

Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis^{1–3}

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ABSTRACT

Background: The associations of egg consumption with cardiovascular disease (CVD) and diabetes are still unclear.

Objective: We aimed to quantitatively summarize the literature on egg consumption and risk of CVD, cardiac mortality, and type 2 diabetes by conducting a meta-analysis of prospective cohort studies.

Design: A systematic literature review was conducted for published studies in PubMed and EMBASE through March 2012. Additional information was retrieved through Google or a hand review of the reference from relevant articles. Studies were included if they had a prospective study design, were published in English-language journals, and provided HRs and 95% CIs for the associations of interest. Data were independently extracted by 2 investigators, and the weighted HRs and 95% CIs for the associations of interest were estimated by using a random-effects model.

Results: A total of 22 independent cohorts from 16 studies were identified, including participants ranging in number from 1600 to 90,735 and in follow-up time from 5.8 to 20.0 y. Comparison of the highest category (≥ 1 egg/d) of egg consumption with the lowest (< 1 egg/wk or never) resulted in a pooled HR (95% CI) of 0.96 (0.88, 1.05) for overall CVD, 0.97 (0.86, 1.09) for ischemic heart disease, 0.93 (0.81, 1.07) for stroke, 0.98 (0.77, 1.24) for ischemic heart disease mortality, 0.92 (0.56, 1.50) for stroke mortality, and 1.42 (1.09, 1.86) for type 2 diabetes. Of the studies conducted in diabetic patients, the pooled HR (95% CI) was 1.69 (1.09, 2.62) for overall CVD.

Conclusions: This meta-analysis suggests that egg consumption is not associated with the risk of CVD and cardiac mortality in the general population. However, egg consumption may be associated with an increased incidence of type 2 diabetes among the general population and CVD comorbidity among diabetic patients.

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INTRODUCTION

Although elevated circulating cholesterol is an established risk factor for cardiovascular disease (CVD)⁴ (1–5), studies have shown inconsistent results on dietary cholesterol intake and risk of CVD (6–14). On the basis of 2 meta-analyses (15, 16), a 100-mg dietary cholesterol intake would increase plasma total cholesterol by 2.2–2.5 mg/dL, LDL cholesterol by 1.9 mg/dL, and HDL cholesterol by 0.4 mg/dL. In addition, some cholesterol feeding studies (17–19) observed that dietary cholesterol intake had little effect on the change in the ratio of LDL to HDL cholesterol. However, the association between dietary cholesterol intake and risk of CVD remains unclear (20).

Egg consumption is one of the main sources of dietary cholesterol. A medium egg contains ~ 225 mg cholesterol (21). A meta-analysis of clinical trials (22) found that the addition of 100 mg dietary cholesterol from eggs increased the ratio of total to HDL cholesterol by 0.02 units as well as plasma total cholesterol by 2.2 mg/dL and HDL cholesterol by 0.3 mg/dL. However, a few randomized controlled trials (RCTs) published later reported that egg consumption did not appreciably alter plasma total cholesterol, LDL cholesterol (23–25), HDL cholesterol (24, 25), or the ratio of total to HDL cholesterol (19, 25, 26). In addition, 2 RCTs (27, 28) found that consuming 2 eggs/d for 6 wk had no adverse effect on endothelial function. To date, no RCT data are available, whereas many observational studies relating egg consumption to the risk of CVD (29–36) and diabetes (37–41) have been published. However, the findings from these studies are inconsistent. To quantitatively investigate the overall longitudinal associations of egg consumption with incidence of CVD, type 2 diabetes, and cardiac mortality, we conducted a meta-analysis of prospective cohort studies.

SUBJECTS AND METHODS

Data sources and searches

We performed this meta-analysis according to the guidelines of the Meta-analysis Of Observational Studies in Epidemiology (42). A systematic literature search was conducted to identify published studies in PubMed (<http://www.ncbi.nlm.nih.gov/pubmed/>) and EMBASE (<http://www.embase.com/>) through March 2012;

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⁴ Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; IHD, ischemic heart disease; RCT, randomized controlled trial.

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the terms “egg intake or consumption,” “coronary heart disease,” “myocardial infarction,” “stroke,” “cardiovascular disease,” “mortality or death,” and “diabetes mellitus” were used. Additional information was retrieved through a Google search or a hand review of the references from relevant articles. To get additional data or de novo results for this meta-analysis, we contacted authors of the primary studies (43, 44).

Study selection

Studies were included in this meta-analysis if they had a prospective study design, were published in English-language journals, and provided HRs with 95% CIs for CVD, mortality, or type 2 diabetes in relation to egg consumption.

As shown in **Figure 1**, we retrieved 72 articles from PubMed and EMBASE or by hand-searching. Of these articles, 53 were excluded for one of the following reasons: 1) did not relate egg consumption to an outcome of interest; 2) was a review, editorial, abstract, or letter to editor; 3) was an animal study; 4) was not in English; or 5) was not a prospective cohort study. Of the 19 remaining articles (29–37, 41, 43–51), 2 (29, 45) were excluded because they did not report HRs with corresponding 95%

CIs, and 1 study (49) was excluded because it used continuous variable (g/d) for egg consumption. Of the 16 identified eligible studies (30–37, 41, 43, 44, 46–48, 50, 51), 2 studies (30, 37) reported results from 4 independent cohorts, 3 studies (37, 43, 50) reported results stratified by sex, and 2 studies (33, 34) reported results for both CVD and mortality. In addition, 2 studies (31, 48) updated the results of early studies conducted in the same cohorts. In summary, 22 independent cohorts from 16 studies were included in the final data set for the meta-analysis: 8 eligible studies (30–36, 44) (8 cohorts) provided data on CVD, 6 studies (33, 34, 43, 46, 47, 50) (8 cohorts) on mortality, 3 studies (37, 41, 51) (5 cohorts) on type 2 diabetes in the general population, 4 studies (30, 33, 35, 48) (4 cohorts) on CVD, and 3 studies (33, 34, 50) (3 cohorts) on mortality in diabetic patients.

Data extraction and quality assessment

The following data were extracted from each included study: name of the first author, publication year, study population, country of origin, size of the sample, age range or mean age of the participants, proportion of men, duration of follow-up, methods

