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Review

Meta-analysis of Egg Consumption and Risk of Coronary Heart Disease and Stroke

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Key words: epidemiology, meta-analysis, diet, coronary heart disease, stroke

The possible relationship between dietary cholesterol and cardiac outcomes has been scrutinized for decades. However, recent reviews of the literature have suggested that dietary cholesterol is not a nutrient of concern. Thus, we conducted a meta-analysis of egg intake (a significant contributor to dietary cholesterol) and risk of coronary heart disease (CHD) and stroke. A comprehensive literature search was conducted through August 2015 to identify prospective cohort studies that reported risk estimates for egg consumption in association with CHD or stroke. Random-effects meta-analysis was used to generate summary relative risk estimates (SRREs) for high vs low intake and stratified intake dose–response analyses. Heterogeneity was examined in subgroups where sensitivity and meta regression analyses were conducted based on increasing egg intake. A 12% decreased risk (SRRE = 0.88, 95% confidence interval [CI], 0.81–0.97) of stroke was observed in the meta-analysis of 7 studies of egg intake (high vs low; generally 1/d vs <2/wk), with little heterogeneity (p-H = 0.37, $I^2 = 7.50$). A nonstatistically significant SRRE of 0.97 (95% CI, 0.88–1.07, p-H = 0.67, $I^2 = 0.00$) was observed in the meta-analysis of 7 studies of egg consumption and CHD. No clear dose–response trends were apparent in the stratified intake meta-analyses or the meta regression analyses. Based on the results of this meta-analysis, consumption of up to one egg daily may contribute to a decreased risk of total stroke, and daily egg intake does not appear to be associated with risk of CHD.

Key Teaching Points:

- The role of egg consumption in the risk of stroke and coronary heart disease has come under scrutiny over many years.
- A comprehensive meta-analysis of prospective cohort studies that reported risk estimates for egg consumption in association with CHD or stroke was performed on the peer-reviewed epidemiologic literature through August 2015.
- Overall, summary associations indicate that intake of up to 1 egg daily may be associated with reduced risk of total stroke.
- Overall, summary associations show no clear association between egg intake and increased or decreased risk of CHD.
- Eggs are a relatively low-cost and nutrient-dense whole food that provides a valuable source of protein, essential fatty acids, antioxidants, choline, vitamins, and minerals.

INTRODUCTION

The potential relationship between dietary cholesterol and risk of cardiovascular disease (CVD) has been debated for decades. Early studies reported strong correlations between cholesterol intake and heart disease; however, recently published studies have shown no or little effect between dietary cholesterol and cardiac outcomes or markers of CVD risk. As a result, the scientific community has acknowledged that other dietary covariates may impact heart disease more than dietary

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cholesterol [1]. Historically, dietary cholesterol recommendations have ranged from <300 mg/d for healthy individuals and <200 mg/d for those at high risk of CVD [1]. Specifically, the American Heart Association recommended that healthy adults limit dietary cholesterol intake to no more than 300 mg/d on average [2,3]. Consistent with this recommendation, the Dietary Guidelines for Americans formerly recommended that cholesterol intake should not exceed 300 mg/d [4]. However, the 2015 Dietary Guidelines for Americans scientific advisory committee stated that they will not bring forward this recommendation "because available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol" and that "cholesterol is not a nutrient of concern for overconsumption" [5]. In 2 2014 reports, the American College of Cardiology/American Heart Association Task Force on Practice Guidelines concluded that there is insufficient evidence to determine whether lowering dietary cholesterol reduces low-density lipoprotein cholesterol, and no recommendations were made to reduce dietary cholesterol to specific levels [6,7]. Similarly, the European Guidelines on Cardiovascular Disease Prevention in Clinical Practice (Version 2012) report concluded that "the impact of dietary cholesterol on serum cholesterol levels is weak compared with that of the fatty acid composition of the diet" [8, p1665]. Thus, the European working group also did not recommend specific guidance on the intake of dietary cholesterol [8].

Eggs are a common source of dietary cholesterol, with a single large egg containing approximately 186 mg of cholesterol [9]. Eggs also contain protein, essential fatty acids, antioxidants, choline, vitamins, and minerals [10,11] and, as such, are a nutrient-dense whole food that should be evaluated based on total consumption rather than specific constituents, such as cholesterol. Although there has been concern that regular egg intake may be associated with risk of CVD due to cholesterol content, most epidemiologic studies have not reported increased risks of CVD, coronary heart disease (CHD), or stroke. In a recent meta-analysis of cohort studies of egg consumption, no statistically significant summary associations were reported for total CVD (hazard ratio [HR] = 0.96, 95% confidence interval [CI], 0.88–1.05), ischemic heart disease (HR = 0.93, 95% CI, 0.86–1.09), or stroke (HR = 0.93, 95% CI, 0.81–1.07) based on high vs low intake levels, although all associations were in the inverse direction [12]. Further, in a dose–response meta-analysis, no evidence of a curvilinear association was observed between egg consumption and risk of coronary heart disease and stroke using restricted cubic spline methodology and, again, the trends were in the inverse direction. [13]. Since these meta-analyses were published, new cohort studies of egg intake and CVD, CHD, and stroke have been published based on analyses of the Nurses' Health Study [14], Health Professionals' Follow-up Study [14], Northern Manhattan Study [10], and Atherosclerosis Risk in Communities Study [15].

The objectives of the present study were to conduct an updated, comprehensive meta-analysis to (1) estimate summary associations between egg consumption and CHD and stroke risk based on high vs low intakes; (2) conduct stratified intake dose–response analyses; (3) conduct dose–response meta regression analyses based on increasing levels of egg intake; (4) conduct subgroup and sensitivity analyses by important study characteristics to identify potential sources of heterogeneity and to estimate patterns of risk by study factors; (5) estimate the influence of each cohort on the overall effect size; and (6) evaluate the likelihood for publication bias.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines for this systematic review and meta-analysis [16] (see supplementary material for Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist).

