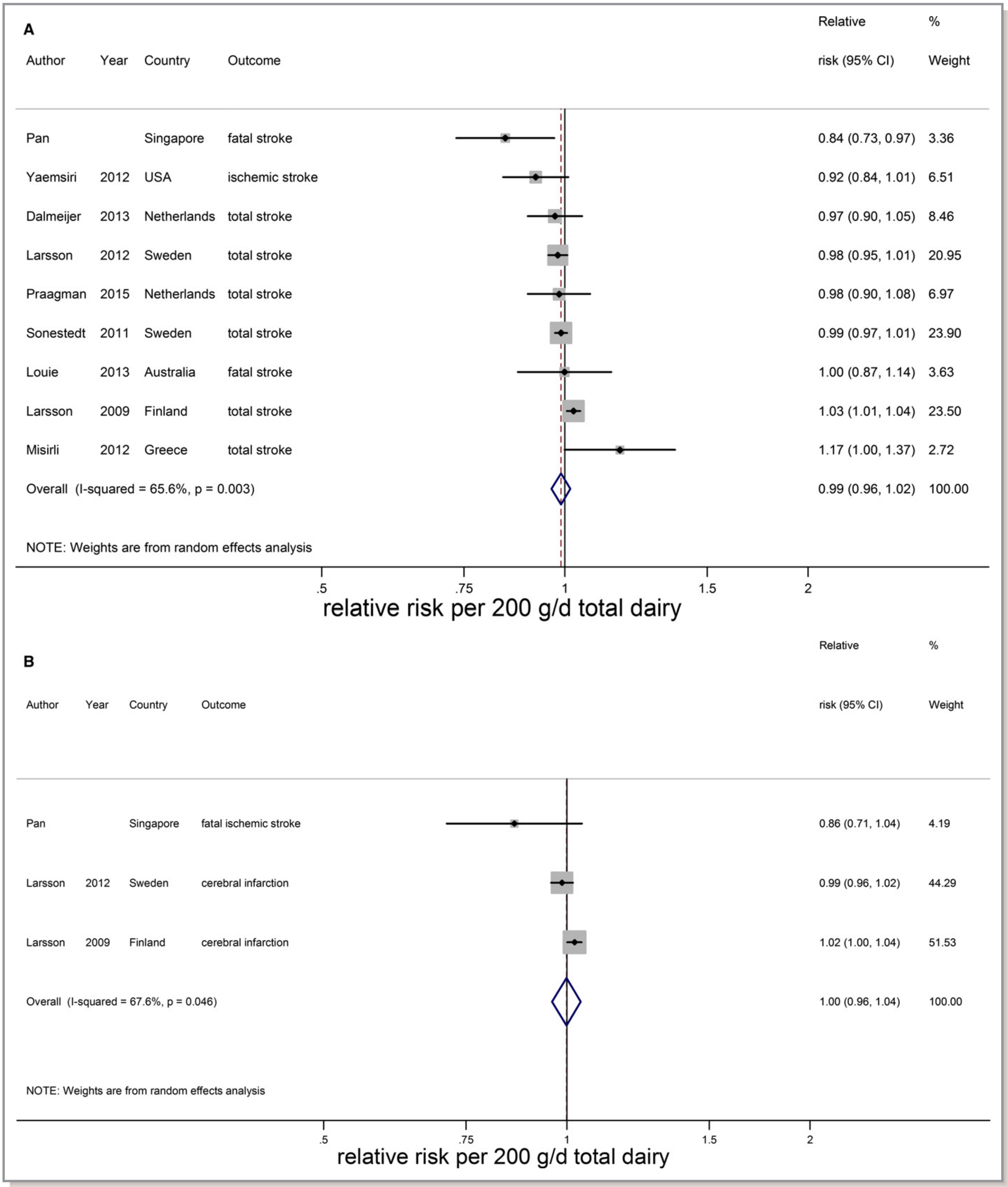

Figure 13. Relative risks of total stroke (A), ischemic stroke (B), hemorrhagic stroke (C), and fatal stroke (D) for an increment of 200 g/day in total dairy intake. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