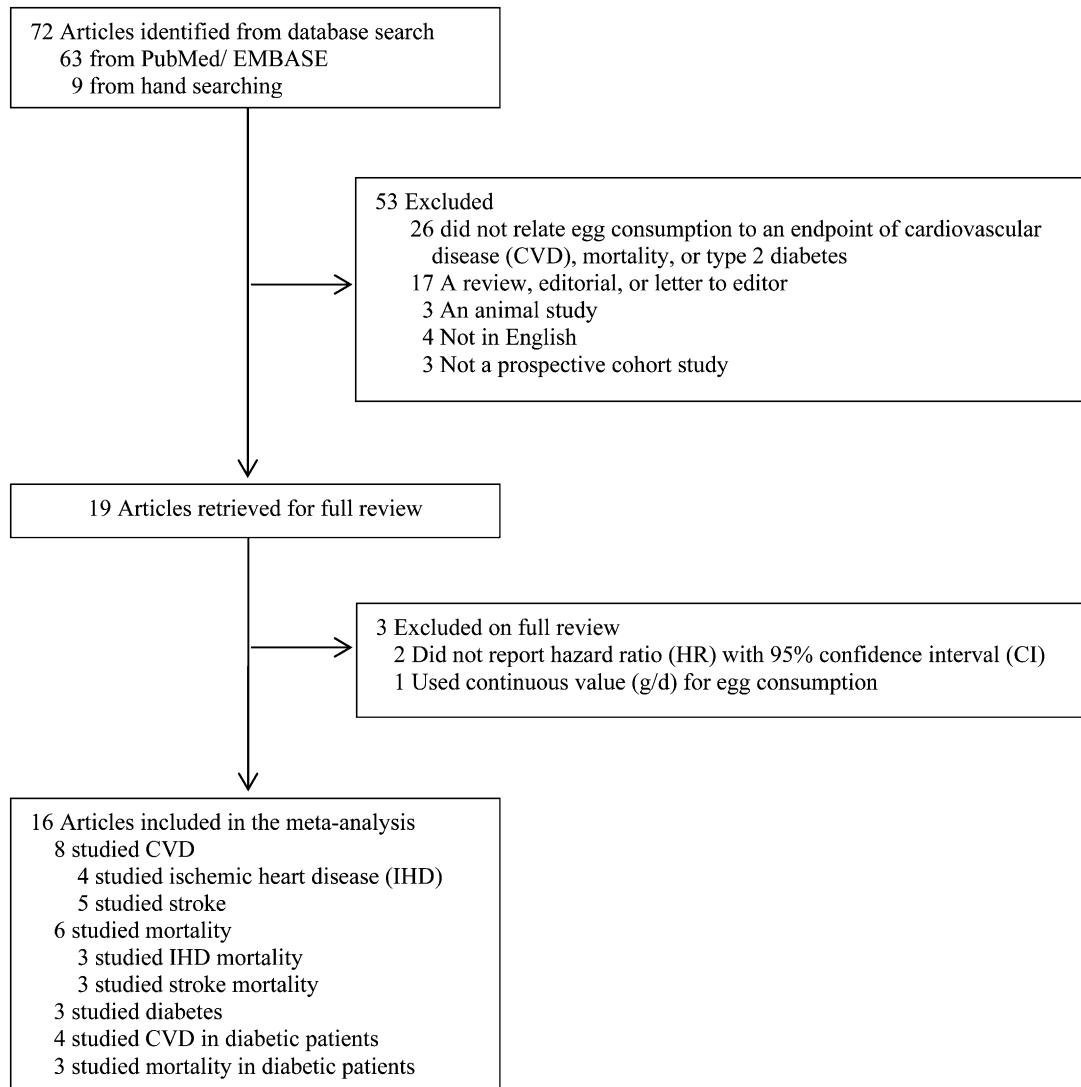


FIGURE 1. Process of study selection.

for diet assessment, categories of egg intake, number of events, methods for case identification, adjusted covariates, and HRs or RRs and their 95% CIs in the corresponding exposure categories. All procedures, including the literature search, study selection, and data extraction, were independently performed by 2 authors (JYS and PX). Any discrepancies were resolved by group discussion.

To evaluate the quality of the studies included, we designed a scoring system with several a priori selected important characteristics that can affect study quality based on the literature. The scoring system was created to account for study eligibility (1 point if inclusion and exclusion criteria were clear), exposure (1 point if egg consumption was assessed by a validated tool, and 1 point if egg consumption was appropriately categorized), outcome (1 point if outcome of interest was not solely based on self-report), and statistical analysis (1 point if adjustment included a few major demographic and lifestyle variables such as age, BMI, smoking, and physical activity). The scoring system was designed with reference to the Meta-analysis Of Observational Studies in Epidemiology (42) and allowed a total score up to 5 points, with 5 reflecting the highest quality.

Statistical analysis

We estimated the pooled HRs (95% CIs), from a comparison of the highest category of egg consumption with the lowest, by using a random-effects model proposed by DerSimonian and Laird (52). All pooled HRs and 95% CIs were estimated by using data from the fully adjusted models. In this meta-analysis, the pooled HRs of overall CVD, type 2 diabetes, stroke, and ischemic heart disease (IHD) [including coronary artery disease, coronary heart disease (CHD), and myocardial infarction in relation to egg consumption were estimated. In addition, the pooled HRs of mortality from overall CVD, IHD, and stroke were assessed. In addition, we computed the pooled HRs of overall CVD and mortality in patients with diabetes. Because the number of exposure categories was heterogeneous across primary studies or cohorts, we could not standardize egg consumption for all of the included studies. Thus, we calculated the pooled HRs (95% CI) by comparing the highest with the lowest category of egg consumption. If the results were generated from the same cohorts in different publications, we used data from the most recent publication. Because most of the studies reported results on total stroke, we combined ischemic and hemorrhagic stroke if the data on total stroke were not available, and the new results were used for the pooled estimation of stroke risk. In addition, the HRs with 95% CIs of overall CVD and mortality were pooled in studies among diabetic patients.

Cochran's test was used to evaluate the statistical heterogeneity and the I^2 statistic was calculated to quantify the degree of inconsistency across individual studies. In addition, the Egger asymmetry test was used to examine publication bias (53). Sensitivity analyses were conducted to assess whether the results could have been affected markedly by any single study. All analyses were performed by using STATA statistical software (version 11.0; STATA Corp). All statistical tests were 2-sided, and a P value ≤ 0.05 was considered statistically significant.

RESULTS

Study characteristics

Characteristics of the 22 included cohorts from 16 eligible studies are shown in **Table 1** (in the general population) and

Table 2 (in diabetic individuals). Of 8 independent cohort studies of CVD in the general population, 7 were conducted in Western countries and 1 in Asia. The number of participants and duration of the follow-up ranged from 1600 to 90,735 and from 6 to 20 y, respectively. Of 8 independent cohort studies of mortality, 5 were conducted in Western countries and 3 in Asia. The number of individuals and duration of the follow-up ranged from 4077 to 37,130 and from 9 to 20 y, respectively. All 5 independent cohort studies of type 2 diabetes were conducted in Western countries. The number of participants and duration of follow-up ranged from 1669 to 36,295 and from 11 to 20 y, respectively (Table 1). In patients with diabetes, 4 studies (30, 33, 35, 48) reported HRs on overall CVD risk, and 3 studies (33, 34, 50) reported results on overall mortality. The number of patients and duration of follow-up ranged from 341 to 5672 and from 7 to 20 y, respectively. All studies in diabetic patients were conducted in Western countries (Table 2). Egg consumption was assessed by using a self-administered or interview-based food-frequency questionnaire and categorized into 3–6 groups. The quality scores for all included studies were ≥ 3 points based on our 5-point scoring system.

Egg consumption and risk of CVD

A total of 9839 incident cases of CVD from 348,420 participants in 8 cohorts were identified during an average of 11.3 y of follow-up, 5401 incident cases of IHD from 239,729 participants in 5 cohorts were documented with an average of 11.9 y follow-up, and 4189 incident cases of stroke from 241,900 participants in 5 cohorts were determined in 12.1 y follow-up. In comparison with those who never consumed egg or ate egg less than once per week, individuals who ate egg once per day or more did not have significantly higher risks of overall CVD, IHD, and stroke. The pooled HRs (95% CIs) were 0.96 (0.88, 1.05) for overall CVD, 0.97 (0.86, 1.09) for IHD, and 0.93 (0.81, 1.07) for stroke (**Figure 2**).

Egg consumption and risk of mortality

Of 103,202 participants in 8 cohorts, 11,845 overall deaths were documented during an average of 15.3 y follow-up. In particular, 510 deaths were from IHD and 1,818 deaths were from stroke. No significant associations were found between egg consumption and mortality. The pooled HRs were 1.13 (95% CI: 0.95, 1.33) for overall mortality, 0.98 (95% CI: 0.77, 1.24) for IHD mortality, and 0.92 (95% CI: 0.56, 1.50) for stroke mortality in a comparison of the highest (≥ 1 egg/d) with the lowest category (never or < 1 egg/wk) of egg consumption (**Table 3**).