Literature Search

Systematic literature searches in the PubMed bibliographic database were performed to identify articles on egg consumption and cardiovascular disease endpoints (focusing on CHD) and stroke. Searches were conducted through August 2015. The searches combined MESH terms (dietary cholesterol, coronary heart disease, ischemic heart disease, coronary artery disease, myocardial infarction, heart failure, cerebrovascular disorder, stroke, cardiovascular disease) with text terms (eggs, egg consumption, egg intake, cholesterol, and dietary cholesterol). Supplementary literature searches included searching EMBASE and screening reference lists from all relevant studies, review articles, meta-analyses, and Cochrane Collaboration reports. In particular, we reviewed the references included in the recent meta-analysis by Shin and colleagues [12]. All search results were screened by 2 researchers, with no discrepancies between reviewers.

Study Selection

To be included in the meta-analysis, a published study had to meet the following criteria: (1) prospective design; (2) analyzed adult human populations; (3) published in the English language; and (4) provided risk estimates and measures of variance (i.e., 95% CIs) for egg intake and cardiovascular outcomes including CHD or stroke. Our study identification protocol was not limited to prospective cohort studies; we also searched for randomized controlled clinical trials, although none were identified that reported relevant results. Studies meeting the eligibility criteria were included in the meta-analysis (Supplemental Fig. 1). Case–control, cross-sectional, ecologic and experimental animal studies, case reports, case series, commentaries, and letters to the editor were excluded.

Data Extraction and Statistical Analysis

Qualitative and quantitative information was extracted from each study. Specifically, we extracted author and year of study, study population name and description, study design, study country, analytic cohort size, years of follow-up, cohort demographic characteristics, outcome classification, number of cases for the outcome of interest, outcome ascertainment and diagnosis method, the year and method of diet assessment, exposure categories and most fully adjusted measures of relative risk and 95% confidence intervals for each intake strata, and any statistical adjustments. If more than one article from the same study cohort was published, data from the publication with the longest follow-up period and/or the most adjusted risk estimate were extracted. Two investigators ascertained individual study information independently, with any discrepancies resolved by discussion.

In the 2 publications by Nakamura and colleagues [17,18], 1 egg per day was used as the referent group. Thus, we used the inverse of the relative risk (RR) and 95% CI in the "seldom" category in our meta-analysis models of daily egg intake. We calculated the RRs and 95% CIs for the other intake categories using their reported outcome data. Some studies were reviewed but not included in the meta-analysis because relevant outcome data were not reported [19,20], the study was updated in a more recent publication [21,22], or persons with prevalent disease were included in the analysis [21]. Other studies were identified (and summarized in the Discussion section) that evaluated unique study populations but were not included in the meta-analyses (vegetarian study population [23,24]). Data for egg consumption and total CVD were not meta-analyzed because of sparse data and heterogeneity in analytical study populations [3,25]. In the study by Goldberg et al. [10], 2+ eggs/wk was used as the highest intake category; therefore, we included data from this study in the dose–response analyses only.

Random-effects models were used to calculate summary relative risk estimates (SRREs), 95% CIs, and corresponding *p*-values for heterogeneity. Study weights were equal to the inverse of the variance of each study's effect estimate according to the methodology developed by DerSimonian and Laird [26]. Relative risks comparing the highest to the lowest category of intake were combined across all studies to produce summary associations. In general, these comparisons were approximately 1 egg/d vs <2/wk. Most studies provided the median intake levels for quantiles of exposure and an associated relative risk comparing incremental quantiles to the lowest intake group. Thus, to evaluate potential dose–response relationships, we conducted stratified intake meta-analyses by creating summarized intake categories based on the data reported in each study. Meta regression analyses were performed for CHD and total stroke separately based on increasing levels of egg intake. In the meta regression analyses, a numerical moderator variable was created based on weekly egg intakes. These analyses produced a beta coefficient representing the risk per incremental unit of weekly egg intake. In addition, we created dummy-coded categorical variables and continuous variables as covariates in meta regression models to assess their impact on the outcome variable.

One-study-removed sensitivity analyses were conducted to determine the relative influence each study had on the overall model. Additional sensitivity and subgroup analyses were generated based on descriptive study characteristics. Statistical heterogeneity was assessed using the Cochran's Q test and I^2 statistic, which indicate the percentage of variation attributable to between-study heterogeneity [27]. Publication bias was assessed visually by examining a funnel plot measuring the standard error as a function of effect size and by performing Egger's regression method [28]. Forest plots were created for models of egg intake and CHD and stroke. All statistical analyses were performed using Comprehensive Meta-Analysis Software (version 3.2.00089; Biostat, Englewood, NJ).

RESULTS

Descriptive Study Characteristics

Seven studies [11,113,17,29–32] were included in the meta-analysis of egg intake and stroke (Fig. 1), and 7 studies [11,15,17,18,29,31,33] were included in the meta-analyses for CHD (Fig. 2). Descriptive characteristics of these studies are summarized in Table 1. Approximately 276,000 and 308,000 adult participants were included in the studies of CHD and stroke, respectively, and studies were conducted primarily among populations in the United States, with other studies in Japan, Australia, Spain, and the United Kingdom. Studies were published between 1982 and 2014 with follow-up periods ranging from 6 years to 26 years. Most studies adjusted for important CHD and stroke risk factors such as age, race, body mass index (BMI), physical activity, smoking, alcohol, and blood pressure.

Results from Meta-analysis

The meta-analysis results are summarized in Table 2 and Figs. 1–4.