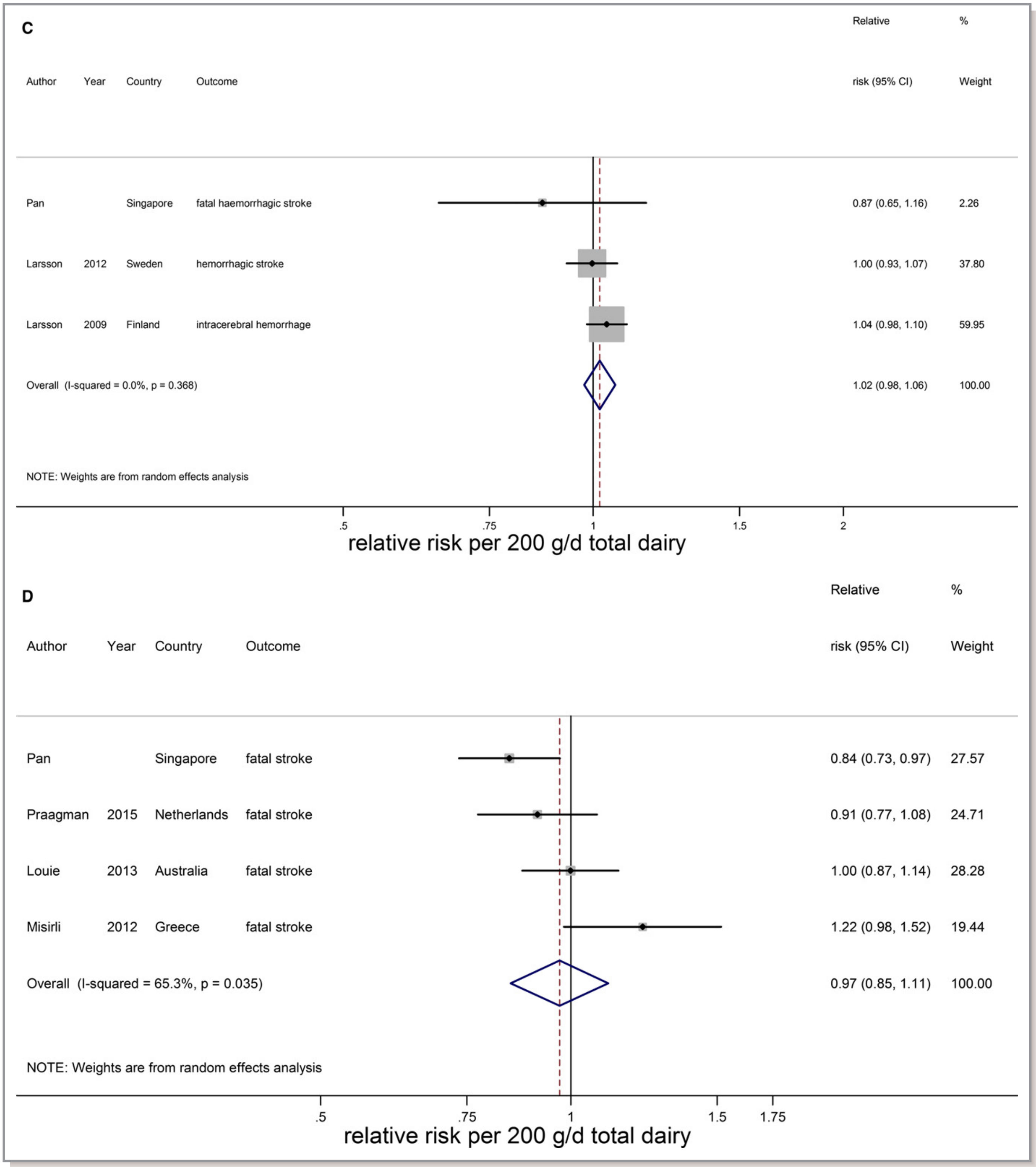

Figure 13. Continued.

associated with stroke risk, based on 3 studies, whereas total fermented dairy showed a borderline inverse association with stroke risk. In general, results for fermented dairy products were only based on Western populations.

Limited information was available regarding the role of dairy fat in relation to stroke risk. For high-fat milk a direct association was observed, whereas for low-fat milk the association was (nonsignificantly) inverse. However, the