Egg consumption and risk of type 2 diabetes

A total of 4889 of 69,297 participants in 5 cohorts developed type 2 diabetes during an average of 14.8 y follow-up. Egg consumption was associated with an elevated risk of incident type 2 diabetes. The pooled HR was 1.42 (95% CI: 1.09, 1.86) in a comparison of the highest with the lowest category of egg consumption (Table 3).

Egg consumption and risk of CVD and mortality in patients with diabetes

The pooled database for CVD includes 7549 diabetic patients in 4 cohorts during an average of 9.5 y follow-up and 606 deaths were documented among 1529 diabetic participants in 3 cohorts

TABLE 1
Characteristics of the general population in the included studies¹

Source	Participants	Age	Men	Duration of follow-up	Exposure assessment	Exposure categories	No. of incidents	Case identification methods	Adjusted variables
Type 2 diabetes Vang et al, 2008 (51), AMS and AHS, USA	n 8401	y 45–88	% 61.1	y 17.0	Semiquantitative questionnaire	0, 1/wk, ≥1/wk	543 diabetes	Self-administered questionnaires	Age and sex
Djousse et al, 2009 (37), PHS I, USA	20,703	40–86	100	20.0	Self-administered questionnaire	<1/wk, 1/wk, 2–4/wk, 5–6/wk, ≥7/wk	1921 diabetes	Physician's self-reported	Age, BMI, smoking, alcohol consumption, vigorous exercise, and history of hypercholesterolemia and hypertension
Djousse et al, 2009 (37), WHS, USA	36,295	39–90	0	11.7	Self-administered questionnaire	<1/wk, 1/wk, 2–4/wk, 5–6/wk, ≥7/wk	2112 diabetes	Self-reported diabetes was confirmed by telephone interviews, supplemental questionnaire, or review of medical records	Age, BMI, smoking, alcohol consumption, exercise, red meat intake, quintiles of energy intake, fruit and vegetables, SFAs, <i>trans</i> fatty acids, PUFAs, family history of diabetes, and history of hypercholesterolemia and hypertension
Djousse et al, 2010 (41), CHS, USA	1669	65–95	100	11.3	Picture-sort questionnaire	Never, <1/mo, 1–3/mo, 1–4/wk, almost daily	142 diabetes	Diagnosed by clinical examination according to ADA 2010 criteria	Age, race, BMI, smoking status, alcohol consumption, physical activity, cereal-fiber intake, and field center
Djousse et al, 2010 (41), CHS, USA	2229	65–98	0	11.3	Picture-sort questionnaire	Never, <1/mo, 1–3/mo, 1–4/wk, almost daily	171 diabetes	Diagnosed by clinical examination according to ADA 2010 criteria	Age, race, BMI, smoking status, alcohol consumption, physical activity, cereal-fiber intake, and field center

(Continued)

TABLE 1 (Continued)

Source	Participants	Age	Men	Duration of follow-up	Exposure assessment	Exposure categories	No. of incidents	Case identification methods	Adjusted variables
Cardiovascular disease Hu et al, 1999 (30), HPFS, USA ²	37,851	40-75	100	7.2	Self-administered questionnaire	<1/wk, 1/wk, 2-4/wk, 5-6/wk, ≥ 1/d	866 CHD, 258 stroke	Review medical record	Age, BMI, 2-y time periods, cigarette smoking, parental history of myocardial infarction, multivitamin supplement use, vitamin E supplement use, alcohol consumption, history of hypertension, physical activity, and total energy intake
Hu et al, 1999 (30), NHS, USA	80,082	34-59	0	13.2	Self-administered questionnaire	<1/wk, 1/wk, 2-4/wk, 5-6/wk, ≥ 1/d	939 CHD, 563 stroke	Review medical record	Age, BMI, 2-y time periods, cigarette smoking, parental history of myocardial infarction, multivitamin supplement use, vitamin E supplement use, alcohol consumption, menopausal status and postmenopausal hormone use, history of hypertension, physical activity, and total energy intake
He et al, 2003 (31), HPFS, USA ²	43,732	40-75	100	14.0	Semi-quantitative questionnaire	<1/wk, 1/wk, 2-4/wk, 5-6/wk, ≥ 1/d	455 ischemic stroke, 125 hemorrhagic stroke	Medical record	Age, BMI, physical activity, history of hypertension, smoking status, aspirin use, multivitamin use, total servings of fruit and vegetables, total energy intake, hypercholesterolemia, and consumption of alcohol, potassium, fiber, and vitamin E
Nakamura et al, 2006 (32), JPHCPS, Japan	Total: 90,735; cohort I: 41,234; cohort II: 49,471	I: 40-59; II: 40-69	I: 48.2; II: 47.4	10.2	Self-administered questionnaire	<1 d/wk, 1-2 d/wk, 3-4 d/wk, almost daily	462 CHD	Medical record	Age, sex, BMI, hypertension, diabetes, use of cholesterol-lowering drugs, smoking, alcohol, intention to avoid cholesterol-rich diets, cohort effects, and consumption frequencies of meat, fish, vegetables, and fruit

(Continued)

TABLE 1 (Continued)

Source	Participants	Age	Men	Duration of follow-up	Exposure assessment	Exposure categories	No. of incidents	Case identification methods	Adjusted variables
Qureshi et al, 2007 (33), NHANES I, USA	9734	25-74	38.6	16.6	Self-administered questionnaire	<1/wk, 1-6/wk, ≥7/wk	655 total stroke, 591 ischemic stroke (ICD-9-CM codes 430, 431-434.9, or 437.0-437.1); 1584 CAD (ICD-9-CM codes 410-414)	Registry	Age, sex, race-ethnicity, systolic BP, DM, serum cholesterol, cigarette smoking, BMI, and education status
Djousse and Gaziano, 2008 (34), PHS, USA	21,327	40-86	100	20.0	Self-administered questionnaire	<1/wk, 1/wk, 2-4/wk, 5-6/wk, ≥7/wk	1550 new MI, 1342 total stroke	Questionnaire	Age, BMI, smoking, history of hypertension, vitamin intake, alcohol consumption, vegetable consumption, breakfast cereal, physical activity, treatment arm a-fib, DM, hypercholesterolemia, and parental history of premature MI
Houston et al, 2011 (35), Health ABC Study, USA	1600	70-79	44.5	9.0	Self-administered questionnaire	<1/wk, 1-2/wk, ≥3/wk	158 CVD	Annual clinical examination and medical record	Age, sex, race, education, field center, smoking, alcohol use, physical activity, BMI, total energy intake, protein intake, fiber intake, multivitamin use, supplemental vitamin E use, statin use, aspirin use, oral estrogen use (women), prevalent hypertension, and SFAs
Zazpe et al, 2011 (36), SUN Project, Spain	14,185	20-90	40.9	5.8	Self-administered questionnaire	<1/wk, 1/wk, 2-4/wk, >4/wk	91 CVD	Self-reported questionnaire and medical record	Age, sex, total energy intake, adherence to the Mediterranean food pattern, alcohol intake, BMI, smoking status, physical activity, family history of CVD, diabetes, hypertension, and hypercholesterolemia

(Continued)

TABLE 1 (Continued)