Stroke

In the meta-analysis of high vs low egg intake (generally 1 egg/d vs <2 eggs/wk), a statistically significant 12% decreased risk of stroke was observed (SRRE = 0.88, 95% CI, 0.81–0.97, p-H = 0.37, I^2 = 7.50; Table 2, Fig. 1). The study by Bernstein et al. [14] provided approximately 50% of the relative weight in this model; removal of this study in a sensitivity analysis did not appreciably alter the magnitude of the summary estimate (SRRE = 0.87, 95% CI, 0.74–1.03, p-H = 0.23, I^2 = 25.0). There was no evidence of

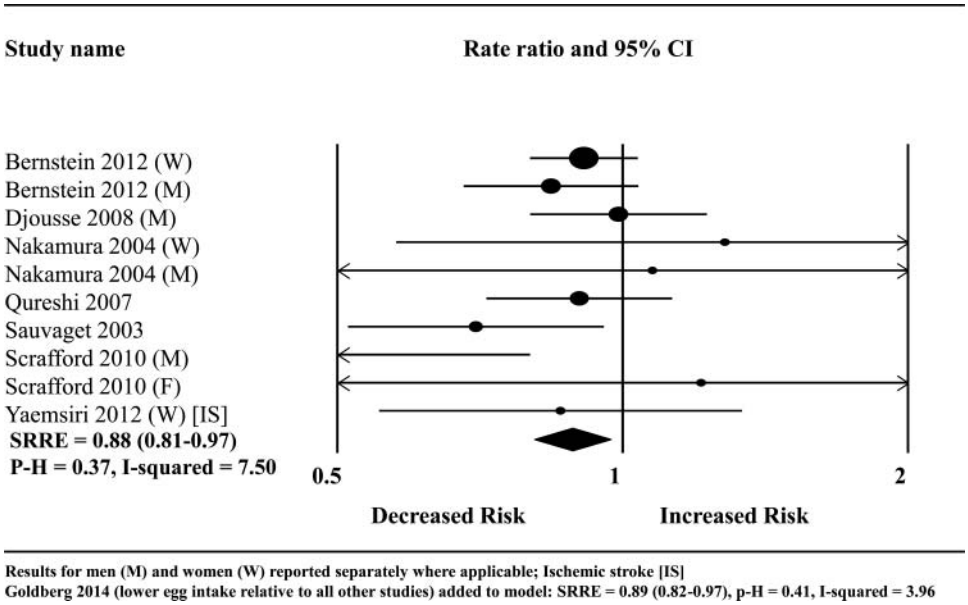

Fig. 1. Meta-analysis of egg consumption and stroke.

publication bias based on visual inspection of the funnel plot of standard error by log rate ratio and no statistical evidence of publication bias (Egger's regression p-value = 0.61). Goldberg et al. [10] reported intake data for 2+ eggs/wk as their highest stratum, which is relatively lower than the highest intake category for all other studies (i.e., generally daily egg intake). Addition of this study in a sensitivity analysis did not change the overall effect size (SRRE = 0.89, 95% CI, 0.82–0.97, p-H = 0.41, I^2 = 3.96; Table 2, Fig. 1). The SRRE based on 4 data points for fatal stroke was 0.78 (95% CI, 0.52–1.19). Nonstatistically significant inverse summary associations were found in the analyses of ischemic stroke (SRRE = 0.92, 95% CI, 0.82–1.02) and hemorrhagic stroke (SRRE = 0.85, 95% CI, 0.56–1.28). A statistically significant reduction in stroke risk was found in the subgroup meta-analysis of studies conducted in the United States (SRRE = 0.90, 95% CI, 0.82–0.99), and a nonstatistically significant decreased risk of stroke was observed in the meta-analysis of 2 studies conducted in Japan (SRRE = 0.82, 95% CI, 0.58–1.18). Nonstatistically significant inverse associations between egg intake and stroke risk were observed for both men and women (Table 2).

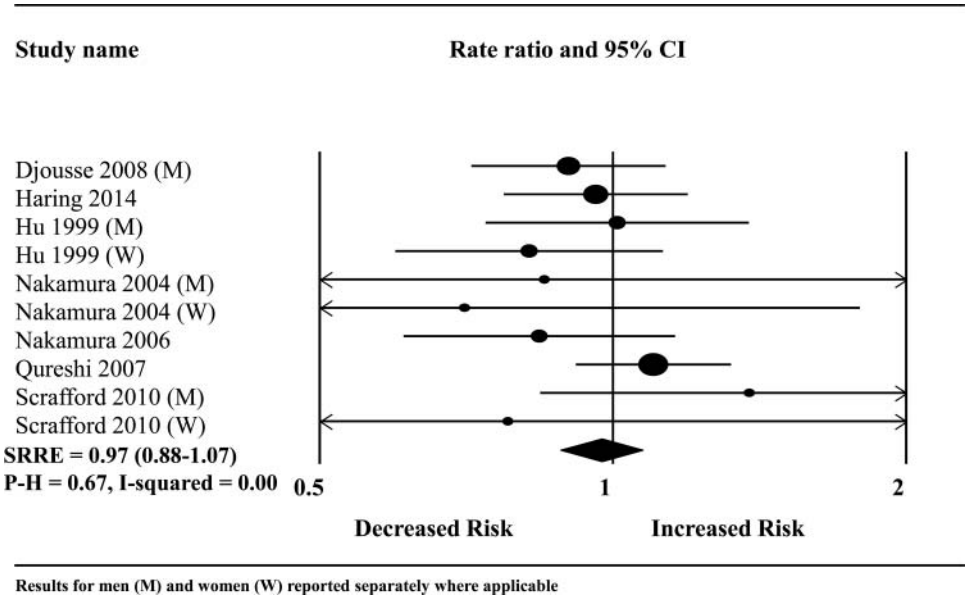

Fig. 2. Meta-analysis of egg consumption and coronary heart disease.