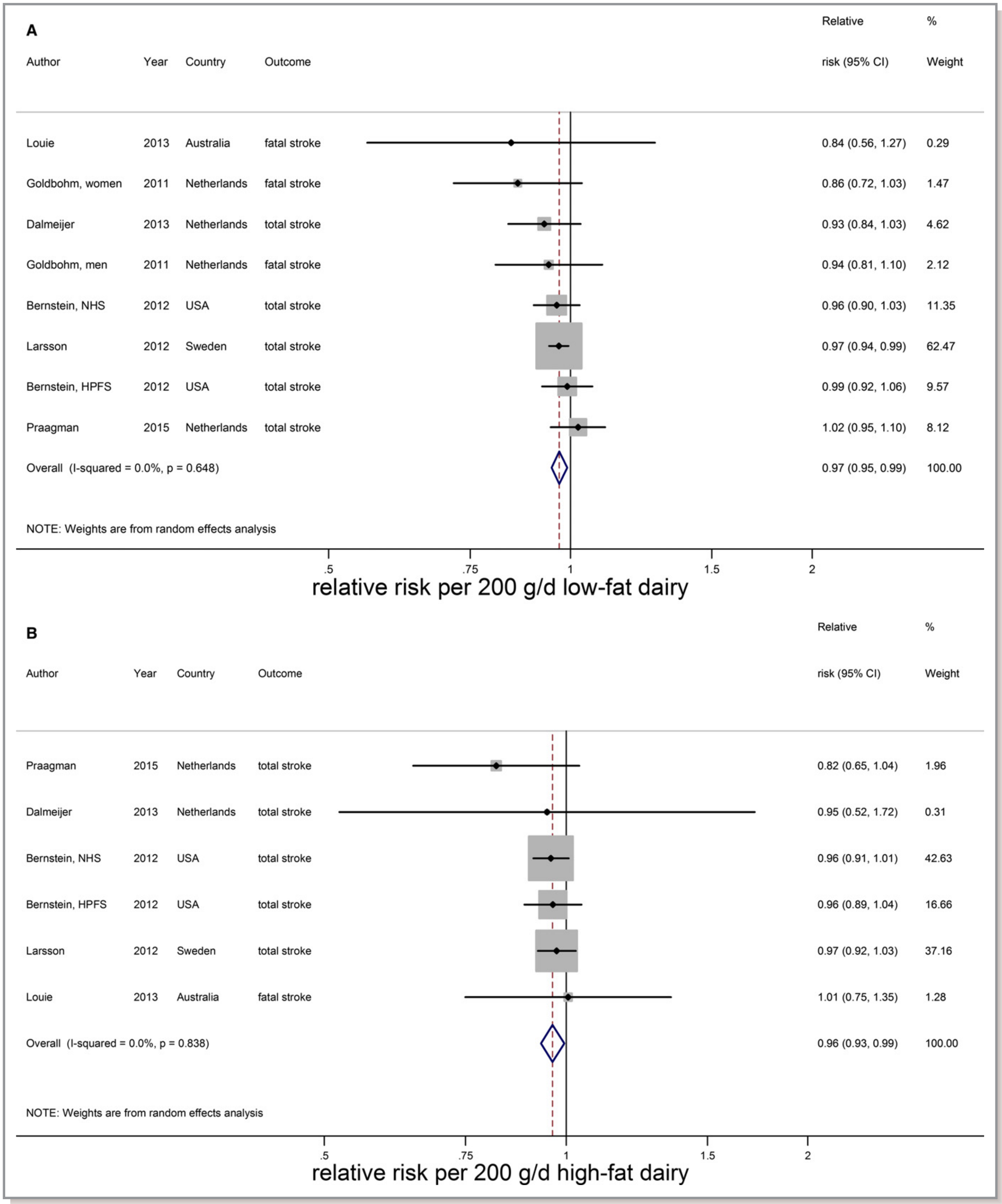

Figure 14. Relative risks of total stroke for an increment of 200 g/day in low-fat dairy (A) and high-fat dairy (B) intake. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamonds represent summary relative risk estimates with 95% CIs.