Source	Participants	Age	Men	Duration of follow-up	Exposure assessment	Exposure categories	No. of incidents	Case identification methods	Adjusted variables
Yaemsiri et al, 2012 (44), WHI-OS, USA	87,025	50-79	0	7.6	Self-administered questionnaire	<1/wk, 1/wk, 2-4/wk, 5-6/wk, \geq 1/d	1049 ischemic stroke	Self-report and medical record	Age, race, education, family income, years as a regular smoker, hormone replacement therapy use, physical activity, alcohol intake, aspirin use, use of antihypertensive medication and cholesterol-lowering medication, BMI, systolic BP, total energy intake, dietary vitamin E, intake of fruit and vegetables and fiber, and history of CHD, a-fib, and diabetes
Mortality Mann et al, 1997 (46), UK	10,802 392 all-cause death	16-79	38.0	13.3	Self-administered questionnaire	<1/wk, 1-5/wk, \geq 6/wk	64 IHD death	Registry	Age, sex, smoking, and social class
Sauvaget et al, 2003 (47), LSS, Japan	37,130	34-103	38.3	16.0	Self-administered questionnaire	Never, \leq 1/wk, 2-4/wk, almost daily	1462 stroke death	Registry	HR stratified by sex and birth cohort and adjusted for city, radiation dose, BMI, smoking status, alcohol habits, education level, history of diabetes, or hypertension
Nakamura et al, 2004 (43), NIPPON DATA80, Japan	4077	Mean 50.3 (>30)	100	13.0	Self-administered questionnaire	<1/wk, 1-2/wk, 0.5/d, 1/d	39 IHD death, 112 stroke death, 640 all-cause death	Registry	Age, serum creatinine, total cholesterol, blood glucose, BMI, systolic and diastolic BP, use of BP-lowering drugs, cigarette smoking, and alcohol intake
Nakamura et al, 2004 (43), NIPPON DATA80, Japan	5186	Mean 50.7 (>30)	0	13.3	Self-administered questionnaire	<1/wk, 1-2/wk, 0.5/d, 1/d	41 IHD death, 107 stroke death, 562 all-cause death	Registry	Age, serum creatinine, total cholesterol, blood glucose, BMI, systolic and diastolic BP, use of BP-lowering drugs, cigarette smoking, and alcohol intake
Qureshi et al, 2007 (33), NHANES-I, USA	9734	25-74	38.6	16.6	Self-administered questionnaire	<1/wk, 1-6/wk, \geq 7/wk	3117 all-cause death	Registry	Age, sex, race-ethnicity, systolic BP, DM, serum cholesterol, cigarette smoking, BMI, and education status

(Continued)

TABLE 1 (Continued)

Source	Participants	Age	Men	Duration of follow-up	Exposure assessment	Exposure categories	No. of incidents	Case identification methods	Adjusted variables
Djousse and Gaziano, 2008 (34), PHS, USA	21,327	40-86	100	20.0	Self-administered questionnaire	<1/wk, 1/wk, 2-4/wk, 5-6/wk, ≥7/wk	5169 all-cause death	Self or family-reported questionnaire	Age, BMI, smoking, history of hypertension, vitamin intake, alcohol consumption, vegetable consumption, breakfast cereal, physical activity, treatment arm a-fib, DM, hypercholesterolemia, and parental history of premature MI
Scrafford et al, 2010 (50), NHANES III, USA	6833	>17	100	8.8	Self-administered questionnaire	<1/wk, 1-6/wk, ≥7/wk	198 CHD death (ICD-10 codes I20-I25), 63 stroke death (ICD-10 codes I60-I69)	Registry	Age, energy, marital status, education status, race-ethnicity, BMI, diabetes, hypertension, and alcohol intake
Scrafford et al, 2010 (50), NHANES III, USA	8113	>17	0	8.9	Self-administered questionnaire	<1/wk, 1-6/wk, ≥7/wk	168 CHD death, 74 stroke death	Registry	Age, energy, marital status, education status, race-ethnicity, BMI, diabetes, hypertension, and alcohol intake

¹ ADA, American Diabetes Association; a-fib, atrial fibrillation; AMS and AHS, Adventist Mortality Study and Adventist Health Study; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CHS, Cardiovascular Health Study; CVD, cardiovascular disease; DM, diabetes mellitus; Health ABC, Health, Aging and Body Composition; HPFS, Health Professionals Follow-Up Study; ICD, International Classification of Diseases; IHD, ischemic heart disease; JPHCPS, Japan Public Health Center-based Prospective Study; LSS, the Life Span Study; MI, myocardial infarction; NHS, Nurses' Health Study; NIPPON DATA80, National Integrated Project for prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980; PHS, Physicians' Health Study; WHI-OS, Women's Health Initiative Observational Study; WHS, Women's Health Study.

²Two cohort studies have the outcomes for stroke from the same cohort, HPFS.

TABLE 2
Characteristics of individuals with diabetes in the included studies¹

Source	Participants	Age	Men	Duration of follow-up	Exposure assessment	Exposure categories	Incidence	Case identification methods	Adjusted variables
Cardiovascular disease									
Hu et al, 1999 (30), HPS, USA	n 1187	y 40–75	% 100	y 7.2	Self-administered questionnaire	<1/wk, 1/wk, 2–4/wk, 5–6/wk, ≥1/d	Not reported	Review medical record	Age, BMI, 2-y time periods, cigarette smoking, parental history of myocardial infarction, multivitamin supplement use, vitamin E supplement use, alcohol consumption, history of hypertension, physical activity, and total energy intake
Hu et al, 1999 (30), NHS, USA ²	4122	34–59	0	13.2	Self-administered questionnaire	<1/wk, 1/wk, 2–4/wk, 5–6/wk, ≥1/d	Not reported	Review medical record	Age, BMI, 2-y time periods, cigarette smoking, parental history of myocardial infarction, multivitamin supplement use, vitamin E supplement use, alcohol consumption, menopausal status and postmenopausal hormone use, history of hypertension, physical activity, and total energy intake
Tanasescu et al, 2004 (48), NHS, USA ²	5672	Mean: 48.4 (≥30)	0	10.1	Semiquantitative questionnaire	<1/wk, 1 to <3/wk, 3/wk, >3–6/wk, >6/wk	619 CVD	Review medical record	Age, sex, race-ethnicity, systolic BP, DM, serum cholesterol, cigarette smoking, BMI, and education status
Qureshi et al, 2007 (33), NHANES I, USA	349	25–74	38.6	16.6	Self-administered questionnaire	<1/wk, 1–6/wk, ≥7/wk	57 total stroke, 132 CAD	Registry	Age, sex, race-ethnicity, systolic BP, DM, serum cholesterol, cigarette smoking, BMI, and education status
Houston et al, 2011 (35), Health ABC Study, USA	341	70–79	44.5	9.0	Self-administered questionnaire	<1/wk, 1–2/wk, ≥3/wk	45 CVD	Annual clinical examination and medical record	Age, sex, race, education, field center, smoking, alcohol use, physical activity, BMI, total energy intake, protein intake, fiber intake, multivitamin use, supplemental vitamin E use, statin use, aspirin use, oral estrogen use (women), prevalent hypertension, and SFAs
Mortality									
Qureshi et al, 2007 (33), NHANES I, USA	349	25–74	38.6	16.6	Self-administered questionnaire	<1/wk, 1–6/wk, ≥7/wk	253 all-cause death	Registry	Age, sex, race-ethnicity, systolic BP, DM, serum cholesterol, cigarette smoking, BMI, and education status
Djoussé and Gaziano, 2008 (34), PHS, USA	437	40–86	100	20.0	Self-administered questionnaire	<1/wk, 1/wk, 2–4/wk, 5–6/wk, ≥7/wk	263 all-cause death	Self or family-reported questionnaire	Age, BMI, smoking, history of hypertension, vitamin intake, alcohol consumption, vegetable consumption, breakfast cereal, physical activity, treatment arm a-fib, hypercholesterolemia, and parental history of premature MI
Scraftford et al, 2010 (50), NHANES III, USA	743	>17	45.7	8.8	Self-administered questionnaire	<1/wk, 1–6/wk, ≥7/wk	66 CHD death, 24 stroke death	Registry	Age, sex, and energy intake

¹ a-fib, atrial fibrillation; BP, blood pressure; CAD, coronary artery disease; CHD, coronary heart disease; CVD, cardiovascular disease; DM, diabetes mellitus; Health ABC, Health, Aging and Body Composition; HPS, Health Professionals Follow-Up Study; MI, myocardial infarction; NHS, Nurses' Health Study; PHS, Physicians' Health Study.