Table 1. Descriptive Study Characteristics of Prospective Cohorts of Egg Intake and Coronary Heart Disease and Stroke

Study country; cohort	Year baseline diet assessed	Follow-up (years)	No. of subjects (no. of cases/deaths)	Age range (mean)	Relative risk (95% CI) for highest egg exposure category	Cardiovascular outcome	Statistical adjustments	Reference
United States; NHS	1980	26	84,010 (stroke: 2633)	30–55 at baseline	0.67 servings/d vs 0.07 servings/d: RR = 0.91 (0.80–1.04)	Incident stroke	Stratified by age and time period; adjusted for BMI, smoking, physical activity, parental history of early MI, menopausal status, multivitamin use, vitamin E use, aspirin use, total energy, cereal fiber, alcohol, trans fat, fruit and vegetable intake, other protein sources	[14]
United States; HPFS	1986	22	43,150 (stroke: 1397)	40–75 at baseline	0.79 servings/d vs 0.02 servings/d: RR = 0.84 (0.68–1.04)	Incident stroke	Stratified by age and time period; adjusted for BMI, smoking, physical activity, parental history of early MI, multivitamin use, vitamin E use, aspirin use, total energy, cereal fiber, alcohol, trans fat, fruit and vegetable intake, other protein sources	[14]
Australia; Western Australian Aborigines	1988	14	514 (CHD: 24)	15–88	>8 eggs/mo vs ≤8 eggs/mo: RR = 2.59 (1.11–6.04)	CHD including mortality	Sex, age, total cholesterol, mean arterial pressure, waist girth	[24]
United States; Framingham Study	1949	24	912 (CHD: 147)	30–59	None reported	Incident CHD	None reported	[19]
					None reported	Incident MI		
					None reported	Incident angina pectoris		
United States; Physicians Health Study	1981	20	21,327 (stroke: 1342; MI: 1550)	40–86 (53.7)	≥7 eggs/wk vs <1/wk: RR = 0.90 (0.72–1.14)	Incident MI	BMI, smoking, hypertension, vitamin intake, alcohol, vegetable consumption, breakfast cereal, physical activity, treatment arm, atrial fibrillation, diabetes, hypercholesterolemia, parental history of early MI	[29]
					RR = 0.99 (0.80–1.23)	Incident stroke		
United States; Seventh-day Adventists	Not reported	Not reported	26,473 (not reported)	≥25	≥3 eggs/wk vs <1/wk: RR = 1.01 (no CI reported)	Incident coronary events	None reported	[20]
United States; NOMAS	1993	11	2669 (stroke: 266; MI: 226; vascular death: 452)	65.8	≥2 eggs/wk vs 0 or <1/mo: RR = 1.18 (0.60–2.30)	Incident stroke	Age, sex, race/ethnicity, BMI, diabetes, hypertension, LDL, HDL, TG, cholesterol-lowering medication, moderate alcohol use, moderate–heavy physical activity, smoking, high school completion, total daily kilocalories, Mediterranean diet score, family history of stroke or MI in siblings, daily consumption of saturated fat, unsaturated fat, carbohydrates, and protein	[10]

(*Continued on next page*)

Table 1. Descriptive Study Characteristics of Prospective Cohorts of Egg Intake and Coronary Heart Disease and Stroke *(Continued)*

Study country; cohort	Year baseline diet assessed	Follow-up (years)	No. of subjects (no. of cases/deaths)	Age range (mean)	Relative risk (95% CI) for highest egg exposure category	Cardiovascular outcome	Statistical adjustments	Reference
					RR = 0.81 (0.34–1.93)	Incident MI		
United States; ARIC	1987	22	12,066 (CHD: 1147)	45–64 at baseline	1 serving/d vs 0/d: RR = 0.96 (0.77–1.19)	Incident CHD	Age, sex, race, study center, total energy intake, smoking, education, systolic blood pressure, use of antihypertensive medication, HDL, total cholesterol, use of lipid-lowering medication, BMI, WHR, alcohol intake, sports-related physical activity, leisure-related physical activity, carbohydrate intake, fiber intake, magnesium intake	[15]
United States; HPFS	1986	14	43,732 (stroke: 725)	40–75	≥1 egg/d vs <1/wk: RR = 1.09 (0.69–1.71)	Incident ischemic stroke	BMI, physical activity, history of hypertension, smoking status, aspirin use, multivitamin use, consumption of alcohol, potassium, fiber, vitamin E, total servings of fruit and vegetables, total energy intake, hypercholesterolemia at baseline	[22]
					RR = 0.32 (0.07–1.37)	Incident hemorrhagic stroke		
United States; Health ABC study	1999	9	1941 (CVD: 203)	70–79 (74.5)	≥3 eggs/wk vs <1/wk: RR = 1.85 (1.3–2.64)	Incident CVD All subjects	Age	[25]
					RR = 1.38 (0.88–2.16)	Subjects without diabetes		
United States; HPFS	1986	8	37,851 (stroke: 259; CHD: 866)	40–75 at baseline	≥7 eggs/wk vs <1/wk: RR = 1.08 (0.79–1.48)	Incident CHD	Age, BMI, smoking, parental history of MI, multivitamin use, vitamin E use, alcohol, history of hypertension, physical activity, total energy intake	[33]
					RR = 1.07 (0.66–1.75)	Incident stroke		
United States; NHS	1980	14	80,082 (stroke: 563; CHD: 939)	34–59 at baseline	≥7 eggs/wk vs <1/wk: RR = 0.82 (0.60–1.13)	Incident CHD	Age, BMI, smoking, parental history of MI, multivitamin use, vitamin E use, alcohol, history of hypertension, physical activity, total energy intake	[33]
					RR = 0.89 (0.60–1.31)	Incident stroke		
United Kingdom	1980	13.3	10,802 (CHD: 64)	16–79	≥6 eggs/wk vs <1/wk: RR = 2.68 (1.19–6.02)	Ischemic heart disease mortality	Age, sex, smoking, social class	[23]
Japan; NIPPON DATA80	1980	14	9263 (stroke: 107 women; 112 men; CHD: 41 women; 39 men)	30+ at baseline (average age at event early 50s)		Stroke mortality	Age, serum creatinine, total cholesterol, blood glucose, BMI, blood pressure, use of blood pressure–lowering drugs, smoking, alcohol	[17]
					Daily intake vs seldom: RR = 0.85 (0.18–3.85)	Men		
					Daily intake vs seldom: RR = 1.28 (0.58-2.86)	Women		