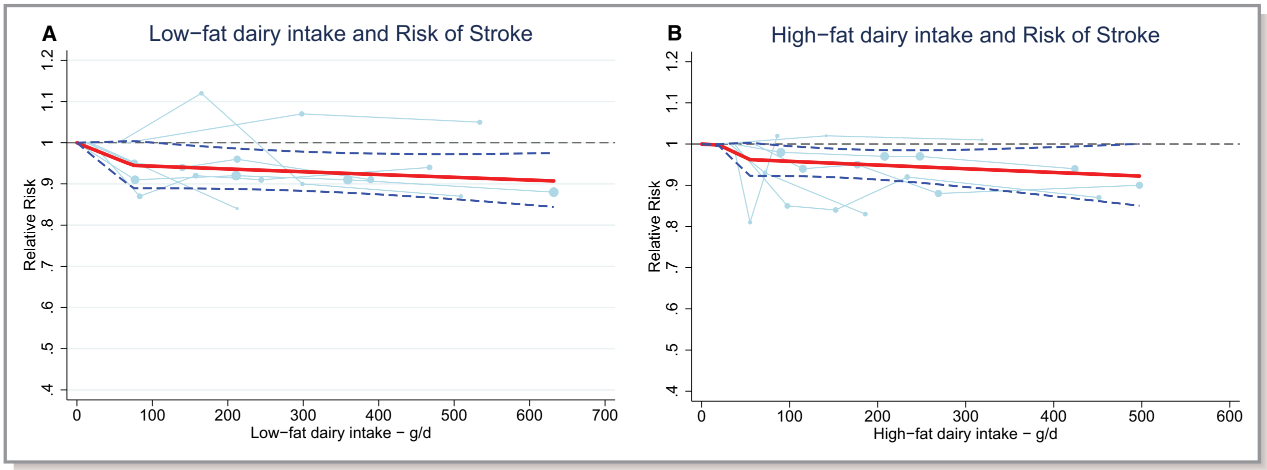

Figure 15. Ding's spaghetti plots for (A) the nonlinear association (*P* for nonlinearity=0.01; knot at 75 g/day) between low-fat dairy intake and total stroke (n=6) and (B) the nonlinear association (*P* for nonlinearity=0.01; knot: 55 g/day) between high-fat dairy intake and total stroke (n=6). Light blue lines represent Western studies. The circles are placed at the study-specific relative risks that are related to the corresponding quantity of intake. The area of the circles is proportional to the study-specific statistical weight. The solid red line represents the pooled relative risk at each quantity of intake and the 2 dashed dark blue lines the corresponding 95% CI.

number of studies that reported on types of milk was limited and only comprised Western populations. In addition, results for low-fat total dairy did not differ from those of high-fat total dairy.

In a previous meta-analysis of 9 prospective cohort studies, we reported that milk and low-fat dairy were inversely associated with hypertension, a major risk factor for stroke.[43] Apart from butter, dairy is an important source of calcium,