² Two cohort studies have the outcomes for CVD from the same cohort, NHS.

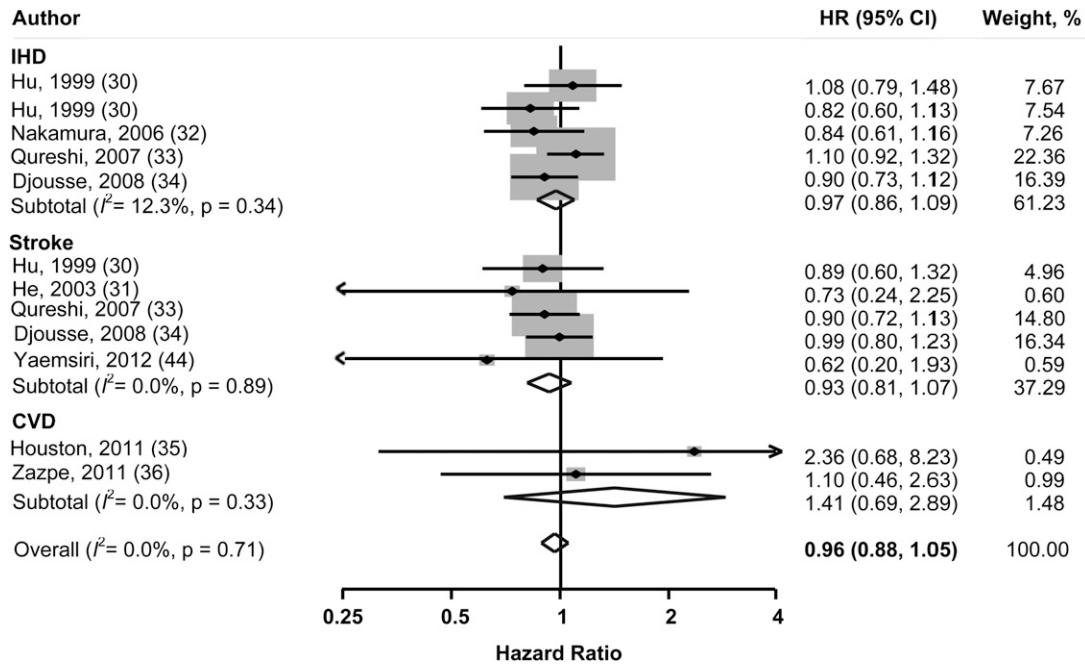


FIGURE 2. Pooled HRs and 95% CIs for incident IHD, stroke, and overall CVD. The pooled estimates were obtained by using a random-effects model. The dots indicate the adjusted HRs from a comparison of the highest category of egg consumption (≥ 1 egg/d) with the lowest (< 1 egg/wk or never). The size of the shaded square is proportional to the weight of the individual study. The horizontal lines represent 95% CIs. The diamond data markers indicate the pooled HRs. CVD, cardiovascular disease; IHD, ischemic heart disease.

with an average of 13.8 y follow-up. Patients with diabetes who ate eggs more than once per day were 1.69 times as likely to develop CVD comorbidity than were those who never ate eggs or ate eggs less than once per week (pooled HR: 1.69; 95% CI: 1.09, 2.62) (Figure 3). However, egg consumption was not significantly associated with risk of overall mortality (Table 3).

Sensitivity analyses

We did not find significant heterogeneity (I^2 : 0.0–59.2%) among the included studies in the main analyses, except for pooled overall mortality (I^2 : 59.2%, $P = 0.01$), which combined death from all causes. In addition to comparing 2 extreme categories, we performed sensitivity analyses by replacing the highest category with the second highest category, and the results were generally consistent. In addition, we found that none of the studies

markedly influenced the pooled estimate when we excluded one study at a time in the meta-analysis.

Publication bias

Publication bias was assessed by using the Egger’s regression asymmetry test. No evidence of substantial publication bias was found: $P = 0.67$ (in the general population) and $P = 0.66$ (in diabetic patients) for overall CVD incidence, $P = 0.999$ (in the general population) and $P = 0.29$ (in diabetic patients) for overall mortality, and $P = 0.47$ for incidence of type 2 diabetes.

DISCUSSION

Accumulated epidemiologic evidence generated from this meta-analysis suggests that egg consumption is not associated

TABLE 3
Pooled HRs (95% CIs) of diabetes and mortality according to egg consumption¹

Source	No. of cohorts	No. of participants (events)	Duration of follow-up y	Egg consumption		Homogeneity	
				Lowest	Highest	I^2 %	P
Mortality							
Overall	8	103,202 (11,845)	15.3	1.0	1.13 (0.95, 1.33)	59.2	0.01
IHD ²	5	35,011 (510)	11.4	1.0	0.98 (0.77, 1.24)	0.0	0.61
Stroke	5	61,339 (1818)	13.8	1.0	0.92 (0.56, 1.50)	40.5	0.15
Overall in diabetic patients	3	1529 (606)	13.8	1.0	1.27 (0.78, 2.06)	55.9	0.08
Type 2 diabetes	5	69,297 (4889)	14.8	1.0	1.42 (1.09, 1.86)	53.5	0.07

¹ The pooled estimates were obtained by using a random-effects model.

² IHD, ischemic heart disease.

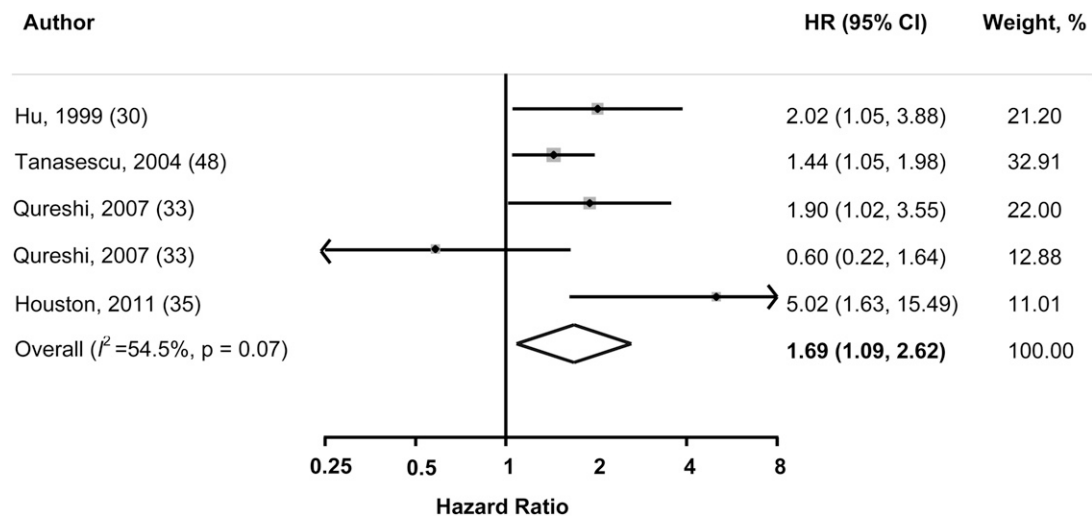


FIGURE 3. Pooled HRs and 95% CIs of incident overall CVD in diabetic patients. The pooled estimates were obtained by using a random-effects model. The dots indicate the adjusted HRs from a comparison of the highest category of egg consumption (≥ 1 egg/d) with the lowest (< 1 egg/wk or never). The size of the shaded square is proportional to the weight of the individual study. The horizontal lines represent 95% CIs. The diamond data markers indicate the pooled HR. CVD, cardiovascular disease.

with an increased risk of overall CVD, IHD, stroke, or mortality. However, compared with those who never consume eggs, those who eat 1 egg per day or more are 42% more likely to develop type 2 diabetes. Among diabetic patients, frequent egg consumers (ie, ≥ 1 egg/d) are 69% more likely to have CVD comorbidity.