						Ischemic heart disease mortality		
					Daily intake vs Seldom: RR = 0.70 (0.28–1.79)	Men Women		
Japan; JPHC	1990	10.2	90,735 (CHD: 462)	Cohort 1: 40–59; Cohort 2: 40–69	Almost daily vs <1/wk: RR = 0.84 (0.61–1.16)	Incident CHD	Age, sex, BMI, hypertension, diabetes, use of cholesterol-lowering drugs, smoking, alcohol, intention to avoid cholesterol-rich diet, consumption of meat, fish, vegetable, fruit	[18]
United States; ARIC study	1987	13.3	14,153 (heart failure: 1140)	45–64	Per 1 egg daily: RR = 1.23 (1.08–1.41)	Incident, hospitalized or fatal HF	Energy intake, age, sex, race, center, education level, physical activity level, smoking, drinking status, prevalent cardiovascular disease, diabetes, and/or hypertension	[20]
United States; NHANES	1971	15.9 ± 5.6	9734 (stroke: 655; MI: 1584)	25–74	>6 eggs/wk vs <1/wk: RR = 0.90 (0.70–1.10)	All stroke	Age, gender, race/ethnicity, systolic blood pressure, diabetes mellitus, serum cholesterol, cigarette smoking, BMI, educational status	[11]
					RR = 1.10 (0.90–1.30) RR = 0.90 (0.70–1.10)	Ischemic stroke CAD		
Japan; Life Span Study	1979	16	37,130 (stroke: 1462)	34–103 (56)	Almost daily vs never: RR = 0.70 (0.51–0.95)	Stroke mortality	Stratified by sex and birth cohort; adjusted for city, radiation dose, self-reported BMI, smoking status, alcohol habits, education level, history of diabetes, history of hypertension	[30]
United States; NHANES III	1988	8.8	14,946 (stroke: 74 women; 63 men; CHD: 168 women; 198 men)	17+ at baseline	≥7 eggs/wk vs <1/wk: RR = 1.38 (0.84–2.26)	CHD mortality Men Women Stroke mortality	Age, energy, marital status, educational status, race/ethnicity, WHR, diabetes, hypertension, vitamin E	[31]
					RR = 0.78 (0.26–2.30) RR = 0.33 (0.14–0.82)			
					RR = 1.21 (0.39–3.75)	Men Women		
United States, WHI-OS	1994	7.6	87,025 (stroke: 1049)	50–79 (63.5)	Per 1 medium egg serving/d: RR = 0.86 (0.55–1.33)	Incident ischemic stroke	Age, race, education, family income, years as a regular smoker, hormone replacement therapy use, total metabolic equivalent task hours per week, alcohol intake, history of coronary heart disease, history of atrial	[32]

(*Continued on next page*)

Table 1. Descriptive Study Characteristics of Prospective Cohorts of Egg Intake and Coronary Heart Disease and Stroke *(Continued)*

Study country; cohort	Year baseline diet assessed	Follow-up (years)	No. of subjects (no. of cases/deaths)	Age range (mean)	Relative risk (95% CI) for highest egg exposure category	Cardiovascular outcome	Statistical adjustments	Reference
							fibrillation, history of diabetes, aspirin use, use of antihypertensive medication, use of cholesterol-lowering medication, BMI, systolic blood pressure, total energy intake, dietary vitamin E, fruits and vegetable intake, fiber	
					RR = 0.15 (0.02–0.95)	Incident atherothrombotic stroke		
					RR = 1.2 (0.53–2.71)	Incident cardioembolic stroke		
					RR = 0.89 (0.38–2.10)	Incident lacunar infarctions		
Spain; SUN project	1999	5.8	14,185 (stroke: 28; MI: 34; revascularization procedures: 29)	20–90 (38.4)	>4 eggs/wk vs <1/wk: RR = 1.1 (0.46–2.63)	Incident CVD	Age, sex, total energy intake, adherence to the Mediterranean food pattern, alcohol intake, baseline BMI, smoking status, physical activity during leisure time, family history of CVD, self-reported diabetes, self-reported hypertension, self-reported hypercholesterolemia	[3]

CI = confidence interval, NHS = Nurses' Health Study, RR = relative risk, BMI = body mass index, MI = myocardial infarction, HPFS = Health Professionals Follow-up Study, CHD = coronary heart disease, NOMAS = Northern Manhattan Study, LDL = low-density lipoprotein, HDL = high-density lipoprotein, TG = triglycerides, ARIC = Atherosclerosis Risk in Communities Study, WHR = waist–hip ratio, Health ABC = Health, Aging and Body Composition, CVD = cardiovascular disease, JPHC = Japan Public Health Center; HF = heart failure, NHANES = National Health and Nutrition Examination Survey Epidemiologic Follow-up Study, CAD = coronary artery disease; WHIOS = Women's Health Initiative Observational Study, SUN = Seguimiento Universidad de Navarra.