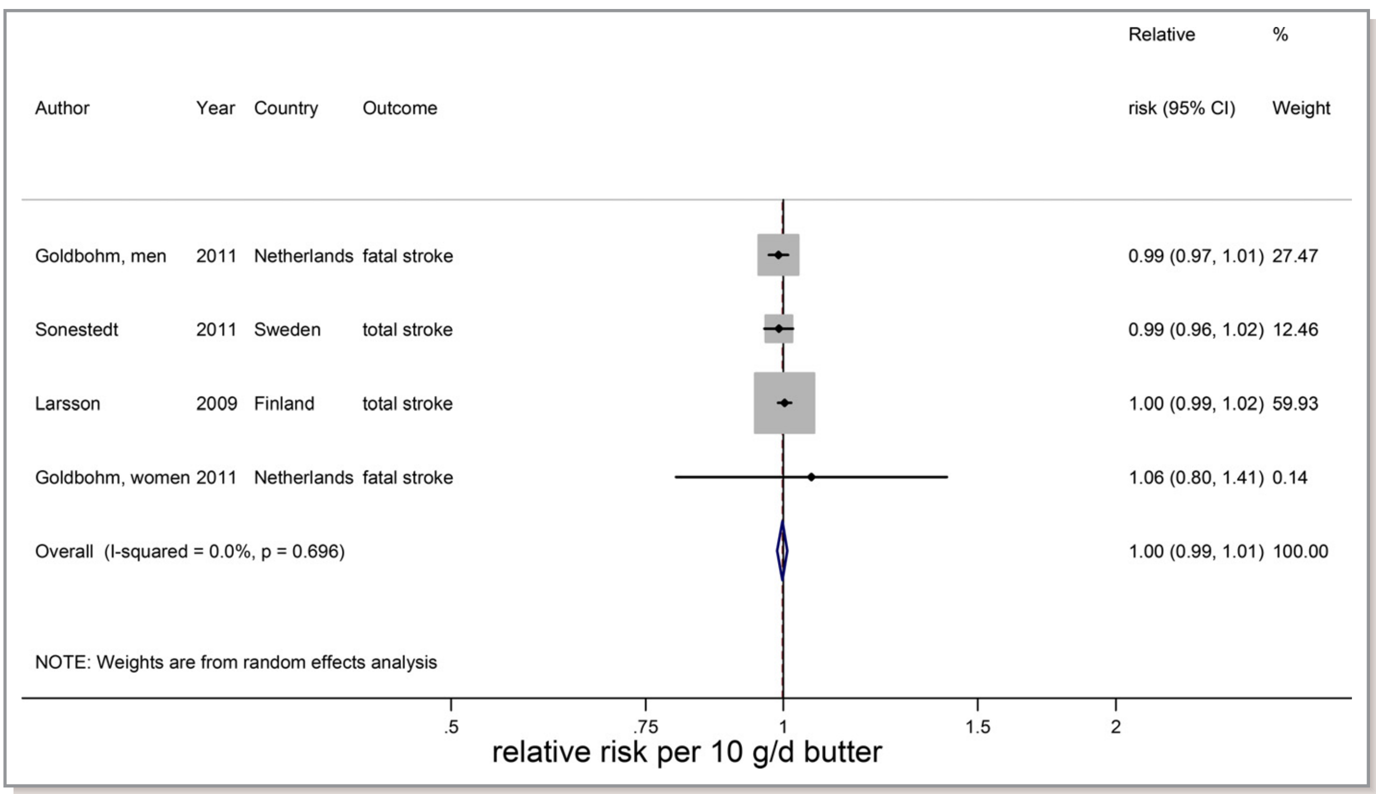

Figure 16. Relative risks of total stroke for an increment of 10 g/day in butter intake. Squares represent study-specific relative risk estimates (size of the square reflects the study-specific statistical weight, ie, the inverse of the variance); horizontal lines represent 95% CIs; diamond represents summary relative risk estimates with 95% CIs.

which was inversely associated with stroke risk in a meta-analysis of 11 prospective cohort studies including populations with low-to-moderate calcium intakes and Asian populations.[44] That meta-analysis also suggested protective effects of dairy calcium rather than nondairy calcium against stroke.[44] A recent update of these meta-analyses including updated results from the Nurses' Health Study I and II, however, showed no association between dietary (dairy and other sources) calcium and stroke risk with a RR (95% CI) of 0.98 (0.94–1.02) for a 300 mg/day increase of calcium intake.[45] Calcium may play a role in the inverse association of milk and cheese with stroke risk. However, we only found inverse associations for milk and cheese, and not for the other calcium-containing sources of dairy. Milk and dairy also contain other minerals, such as potassium and magnesium, which were also found to be inversely associated with stroke risk.[45–47] On the other hand, cheese contains a lot of sodium, which is directly associated with hypertension. A meta-analysis of prospective cohort studies, however, did not show a relation of cheese consumption to hypertension.[43] The mechanism of how dairy would protect against stroke is therefore not yet clear.

Strengths of our meta-analysis are our comprehensive dose–response analyses and the careful evaluation of nonlinearity of the associations based on a large number of studies from Asian and Western countries by contacting authors for additional information and by contacting researchers in the field for inclusion of additional cohorts. A limitation is that it is difficult to disentangle the effects of the dosages of milk intake from Western compared to those of East Asian countries, because consumption levels in East Asia were considerably lower than those in Western countries. In addition, reported dairy types differed between studies, which complicates direct comparison of results between dairy types. Another limitation was that the number of studies, except for milk intake, was rather low ($n \leq 8$). Therefore, options for meta-regression or subgroup analyses were limited for several exposure categories. The quality of a meta-analysis is dependent on the quality of the included studies. The degree of adjustment for confounders varied widely between studies. Regarding the results on milk, 3 of 6 Asian studies had a low study quality score[11,24,31] as opposed to 1 of 10 Western studies.[30] Therefore, influences of study quality and continent cannot easily be separated. However, the (unpublished) results of Pan et al, which were fully adjusted for potential confounders, supported the inverse association that we observed for other East Asian countries. We therefore believe that our results on milk consumption are not solely due to confounding. Residual confounding will, as in any cohort study, always be of concern.

In conclusion, this meta-analysis of 18 prospective observational studies indicates a possible role for milk and cheese consumption in stroke prevention. Results should be placed in the context of the observed heterogeneity. Future epidemiological studies should provide more details about types of dairy, including fat content. In addition, the role of milk and dairy in Asian populations deserves further attention.

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Disclosures

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SUPPLEMENTAL MATERIAL

CONTENT

Supplemental methods

- Supplement I. MOOSE Checklist
- Supplement II. Search strategy
- Supplement III. Quality assessment of cohort studies on dairy intake and stroke risk.
- Supplement IV: Definition of dairy foods as described in the individual cohort studies included in the meta-analyses

Supplement I MOOSE checklist[1]