A few strengths of this meta-analysis need to be highlighted. First, most of the studies or cohorts involved in this meta-analysis had a large sample size and long-term follow-up period, which potentiated the statistical power to evaluate the relation between egg consumption and risk of CVD, mortality and type 2 diabetes. For example, our meta-analysis for the risk of CVD comprises $>345,000$ male and female individuals with a wide age range (20–90 y) and an average of 11.3 y of follow-up. Also, our pooled estimation was based on prospective cohort studies, which largely reduced the likelihood of inherent selection bias and recall bias from the included primary studies. Because of practical and ethical considerations, it may not be feasible to conduct a long-term, double-blinded, and placebo-controlled randomized trial on egg consumption and chronic diseases. Thus, the value of this meta-analysis of prospective cohort studies is enhanced. In addition, this meta-analysis allowed us to examine the longitudinal associations of egg consumption with multiple chronic diseases. Moreover, sensitivity analyses showed that our findings were robust, and the pooled estimates were not substantially affected by any of the included primary studies.

Several limitations also need to be considered. First, our results may have been affected by the inherent limitations of primary studies. The possibility of residual confounding or bias, including diet measurement errors, cannot be excluded. In particular, our inability to standardize egg consumption in all of the included studies might have confounded our results, although the likelihood should be small because the reference group and the highest egg consumption group were similar in most primary studies. In addition, the heterogeneity of exposure categories across the individual studies limited our capability to examine a possible dose-response relation. In addition, although we found little evidence of publication bias by statistical tests, publication bias may have existed because of unpublished data or publications in non-English journals.

It has been thought that egg consumption may increase the risk of CVD because egg is a major dietary source of cholesterol. However, whether dietary cholesterol intake significantly affects the lipid profile and, consequently, is associated with the risk of CVD is still unclear. There are several possible explanations for the null association findings between egg consumption and the risk of CVD in this meta-analysis. First, the overall effect of egg consumption on circulating cholesterol concentrations may not be sufficient to appreciably increase the risk of CVD (54). A meta-analysis (22) found that the addition of 100 mg dietary cholesterol from eggs (approximately half of an egg) per day would increase plasma LDL cholesterol by 1.9 mg/dL, HDL cholesterol by 0.3 mg/dL, and the ratio of total to HDL cholesterol by 0.02 units. Another meta-analysis (15) reported that consuming 1 egg/d increased plasma LDL cholesterol by 4.1 mg/dL, increased HDL cholesterol by 0.9 mg/dL, and had little effect on the ratio of LDL to HDL cholesterol—a major predictor of CHD. Of note, the unfavorable effect of egg consumption on LDL and total cholesterol may be attenuated by its favorable effect on HDL cholesterol. Second, most of the included studies were conducted in Western countries that traditionally have a relatively high-cholesterol diet. Thus, it is likely that the background cholesterol concentration among these participants was already high, so that changes in their cholesterol concentrations might not be sensitive to egg consumption (55, 56). Third, egg is also a good source of nutrients, which may provide a cardioprotective effect. For example, egg is a good source of B vitamins, including choline, which may lower homocysteine concentrations (57, 58). Thus, the overall effect of egg consumption may reflect the interactions of cholesterol with other nutrients in egg. Notably, 2 RCTs showed that consumption of 2 eggs/d for 6 wk did not induce an adverse effect on endothelial function—an indicator of CHD risk (27, 28).

In addition, we found that egg consumption was associated with an increased risk of CVD in diabetic patients. The mechanisms are not fully understood. Presumably, diabetic patients are at high risk of developing CVD and may be more sensitive to egg consumption. A small change in circulating cholesterol may

substantially increase the risk of CVD in patients with diabetes. Also, a study indicated that cholesterol synthesis and plasma lipid concentrations, including total cholesterol and triglyceride, were higher in type 2 diabetic patients with uncontrolled hyperglycemia (59). Hence, egg consumption may induce unfavorable effects on lipid profiles and lead to an increased risk of CVD in patients with diabetes. However, a diet intervention study (60) showed that an energy-restricted high-protein diet with high cholesterol (2 eggs/d) for 12 wk increased HDL cholesterol concentrations compared with an energy-restricted high-protein diet with low cholesterol (egg replaced by 100 g lean animal protein) in type 2 diabetic patients. Of note, both intervention and control diets significantly reduced body weight, total cholesterol, fasting plasma glucose and insulin, and blood pressure.

In the current meta-analysis, we observed a positive association between egg consumption and risk of type 2 diabetes. Although the findings were inconsistent, some animal studies suggested that high cholesterol feeding increased fasting plasma glucose concentrations or induced hyperinsulinemia and impaired glucose tolerance (61–63). Studies have also suggested that elevated serum cholesterol might be associated with an increased islet cholesterol content and directly induce β cell dysfunction by reducing glucose-stimulated insulin secretion (64, 65). In addition, studies have indicated that dietary cholesterol might be associated with chronic, low-grade inflammation (66, 67), which is a mechanism underlying the development of insulin resistance and type 2 diabetes. Moreover, our results on egg consumption and risk of diabetes are supported by some other human studies (38–40, 68) that do not meet our inclusion criteria. Furthermore, some prospective cohort studies found that dietary cholesterol intake was associated with risk of type 2 diabetes (69, 70) and gestational diabetes (71). However, RCTs in participants consuming a carbohydrate-restricted diet showed that consumption of 3 eggs/d for 12 wk did not significantly change plasma fasting glucose (72, 73) and insulin resistance (73) compared with placebo (equivalent amount of egg substitute without dietary cholesterol). Of note, the possibility cannot be completely excluded that the observed positive associations between egg consumption and risk of type 2 diabetes are explained by residual confounding from unmeasured factors, because diabetes was the secondary outcome in most included studies. Nevertheless, future studies are warranted.

In conclusion, this meta-analysis of prospective cohort studies does not support an increase in the risk of CVD and mortality in the general population with regular egg consumption. However, egg consumption may be associated with an increased risk of type 2 diabetes, and diabetic patients with frequent egg consumption may be more likely to develop CVD comorbidity. Clearly, more studies are needed to elucidate the potential mechanisms linking egg consumption to diabetes risk. Particularly, experimental studies are warranted to explore how dietary cholesterol is involved in glucose and insulin homeostasis. Although we have drawn attention to the association between high egg consumption and the risk of type 2 diabetes, and the potential increased risk of CVD with egg consumers in patients with type 2 diabetes, the results of this meta-analysis should be interpreted with caution and may not justify changes in current dietary advice on egg consumption until more scientific data become available.

The authors' responsibilities were as follows—KH: conceived the study concept and design; JYS and PX: completed the literature search, study selection,

and data extraction and prepared the tables and figures; PX: performed the data analysis; and JYS, PX, and KH: interpreted the results and drafted the manuscript. All authors: critically reviewed the manuscript for important intellectual content and approved the final version. None of the authors had any conflicts of interest to disclose.