Table 2. Summary of Meta-analysis Results for Egg Consumption and Stroke and Coronary Heart Disease[a]

Model	Studies (*n*)	SRRE (95% CI)	*p* Value for heterogeneity	I^2
Stroke				
Total stroke	7	0.88 (0.81–0.97)	0.37	7.50
Studies conducted in the United States	5	0.90 (0.82–0.99)	0.38	6.83
Studies conducted in Japan	2	0.82 (0.58–1.18)	0.30	16.35
Men	4	0.85 (0.65–1.11)	0.10	51.76
Women	4	0.92 (0.81–1.04)	0.80	0.00
Ischemic stroke	4	0.92 (0.82–1.02)	0.91	0.00
Hemorrhagic stroke	2	0.85 (0.56–1.28)	0.20	38.13
Fatal stroke	4	0.78 (0.52–1.19)	0.17	38.16
0–1 serving per week	6*	0.87 (0.79–0.96)	0.55	0.00
>1 to 3.5 servings per week	13*	0.90 (0.86–0.95)	0.66	0.00
>3.5 to <7 servings per week	6*	0.91 (0.80–1.04)	0.22	28.82
7+ servings per week	7*	0.92 (0.78–1.08)	0.35	10.64
Coronary heart disease				
Total CHD	7	0.97 (0.88–1.07)	0.67	0.00
Studies conducted in the United States	5	0.99 (0.90–1.10)	0.51	0.00
Studies conducted in Japan	2	0.83 (0.61–1.11)	0.94	0.00
Men	4	0.98 (0.83–1.17)	0.49	0.00
Women	3	0.81 (0.60–1.08)	0.95	0.00
Fatal CHD	2	1.10 (0.75–1.63)	0.54	0.00
0–1 serving per week	8*	0.95 (0.85–1.05)	0.11	39.86
>1 to 3.5 servings per week	12*	0.89 (0.77–1.02)	0.00	69.84
>3.5 to <7 servings per week	6*	1.03 (0.90–1.18)	0.41	1.29
7+ servings per week	9*	0.99 (0.89–1.09)	0.67	0.00

SRRE = summary relative risk estimate, 95% CI = 95% confidence interval, CHD = coronary heart disease.

[a]Analyses based on high vs low intake categories except for the dose–response categorical analyses.

*Represents the number of individual RRs in each model.

Although there was lack of evidence of a monotonic trend based on increasing egg intake and decreasing stroke risk, consuming up to 3.5 eggs per week was associated with statistically significant reductions in risk of total stroke (Table 2). Consuming more than 3.5 eggs per week to more than daily egg intake was associated with nonstatistically significant decreases of stroke risk. Dose–response meta regression did not produce a statistically significant effect based on increasing egg intakes per week and risk of stroke (Fig. 3).

Coronary Heart Disease

Meta-analysis of 7 studies of egg consumption and CHD resulted in an SRRE of 0.97 (95% CI, 0.88–1.07, p-H = 0.67, I^2 = 0.00; high vs low intake; Table 2, Fig. 2). There was no

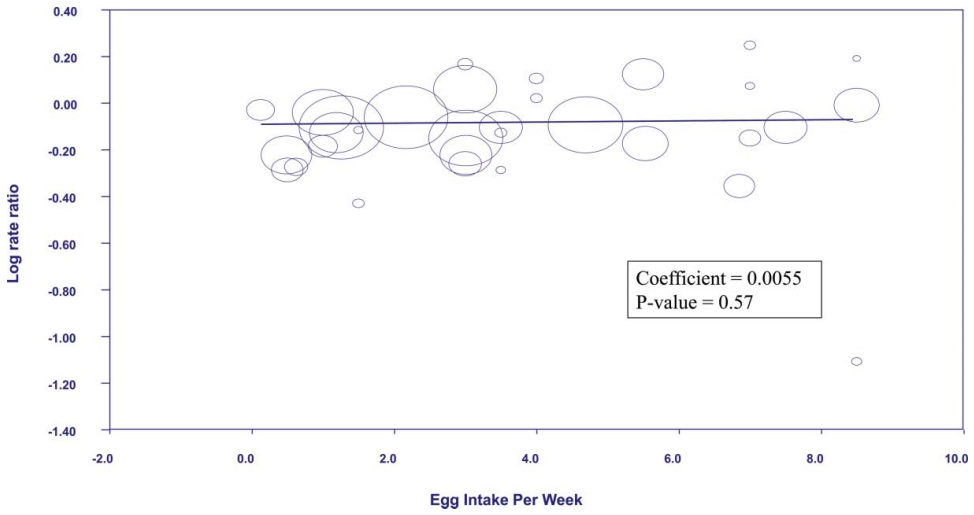

Fig. 3. Regression of log rate ratio for stroke on egg intake per week.

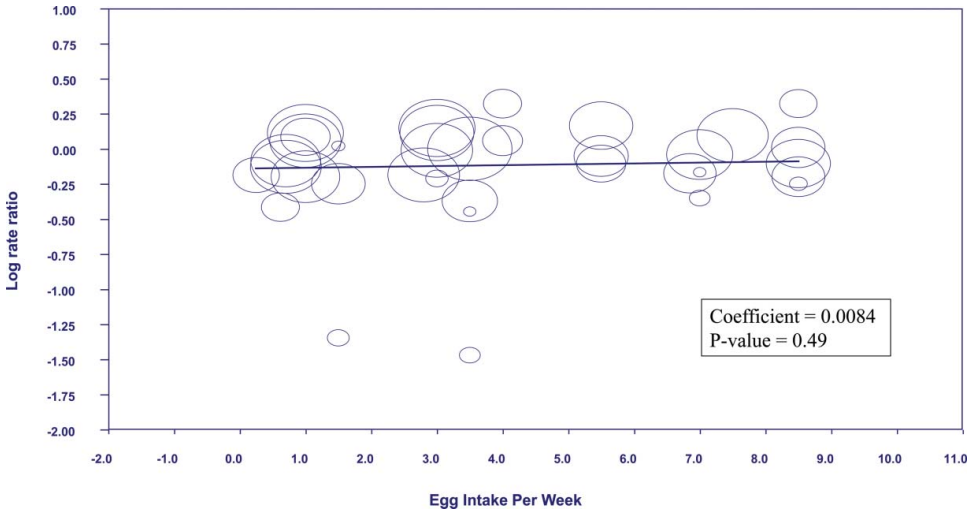

Fig. 4. Regression of log rate ratio for CHD on egg intake per week.