	Reported on page	Comments
Reporting of background should include		
Problem definition	3	
Hypothesis statement	3	
Description of study outcome(s)	3	
Type of exposure or intervention used	3	
Type of study designs used	3	
Study population	3	
Reporting of search strategy should include		
Qualifications of searchers (e.g. librarians and investigators)	4	
Search strategy, including time period used in the synthesis and key words	4, Supplement II	
Effort to include all available studies, including contact with authors	4	
Databases and registries searched	4	
Search software used, name and version, including special features used (e.g. explosion)	4	
Use of hand searching (e.g. reference lists of obtained articles)	4	
List of citations located and those excluded, including justification	4	
Method of addressing articles published in languages other than English	4	
Method of handling abstracts and unpublished studies	4	
Description of any contact with authors	4	
Reporting of methods should include		
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	4	
Rationale for the selection and coding of data (e.g. sound clinical principles or convenience)	4	
Documentation of how data were classified and coded (e.g. multiple raters, blinding and interrater reliability)	4	
Assessment of confounding (e.g. comparability of cases and controls in studies where appropriate)	4	
Assessment of study quality, including blinding of	5	

quality assessors, stratification or regression on possible predictors of study results		
Assessment of heterogeneity	6	
Description of statistical methods (e.g. complete description of fixed 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	5-6	
Provision of appropriate tables and graphics	Supplementary files	
Reporting of results should include		
Graphic summarizing individual study estimates and overall estimate	27-53	
Table giving descriptive information for each study included	17-22	
Results of sensitivity testing (e.g. subgroup analysis)	7-9	
Indication of statistical uncertainty of findings	7-9	By CI's and I^2
Reporting of discussion should include		
Quantitative assessment of bias (e.g. publication bias)	8, Fig 4-5	
Justification for exclusion (e.g. exclusion of non-English language citations)	Na	
Assessment of quality of included studies	10	
Reporting of conclusions should include		
Consideration of alternative explanations for observed results	10	
Generalization of the conclusions (i.e. appropriate for the data presented and within the domain of the literature review)	11	
Guidelines for future research	12	
Disclosure of funding source	13	

Supplement II Search strategy (Pubmed) – updated until June 2015

EMBASE (http://www.embase.com) and SCOPUS (http://www.scopus.com) search strategies were based on the Pubmed (http://www.ncbi.nlm.nih.gov/pubmed) query syntax shown below.

ACTION 1 DETERMINANTS

#1 dairy products[Mesh] OR milk[Mesh] OR cheese[Mesh] OR yogurt[Mesh] OR butter[Mesh] OR cultured milk products[Mesh] OR ice cream[Mesh]

#2 dairy[tiab] OR milk*[tiab] OR cheese*[tiab] OR yogurt*[tiab] OR yoghurt*[tiab] OR butter[tiab] OR buttermilk[tiab] OR custard*[tiab] OR pudding*[tiab] OR cream*[tiab] OR cream[tiab] OR ice cream[tiab] OR ice-cream[tiab] OR curd*[tiab] OR porridge[tiab]

#3 (#1 OR #2

ACTION 2 OUTCOME

#4 mortality[tiab] OR death*[tiab] OR dead[tiab] OR all-cause[tiab] OR all cause[tiab] OR fatal[tiab] OR event[tiab] OR nonfatal[tiab] OR non-fatal[tiab] OR Mortality[Mesh:NoExp] OR mortality[Mesh subheading]

#5 cardiovascular[tiab] OR vascular[tiab] OR CVD[tiab] OR Cardiovascular Diseases[Mesh:NoExp]

#6 cerebrovascular[tiab] OR stroke[tiab] OR TIA[tiab] OR transient ischemic*[tiab] OR CVA[tiab] OR cerebral infarction[tiab] OR Cerebrovascular accident[Mesh:NoExp] OR stroke[Mesh:NoExp]

#7 #4 OR #5 OR #6

ACTION 3 COMBINE EXPOSURE AND OUTCOME

#8 #3 AND #7

ACTION 4 LIMITS

#9 ((animals[MeSH] NOT (humans[MeSH] AND animals[MeSH])))

#10 #8 NOT #9

#11 breast [tiab]

#12 #10 NOT #11

Supplement III. Quality assessment of cohort studies on dairy intake and risk of stroke

	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Bernstein et al., 2012 - HPFS[2]	C	A★	C	A★	A★B★	B★	A★	B★	7
Bernstein et al., 2012 - NHS[2]	C	A★	C	A★	A★B★	B★	A★	B★	7
Dalmeijer et al., 2013[3]	A★	A★	B★	A★	A★B★	B★	A★	B★	9
Elwood et al., 2004[4]	A★	A★	C	A★	A★	B★	A★	B★	7
Goldbohm et al., 2011[5]	A★	A★	B★	A★	A★B★	B★	A★	B★	9
Iso et al., 1999[6]	C	A★	B★	A★	A★	B★	A★	B★	7
Kinjo et al., 1999[7]	A★	A★	C	A★	.	B★	A★	D	5
Kondo et al., 2013[8]	A★	A★	B★	A★	A★	B★	A★	B★	8