REFERENCES

- Castelli WP. Epidemiology of coronary heart disease: the Framingham study. *Am J Med* 1984;76(2A):4–12.
- Martin MJ, Hulley SB, Browner WS, Kuller LH, Wentworth D. Serum cholesterol, blood pressure, and mortality: implications from a cohort of 361,662 men. *Lancet* 1986;2:933–6.
- Castelli WP, Garrison RJ, Wilson PW, Abbott RD, Kalousdian S, Kannel WB. Incidence of coronary heart disease and lipoprotein cholesterol levels. The Framingham Study. *JAMA* 1986;256:2835–8.
- Klag MJ, Ford DE, Mead LA, He J, Whelton PK, Liang KY, Levine DM. Serum cholesterol in young men and subsequent cardiovascular disease. *N Engl J Med* 1993;328:313–8.
- Stamler J, Daviglus ML, Garside DB, Dyer AR, Greenland P, Neaton JD. Relationship of baseline serum cholesterol levels in 3 large cohorts of younger men to long-term coronary, cardiovascular, and all-cause mortality and to longevity. *JAMA* 2000;284:311–8.
- McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program. Relationship to nutrient intake. *Am J Epidemiol* 1984;119:667–76.
- Shekelle RB, Stamler J. Dietary cholesterol and ischaemic heart disease. *Lancet* 1989;1:1177–9.
- Posner BM, Cobb JL, Belanger AJ, Cupples LA, D'Agostino RB, Stokes J III. Dietary lipid predictors of coronary heart disease in men. The Framingham Study. *Arch Intern Med* 1991;151:1181–7.
- Kromhout D, Menotti A, Bloemberg B, Aravanis C, Blackburn H, Buzina R, Dontas AS, Fidanza F, Giampaoli S, Jansen A, et al. Dietary saturated and trans fatty acids and cholesterol and 25-year mortality from coronary heart disease: the Seven Countries Study. *Prev Med* 1995;24:308–15.
- Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ* 1996;313:84–90.
- Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med* 1997;337:1491–9.
- Oh K, Hu FB, Manson JE, Stampfer MJ, Willett WC. Dietary fat intake and risk of coronary heart disease in women: 20 years of follow-up of the Nurses' Health Study. *Am J Epidemiol* 2005;161:672–9.
- Xu J, Eilat-Adar S, Loria C, Goldbourt U, Howard BV, Fabsitz RR, Zephier EM, Mattil C, Lee ET. Dietary fat intake and risk of coronary heart disease: the Strong Heart Study. *Am J Clin Nutr* 2006;84:894–902.
- Skeaff CM, Miller J. Dietary fat and coronary heart disease: summary of evidence from prospective cohort and randomised controlled trials. *Ann Nutr Metab* 2009;55:173–201.
- Clarke R, Frost C, Collins R, Appleby P, Peto R. Dietary lipids and blood cholesterol: quantitative meta-analysis of metabolic ward studies. *BMJ* 1997;314:112–7.
- Howell WH, McNamara DJ, Tosca MA, Smith BT, Gaines JA. Plasma lipid and lipoprotein responses to dietary fat and cholesterol: a meta-analysis. *Am J Clin Nutr* 1997;65:1747–64.
- Herron KL, Vega-Lopez S, Conde K, Ramjiganesh T, Roy S, Shachter NS, Fernandez ML. Pre-menopausal women, classified as hypo- or hyperresponders, do not alter their LDL/HDL ratio following a high dietary cholesterol challenge. *J Am Coll Nutr* 2002;21:250–8.
- Herron KL, Vega-Lopez S, Conde K, Ramjiganesh T, Shachter NS, Fernandez ML. Men classified as hypo- or hyperresponders to dietary cholesterol feeding exhibit differences in lipoprotein metabolism. *J Nutr* 2003;133:1036–42.
- Greene CM, Zern TL, Wood RJ, Shrestha S, Aggarwal D, Sharman MJ, Volek JS, Fernandez ML. Maintenance of the LDL cholesterol:HDL cholesterol ratio in an elderly population given a dietary cholesterol challenge. *J Nutr* 2005;135:2793–8.
- Djoussé L, Gaziano JM. Dietary cholesterol and coronary artery disease: a systematic review. *Curr Atheroscler Rep* 2009;11:418–22.
- McCance RA, Widdowson EM. The composition of foods. 6th summary ed. Cambridge, UK: Royal Society of Chemistry, 2004.