evidence of publication bias based on visual inspection of the funnel plot of standard error by log rate ratio. Furthermore, statistical testing using the Egger's regression method produced a *p*-value of 0.47. The study by Qureshi et al. [11] provided the most relative weight to this model (28%); removal of this study in a sensitivity analysis resulted in an SRRE of 0.93 (95% CI, 0.83–1.04) while increasing homogeneity (p-H = 0.83). Inclusion of data from Goldberg et al.'s study [10] (lower egg intake) did not change the overall summary association (SRRE = 0.97, 95% CI, 0.88–1.07). No association was observed for egg intake and CHD in the model of U.S. studies only (SRRE = 0.99, 95% CI, 0.90–1.10), and the SRRE for the 2 studies conducted in Japan was 0.83 (95% CI, 0.61–1.11). Similarly, no association was found in the meta-analysis of men only (SRRE = 0.98, 95% CI, 0.83–1.17), whereas an inverse association was observed among women (SRRE = 0.81, 95% CI, 0.60–1.08). Five studies reported results data for incident CHD, resulting in an SRRE of 0.96 (95% CI, 0.87–1.07). The SRRE for the 2 studies that reported results data for fatal CHD events was 1.10 (95% CI, 0.75–1.63); this finding was due largely to the RR for men in Scrafford et al.'s study [29], which contributed 63% of the relative weight in this model. Removal of data for men in this study resulted in an SRRE of 0.75 (95% CI, 0.40–1.44) with no evidence of heterogeneity (p-H = 0.98). We created binary variables for gender, study country, and incident/fatal events, and multivariate metaregression of these factors did not yield any statistically significant predictors of CHD risk.

No apparent trend was observed in the stratified intake dose–response analyses for egg consumption and CHD risk (Table 2). Daily or more intake of eggs was not associated with risk of CHD (SRRE = 0.99, 95% CI, 0.89–1.09). Dose–response meta regression did not produce a statistically significant effect based on increasing egg intakes per week and risk of CHD (Fig. 4).

DISCUSSION

Overall, the results of this meta-analysis do not support an increased risk of CHD based on daily egg consumption and indicate that intake of up to 1 egg daily may be associated with reduced risk of total stroke. Specifically, we examined high egg intake (approximately 1 egg/d) vs low egg intake (approximately <2 eggs/wk) and observed no association for CHD risk but found a statistically significant 12% reduction in stroke risk. Stratified meta-analysis and meta regression did not indicate a dose–response trend for risk of stroke based on increasing egg intake (Table 2). Reductions in risk were observed for fatal stroke, ischemic stroke, and hemorrhagic stroke but the summary associations were nonstatistically significant and based on fewer studies. Our findings are relatively consistent with 2 previous meta-analyses of egg consumption and CVD, CHD, and stroke. Shin et al. [12] reported nonstatistically significant inverse associations for high vs low egg intake and risk of CVD, CHD, and stroke. Results from our meta-analysis, particularly for stroke, are slightly stronger in magnitude and more precise than those reported by Shin et al. [12], primarily because we included data from more studies. In a dose–response meta-analysis, Rong et al. [13] used a restricted cubic spline methodology to evaluate curvilinear associations between egg intake and CHD and stroke. Although a curvilinear association between egg intake stroke was not found, the authors reported an RR of 0.91 (95% CI, 0.81–1.02) for incremental egg intake and stroke risk. No associations were observed for CHD.

In an analysis of the Adventist Health Study [20], intake of 3 or more eggs/wk was not associated with incident coronary events (RR = 1.01). A measure of variance was not provided, nor were the data necessary to calculate 95% CIs; thus, this study could not be included in our meta-analysis. In an analysis of over 50% semi-vegetarian/vegetarian/

vegan populations, Mann et al. [23] reported an RR of 2.68 (95% CI, 1.19–6.02) for ischemic heart disease death, but this analysis was only adjusted for age, sex, smoking, and social class. Data from this study were not included in our primary meta-analyses because of the unique analytical study population (high proportion of semi-vegetarians/vegetarians/vegans) and limited adjustments. We included this study in a sensitivity analysis, but the overall summary association did not change because there were relatively few cases observed. In a study of Western Australian Aborigines aged 15–88 years, consumption of 2 or more eggs/wk was associated with CHD (HR = 2.59, 95% CI, 1.11–6.04) [24]. This study was not included in our meta-analysis because of methodological heterogeneity due to a low level of egg intake (2+ eggs/wk), adolescent participants (age range: 15–88 years), and unique study population (Australian Aborigines).

Limited data, from heterogeneous study populations, are available for egg intake and total CVD. Zazpe et al. [3] evaluated the association between egg consumption and incident CVD among Spanish university graduates (average age of approximately 38 years at baseline), most of whom were health professionals, from the SUN (Seguimiento Universidad de Navarra) Project. The authors found no association between egg consumption and CVD (HR = 1.10, 95% CI, 0.46–2.63) for the highest (4+ eggs/wk) versus the lowest (<1 egg/wk) category of egg consumption after adjusting for age, sex, total energy intake, adherence to the Mediterranean food pattern, and other cardiovascular risk factors. In an analysis of the Health, Aging, and Body Composition (Health ABC) study, Houston and colleagues [25] reported a positive association between intake of 3 or more eggs/wk (vs <1 egg/wk) and CVD risk (HR = 1.68, 95% CI, 1.12–2.51) among community-dwelling adults aged 70–79. However, after stratification by diabetes status, the association for egg consumption was only significant among people with diabetes. Interpretation of findings from this study warrants some caution because of the nature of the study population (community-dwelling older adults), the small analytical sample of people with diabetes ($n = 341$), and modest number of incident CVD cases ($n = 45$) with only 5 cases in the referent group.