	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Larsson et al., 2009[9]	C	A★	B★	A★	A★B★	B★	A★	D	7
Larsson et al., 2012[10]	A★	A★	B★	A★	A★B★	B★	A★	B★	9
Lin 2013 et al., 2013[11]	A★	A★	C	A★	.	A★	A★	A★	6
Louie al., 2013[12]	B★	A★	B★	A★	A★	B★	A★	A★	8
Misirli et al., 2012[13]	A★	A★	C	A★	A★	B★	A★	D	6
Ness et al., 2001[14]	C	A★	D	A★	.	C	A★	D	3
Pan et al., unpublished	C	A★	C	A★	A★B★	B★	A★	B★	7
Praagman et al., 2015[15]	A★	A★	B★	A★	A★B★	A★	A★	D	8
Sauvaget et al., 2003[16]	A★	A★	C	A★	.	B★	A★	B★	6

	Selection				Comparability	Outcome			Total score
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Outcome not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Follow up long enough for outcomes to occur	Adequacy of follow-up of cohorts	
Sonestedt et al., 2011[17]	B★	A★	A★	A★	A★B★	A★	A★	A★	9
Yaemsiri et al., 2012[18]	B★	A★	C	A★	A★B★	B★	A★	C	7

NEWCASTLE – OTTAWA QUALITY ASSESSMENT SCALE
COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average *healthy adults* in the community★
b) somewhat representative of the average *healthy adults* in the community ★
c) selected group of users *e.g. nurses, volunteers, smokers*
d) no description of the derivation of the cohort

2) Selection of the non-exposed cohort
a) drawn from the same community as the exposed cohort★
b) drawn from a different source
c) no description of the derivation of the non-exposed cohort

3) Ascertainment of exposure
a) secure record (*e.g. 7 day food diary)* ★
b) structured interview/≥ 2 *dietary recalls/diet history/ food frequency questionnaire validated for dairy or calcium* ★
c) written self-report (*e.g. <2 dietary recalls/non-validated food frequency questionnaire or not reported whether food frequency questionnaire was validated for dairy*)
d) no description

4) Demonstration that outcome of interest was not present at start of study
a) yes★
b) no

Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for *age, sex, body mass index, smoking, and total energy intake* ★
b) study controls for any additional factor (*e.g. physical activity, dietary factors*) ★

Outcome
1) Assessment of outcome
a) independent blind assessment/*Complete medical information available* ★
b) record linkage/*Medical records or validated self-report* ★
c) non-validated self-report
d) no description

2) Was follow-up long enough for outcomes to occur

a) yes ★
b) no

3) <u>Adequacy of follow up of cohorts</u>
a) complete follow up - all subjects accounted for ★
b) subjects lost to follow up unlikely to introduce bias - small number lost ≤*20%* follow up, or description provided of those lost ★
c) follow up rate <*80%* or no description of those lost
d) no statement

Supplement IV

Definition of dairy products as described in the papers of 18 prospective cohort studies included in the meta-analyses (in alphabetical order)

Exposure category original paper	Exposure category meta-analysis	Detailed description if available
Bernstein 2011[2]		
Whole fat dairy	High-fat dairy	whole milk, ice cream, hard cheese, full fat cheese, cream, sour cream, cream cheese, butter
Low-fat dairy	Low-fat dairy	skim/low-fat milk, 1% and 2% milk, yogurt, cottage and ricotta cheeses, low-fat cheese, sherbet
Dalmeijer 2013[3]		
Total dairy	Total dairy	All dairy food products, except butter and ice-cream
Milk and milk products	Milk	All kinds of milk, yogurt, coffee creamers, curd, pudding, porridge, custard, and whipping cream
Fermented dairy	Fermented dairy	Buttermilk, yogurt, cheese
Cheese	Cheese	All types of cheese, except for curd
High-fat dairy	High-fat dairy	Milk and milk products with a fat content ≥2g/100g (whole milk products) or cheese products with a fat content ≥20g/100g.
Low-fat dairy	Low-fat dairy	Milk and milk products with a fat content <2g/100g (skimmed or semi-skimmed milk products), or cheese with a fat content <20g/100g.
Elwood 2004[4]		
Milk	Milk	Liquid milk, not milk used in food preparation
Goldbohm 2011[5]		
Milk products	Milk	
Non-fermented full-fat milk	High-fat milk	Whole milk (3.7% fat), cream (36%, 20% fat), condense whole milk, whole-milk cocoa, pudding, ice cream
Non-fermented low-fat milk	Low-fat milk	Low-fat milk (1.5% fat), skim milk (0.1% fat, condensed low-fat milk, low-fat and skim cocoa
Fermented full-fat milk	-	Yogurt (3.5% fat, full-fat quark (fresh cheese), sour cream
Fermented low-fat milk	Fermented dairy*	Buttermilk, skim yogurt (0.1% fat) nonfat quark (fresh cheese)
Cheese	Cheese	
Fat cheese	-	Not further defined
Low-fat cheese	-	Not further defined
Butter	Butter	
Low-fat dairy	Low-fat dairy	