22. Weggemans RM, Zock PL, Katan MB. Dietary cholesterol from eggs increases the ratio of total cholesterol to high-density lipoprotein cholesterol in humans: a meta-analysis. *Am J Clin Nutr* 2001;73:885–91.
23. Reaven GM, Abbasi F, Bernhart S, Coulston A, Darnell B, Dashti N, Kim H, Kulkarni K, Lamendola C, McLaughlin T, et al. Insulin resistance, dietary cholesterol, and cholesterol concentration in postmenopausal women. *Metabolism* 2001;50:594–7.
24. Goodrow EF, Wilson TA, Houde SC, Vishwanathan R, Scollin PA, Handelman G, Nicolosi RJ. Consumption of one egg per day increases serum lutein and zeaxanthin concentrations in older adults without altering serum lipid and lipoprotein cholesterol concentrations. *J Nutr* 2006;136:2519–24.
25. Wenzel AJ, Gerweck C, Barbato D, Nicolosi RJ, Handelman GJ, Curran-Celentano J. A 12-wk egg intervention increases serum zeaxanthin and macular pigment optical density in women. *J Nutr* 2006;136:2568–73.
26. Mayurasakorn K, Srisura W, Sitphahul P, Hongto PO. High-density lipoprotein cholesterol changes after continuous egg consumption in healthy adults. *J Med Assoc Thai* 2008;91:400–7.
27. Katz DL, Evans MA, Nawaz H, Njike VY, Chan W, Comerford BP, Hoxley ML. Egg consumption and endothelial function: a randomized controlled crossover trial. *Int J Cardiol* 2005;99:65–70.
28. Njike V, Faridi Z, Dutta S, Gonzalez-Simon AL, Katz DL. Daily egg consumption in hyperlipidemic adults—effects on endothelial function and cardiovascular risk. *Nutr J* 2010;9:28.
29. Dawber TR, Nickerson RJ, Brand FN, Pool J. Eggs, serum cholesterol, and coronary heart disease. *Am J Clin Nutr* 1982;36:617–25.
30. Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, Rosner BA, Spiegelman D, Speizer FE, Sacks FM, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA* 1999;281:1387–94.
31. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. *BMJ* 2003;327:777–82.
32. Nakamura Y, Iso H, Kita Y, Ueshima H, Okada K, Konishi M, Inoue M, Tsugane S. Egg consumption, serum total cholesterol concentrations and coronary heart disease incidence: Japan Public Health Center-based prospective study. *Br J Nutr* 2006;96:921–8.
33. Qureshi AI, Suri FK, Ahmed S, Nasar A, Divani AA, Kirmani JF. Regular egg consumption does not increase the risk of stroke and cardiovascular diseases. *Med Sci Monit* 2007;13:CR1–8.
34. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. *Am J Clin Nutr* 2008;87:964–9.
35. Houston DK, Ding J, Lee JS, Garcia M, Kanaya AM, Tylavsky FA, Newman AB, Visser M, Kritchevsky SB. Dietary fat and cholesterol and risk of cardiovascular disease in older adults: the Health ABC Study. *Nutr Metab Cardiovasc Dis* 2011;21:430–7.
36. Zazpe I, Beunza JJ, Bes-Rastrollo M, Warnberg J, de la Fuente-Arillaga C, Benito S, Vazquez Z, Martinez-Gonzalez MA. Egg consumption and risk of cardiovascular disease in the SUN Project. *Eur J Clin Nutr* 2011;65:676–82.
37. Djoussé L, Gaziano JM, Buring JE, Lee IM. Egg consumption and risk of type 2 diabetes in men and women. *Diabetes Care* 2009;32:295–300.
38. Qiu C, Frederick IO, Zhang C, Sorensen TK, Enquobahrie DA, Williams MA. Risk of gestational diabetes mellitus in relation to maternal egg and cholesterol intake. *Am J Epidemiol* 2011;173:649–58.
39. Shi Z, Yuan B, Zhang C, Zhou M, Holmboe-Ottesen G. Egg consumption and the risk of diabetes in adults, Jiangsu, China. *Nutrition* 2011;27:194–8.
40. Radzevičienė L, Ostrauskas R. Egg consumption and the risk of type 2 diabetes mellitus: a case-control study. *Public Health Nutr* 2012;15:1437–41.
41. Djoussé L, Kamineneni A, Nelson TL, Carnethon M, Mozaffarian D, Siscovick D, Mukamal KJ. Egg consumption and risk of type 2 diabetes in older adults. *Am J Clin Nutr* 2010;92:422–7.
42. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
43. Nakamura Y, Okamura T, Tamaki S, Kadowaki T, Hayakawa T, Kita Y, Okayama A, Ueshima H. Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80). *Am J Clin Nutr* 2004;80:58–63.
44. Yaemsiri S, Sen S, Tinker L, Rosamond W, Wassertheil-Smoller S, He K. Trans fat, aspirin, and ischemic stroke in postmenopausal women. *Ann Neurol* 2012;72:704–15.
45. Snowdon DA. Animal product consumption and mortality because of all causes combined, coronary heart disease, stroke, diabetes, and cancer in Seventh-day Adventists. *Am J Clin Nutr* 1988;48(Suppl):739–48.
46. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart* 1997;78:450–5.
47. Sauvaget C, Nagano J, Allen N, Grant EJ, Beral V. Intake of animal products and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *Int J Epidemiol* 2003;32:536–43.
48. Tanasescu M, Cho E, Manson JE, Hu FB. Dietary fat and cholesterol and the risk of cardiovascular disease among women with type 2 diabetes. *Am J Clin Nutr* 2004;79:999–1005.
49. Trichopoulou A, Psaltopoulou T, Orfanos P, Trichopoulos D. Diet and physical activity in relation to overall mortality amongst adult diabetics in a general population cohort. *J Intern Med* 2006;259:583–91.
50. Scrafford CG, Tran NL, Barraj LM, Mink PJ. Egg consumption and CHD and stroke mortality: a prospective study of US adults. *Public Health Nutr* 2011;14:261–70.
51. Vang A, Singh PN, Lee JW, Haddad EH, Brinegar CH. Meats, processed meats, obesity, weight gain and occurrence of diabetes among adults: findings from Adventist Health Studies. *Ann Nutr Metab* 2008;52:96–104.
52. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
53. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
54. Barraj L, Tran N, Mink P. A comparison of egg consumption with other modifiable coronary heart disease lifestyle risk factors: a relative risk apportionment study. *Risk Anal* 2009;29:401–15.
55. Sacks FM, Salazar J, Miller L, Foster JM, Sutherland M, Samonds KW, Albers JJ, Kass EH. Ingestion of egg raises plasma low density lipoproteins in free-living subjects. *Lancet* 1984;1:647–9.
56. Hopkins PN. Effects of dietary cholesterol on serum cholesterol: a meta-analysis and review. *Am J Clin Nutr* 1992;55:1060–70.
57. Cho E, Zeisel SH, Jacques P, Selhub J, Dougherty L, Colditz GA, Willett WC. Dietary choline and betaine assessed by food-frequency questionnaire in relation to plasma total homocysteine concentration in the Framingham Offspring Study. *Am J Clin Nutr* 2006;83:905–11.
58. Olthof MR, Brink EJ, Katan MB, Verhoef P. Choline supplemented as phosphatidylcholine decreases fasting and postmethionine-loading plasma homocysteine concentrations in healthy men. *Am J Clin Nutr* 2005;82:111–7.
59. Bension LJ, Grundy SM. Effects of diabetes mellitus on cholesterol metabolism in man. *N Engl J Med* 1977;296:1365–71.
60. Pearce KL, Clifton PM, Noakes M. Egg consumption as part of an energy-restricted high-protein diet improves blood lipid and blood glucose profiles in individuals with type 2 diabetes. *Br J Nutr* 2011;105:584–92.
61. Adamopoulos PN, Papamichael CM, Zampelas A, Mouloupoulos SD. Cholesterol and unsaturated fat diets influence lipid and glucose concentrations in rats. *Comp Biochem Physiol B Biochem Mol Biol* 1996;113:659–63.
62. Basciano H, Miller AE, Naples M, Baker C, Kohen R, Xu E, Su Q, Allister EM, Wheeler MB, Adeli K. Metabolic effects of dietary cholesterol in an animal model of insulin resistance and hepatic steatosis. *Am J Physiol Endocrinol Metab* 2009;297:E462–73.
63. Collino M, Aragno M, Castiglia S, Miglio G, Tomasinelli C, Boccuzzi G, Thiemermann C, Fantozzi R. Pioglitazone improves lipid and insulin levels in overweight rats on a high cholesterol and fructose diet by decreasing hepatic inflammation. *Br J Pharmacol* 2010;160:1892–902.
64. Hao M, Head WS, Gunawardana SC, Hasty AH, Piston DW. Direct effect of cholesterol on insulin secretion: a novel mechanism for pancreatic beta-cell dysfunction. *Diabetes* 2007;56:2328–38.
65. Kruit JK, Kremer PH, Dai L, Tang R, Ruddle P, de Haan W, Brunham LR, Verchere CB, Hayden MR. Cholesterol efflux via ATP-binding cassette transporter A1 (ABCA1) and cholesterol uptake via the LDL

- receptor influences cholesterol-induced impairment of beta cell function in mice. *Diabetologia* 2010;53:1110–9.
66. Tannock LR, O'Brien KD, Knopp RH, Retzlaff B, Fish B, Wener MH, Kahn SE, Chait A. Cholesterol feeding increases C-reactive protein and serum amyloid A levels in lean insulin-sensitive subjects. *Circulation* 2005;111:3058–62.
67. Subramanian S, Han CY, Chiba T, McMillen TS, Wang SA, Haw A 3rd, Kirk EA, O'Brien KD, Chait A. Dietary cholesterol worsens adipose tissue macrophage accumulation and atherosclerosis in obese LDL receptor-deficient mice. *Arterioscler Thromb Vasc Biol* 2008;28:685–91.
68. Feskens EJ, Kromhout D. Habitual dietary intake and glucose tolerance in euglycaemic men: the Zutphen Study. *Int J Epidemiol* 1990;19:953–9.
69. Meyer KA, Kushi LH, Jacobs DR Jr, Folsom AR. Dietary fat and incidence of type 2 diabetes in older Iowa women. *Diabetes Care* 2001;24:1528–35.
70. Salméron J, Hu FB, Manson JE, Stampfer MJ, Colditz GA, Rimm EB, Willett WC. Dietary fat intake and risk of type 2 diabetes in women. *Am J Clin Nutr* 2001;73:1019–26.
71. Bowers K, Tobias DK, Yeung E, Hu FB, Zhang C. A prospective study of prepregnancy dietary fat intake and risk of gestational diabetes. *Am J Clin Nutr* 2012;95:446–53.
72. Mutungi G, Ratliff J, Puglisi M, Torres-Gonzalez M, Vaishnav U, Leite JO, Quann E, Volek JS, Fernandez ML. Dietary cholesterol from eggs increases plasma HDL cholesterol in overweight men consuming a carbohydrate-restricted diet. *J Nutr* 2008;138:272–6.
73. Ratliff J, Mutungi G, Puglisi MJ, Volek JS, Fernandez ML. Carbohydrate restriction (with or without additional dietary cholesterol provided by eggs) reduces insulin resistance and plasma leptin without modifying appetite hormones in adult men. *Nutr Res* 2009;29:262–8.