Some studies included in this meta-analysis also reported increased risks between egg consumption and CHD and stroke among people with diabetes. Among men with diabetes in the Health Professionals Follow-up Study, intake of one or more eggs/day was associated with an RR of 2.02 (95% CI, 1.05–3.87). The RR among women with diabetes in the Nurses' Health Study was 1.49 (95% CI, 0.88–2.52) [33]. In an analysis of the Physician's Health Study [29], daily or more intakes of eggs was not associated with myocardial infarction among diabetics (HR = 1.06, 95% CI, 0.43–2.64), but a nonstatistically significant positive association for stroke risk (HR = 1.83, 95% CI, 0.71–4.23) was found among people with diabetes. In subgroup analyses among people with diabetes, Qureshi et al. [11] reported an increased risk of coronary artery disease (RR = 2.0, 95% CI, 1.0–3.8) based on consumption of 6 or more eggs/wk. In contrast, nonstatistically significant RRs of 0.6 and 0.5 for total stroke and ischemic stroke, respectively, were observed among people with diabetes. Nonstatistically significant inverse associations for CHD (HR = 0.97, 95% CI, 0.40–2.39) and stroke (HR = 0.32, 95% CI, 0.07–1.42) were reported among people with diabetes in an analysis of data from the Third National Health and Nutrition Examination Survey [31]. In analyses of the Japan Public Health Center–based prospective study, Nakamura et al. [18] found no significant association (p for trend = 0.84) between egg intake and CHD (RRs not reported) among people with diabetes. It is not clear whether the positive associations between egg intake and CHD and stroke among people with diabetes in some studies reflect an independent relationship [34]. It has been postulated that the associations may be related to abnormal cholesterol transport due to decreased levels of apolipoprotein E and increased levels of apolipoprotein C-III among people with diabetes [33,35,36]. Methodological reasons, such as not capturing possible changes in dietary and lifestyle behaviors as a result of diabetes diagnosis, may bias results. Moreover, there are considerably smaller analytical sample sizes in subgroup analyses of egg consumption among people with diabetes. In a recently published meta-analysis of egg consumption and type 2 diabetes, Djousse et al. [37] reported no association between infrequent egg consumption and diabetes risk but observed a modestly elevated risk based on 3 or more eggs per week, although this finding was restricted to studies conducted in the United States. The authors suggested that it is important to account for overall dietary patterns and/or foods consumed with eggs that may bolster the risk of type 2 diabetes, which is a limitation in the currently available prospective cohorts. Additional studies are needed to examine changes in dietary and lifestyle habits before and after diabetes diagnosis to better understand potential relationships between egg consumption and CVD risk among people with diabetes.

Early human feeding studies testing the effect of dietary cholesterol on circulating cholesterol demonstrate an increase in total and low-density lipoprotein cholesterol, but these increases are relatively moderate compared to increases induced by saturated and trans fat intake [33,38,39]. Further, Baraj et al. [40] estimated that consuming one egg per day may at most increase CHD risk by 1%. This modest effect of eggs may be attributed to the observation that eggs are substitutes for high-density lipoprotein–lowering carbohydrates in the diet, that egg intake increases high-density lipoprotein cholesterol [41], that eggs contain antioxidants that may reduce oxidative stress and inflammation [42], and/or that eggs are high in protein, which is associated with lower blood pressure [43]. Discrepancies in results of epidemiological studies could be explained by confounding due to correlations between egg

intake with CHD risk behaviors (low physical activity, smoking, and poor eating habits) [33]. Taken together, the data suggest that the relatively small effect of dietary cholesterol from eggs on serum cholesterol is negated by the potential benefits of eggs consumption. Historically, the role of egg intake on cardiovascular health has been an area of controversy, with apparent scientific misperceptions. This is largely the result of eggs being a prominent source of cholesterol in the human diet and the role of dietary cholesterol on cardiovascular outcomes being an area of debate. However, a growing number of guidance committees suggest that there should be no restrictions on dietary cholesterol intake [6–8]. Eggs are a nutrient-dense food, providing a good and affordable source of protein, essential fatty acids, antioxidants, choline, vitamins, and minerals. Thus, recommendations regarding the consumption of eggs should consider them as a whole food.

The data used in this meta-analysis were generated from cohort studies and, therefore, the validity of a meta-analysis is not immune to the limitations of data generated from observational research. Indeed, information bias (e.g., classification—or misclassification—of self-reported dietary and lifestyle information) is a prominent concern in nutritional epidemiology. Though most analyses produced inverse associations, it may be possible that those who consume eggs regularly may engage in other favorable dietary and lifestyle habits. However, the stronger and more consistent results in our analyses of stroke compared to the weaker to null summary estimates for CHD may argue against a dietary or lifestyle pattern phenomenon because of the fact that stroke and CHD have many of the same underlying risk factors. Furthermore, most of the observational studies included in this analysis adjusted for important factors, such as physical activity, body mass index, and smoking.

We conducted comprehensive meta-analyses of studies of egg consumption and CHD and stroke and found that eggs have a null association with risk of CHD and that eggs may be associated with reduced risk of stroke. Although some studies have reported positive associations between egg intake and CVD among people with diabetes, methodological caveats, such as not accounting for changes in dietary and lifestyle behaviors before and after diabetes diagnosis, may have biased study findings.

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