Iso 1999[6]		
Milk	Milk	Not further defined
Low-fat milk	Low-fat milk	Not further defined
Whole-fat milk	High-fat milk	Not further defined
Yogurt	Yogurt	Not further defined
Cheese	Cheese	Not further defined
Kinjo 1999[7]		
Dairy milk	Milk	Not further defined
Kondo 2013[8]		
Milk and dairy products	Milk	Authors reported that 93% comprises milk
Larsson 2009[9]		
Total dairy	Total dairy	Low-fat milk, whole milk, yogurt, cheese, cream, ice-cream, butter (dairy from mixed dishes included)
Low-fat milk	Low-fat milk	Not further defined
Whole milk	High-fat milk	Not further defined
Total milk (additionally provided by the author)	Milk	
Sour milk	-	
Yogurt	Yogurt	
Cheese	Cheese	
Cream	-	
Ice cream	-	
Butter	Butter	
Larsson 2012[10]		
Total dairy	Total dairy	Low-fat milk (0.5% fat), medium-fat milk (1.5%), full-fat milk (3% fat), milk in pancakes, low-fat sour milk/yogurt (0.5% fat), full-fat sour milk/yogurt (3% fat), cottage cheese (4% fat), low-fat cheese (10-17% fat), full-fat cheese (~28% fat), ice cream, cream, crème fraiche
Low-fat dairy	Low-fat dairy	Low-fat milk, medium-fat milk, low-fat sour milk/yogurt, medium-fat sour milk/yogurt, cottage cheese, low-fat cheese
Full-fat dairy	High-fat dairy	Full-fat milk, full-fat sour milk/yogurt, full-fat cheese, ice cream, cream, crème fraiche
Milk	Milk	Low-fat milk, medium-fat milk, full-fat milk, milk in pancakes
Sour milk and yogurt	Fermented dairy*	
Cheese	Cheese	Low-fat cheese, full-fat cheese
Cream and crème fraiche	-	
Lin 2013[11]		
Dairy	Milk	According to the authors, almost all dairy comprised milk

Louie 2013[12]		
Total dairy	Total dairy	All dairy foods
Low-fat dairy	Low-fat dairy	Reduced fat/skim milk, reduced fat dairy dessert, low-fat cheese
Whole-fat dairy	High-fat dairy	Whole fat milk, whole fat cheese, medium fat dairy dessert
Ratio Low-fat dairy: whole fat dairy	-	
Misirli 2012[13]		
Dairy products	Total dairy	Not further defined
Ness 2001[14]		
Milk	Milk	Not further defined
Pan (unpublished results)		
Total dairy	Total dairy	Not further defined
Milk	Milk	Not further defined
Praagman 2015[15]		
Dairy products	Total dairy	Milk, buttermilk, yogurt, coffee creamer, curd, pudding, porridge, custard, whipped cream, ice cream, cheese (not butter)
Low-fat dairy	Low-fat dairy	Milk and milk products with a fat content of <2g/100g and cheese products with a fat content of <20g/100g
High-fat dairy	High-fat dairy	Milk and milk products with a fat content of ≥2g/100g and cheese products with a fat content of ≥20g/100g
Total milk	Milk	All types of dairy, excluding cheese
Fermented dairy	Fermented dairy	All types of buttermilk, yogurt, curd, and cheese
Cheese	Cheese	All types of cheese, excluding curd
Yogurt	Yogurt	
Sauvaget 2003[16]		
Dairy products	-	Butter, cheese
Milk	Milk	Milk
Sonestedt 2011[17]		
Total dairy	Total dairy	Milk, cheese (>10% fat), cream, butter, milk-based spread Bregott
Milk	Milk	Non-fermented milk, fermented milk
Non-fermented milk	-	
Fermented milk	Fermented dairy*	Yogurt, processed sour milk
Low-fat milk	Low-fat milk	≤2.4% fat
High-fat milk	High-fat milk	>2.4% fat
Cheese	Cheese	>10% fat
Butter	Butter	Butter, milk-based spread Bregott
Cream	-	
Yaemsiri 2012[18]		
Total dairy	Total dairy	Not further defined

* Fermented milk includes cheese, yogurt and sour milk. We included studies that combined at least two of these products in our analysis of fermented dairy.

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