Original Article

Angiology
1-13

DOI: 10.1177/0003319719897493
journals.sagepub.com/home/ang
SAGE

Egg Consumption and Coronary Artery Disease: A Nice Knockdown Argument

Hisato Takagi, MD, PhD[1,2], Yosuke Hari, MD[1,2], Kouki Nakashima, MD, PhD[1,2], Toshiki Kuno, MD, PhD[3], and Tomo Ando, MD[4]; for The ALICE (All-Literature Investigation of Cardiovascular Evidence) Group

Abstract

To identify prospective cohort studies enrolling adults and investigating an association of egg consumption with incidence and mortality of coronary artery disease (CAD), PubMed and Web of Science were searched through June 2019. Adjusted hazard ratios (HRs) of CAD incidence/mortality for more versus the least frequent egg consumption were extracted from each study. Study-specific estimates were pooled in the random-effects model. Sixteen eligible studies with a total of 1 285 505 participants were identified and included in the present meta-analysis. The primary meta-analysis pooling all HRs for the most versus least frequent egg consumption demonstrated that egg consumption was associated with significantly low CAD incidence/mortality (pooled HR: 0.93; 95% confidence interval: 0.89-0.98; $I^2 = 9\%$). In the secondary meta-analyses (separately combining HRs for the third vs first tertile, the fourth vs first quartile, the third vs first quartile, the fifth vs first quintile, the fourth vs first quintile, and the third vs first quintile egg consumption), the fifth (vs first) quintile egg consumption was only associated with significantly low CAD incidence/mortality. In conclusion, egg consumption is independently associated with low incidence/mortality of CAD, which may be derived from the comparisons of the fifth versus first quintile egg consumption.

Keywords
coronary artery disease, egg consumption, meta-analysis

Introduction

The relation of egg consumption to incidence and mortality of coronary artery disease (CAD, synonym of coronary heart disease and ischemic heart disease including myocardial infarction) has been insufficiently understood.[1] Previous meta-analyses suggest that egg consumption may not be associated with low cardiovascular disease (CVD) mortality,[1] all-cause mortality,[1-3] CAD incidence,[3-6] and CAD mortality.[1-3] The potential association of dietary cholesterol with cardiac outcomes has been investigated for several decades.[5] Although eggs are rich in nutrition, their cholesterol content is a concern.[2] However, a recent large (>400 000 participants) prospective cohort study[7] reported a strong trend toward an association of fifth (vs first) quintile egg consumption with low CAD incidence, and another recent large (>460 000 participants) prospective cohort study[8] showed significant associations of fifth/fourth/third/second (vs first) quintile egg consumption with low CAD incidence.

We hypothesized that egg consumption may be associated with low incidence and mortality of CAD. To verify our hypothesis, we performed an updated meta-analysis of currently available prospective cohort studies.

Methods

The present meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (http://www.prisma-statement.org).

Search Strategy

PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) and Web of Science (http://www.webofknowledge.com/wos) were searched through June 2019. Search terms consisted of *egg* and

[1] Department of Cardiovascular Surgery, Shizuoka Medical Center, Shizuoka, Japan
[2] Department of Cardiovascular Surgery, Kitasato University School of Medicine, Sagamihara, Japan
[3] Department of Medicine, Mount Sinai Beth Israel Medical Center, New York, NY, USA
[4] Division of Interventional Cardiology, Department of Cardiology, New York Presbyterian Hospital/Columbia University Medical Center, New York, NY, USA

Corresponding Author:
Hisato Takagi, Department of Cardiovascular Surgery, Shizuoka Medical Center, 762-1 Nagasawa, Shimizu-cho, Sunto-gun, Shizuoka 411-8611, Japan.
Email: kfgth973@ybb.ne.jp

myocardial infarction, *angina*, *acute coronary syndrome*, *coronary artery (arterial) disease*, *coronary heart disease*, or *ischemic (ischaemic) heart disease* (Supplementary Appendix).

Study Selection

Our study selection criteria were the following: The study design was a prospective cohort study; the study population was adults; and an association of egg consumption with incidence/mortality of CAD was investigated. Eligible studies were selected by 2 co-authors (Y.H. and K.N.) and then verified by another co-author (T.A.); disagreements were resolved by consensus.

Quality Assessment

The quality of the studies was assessed using the Risk of Bias Assessment Tool for Nonrandomized Studies,[9] and risk of bias was evaluated ranging low, high, and unclear in accordance with 6 components (selection of participants, confounding variables, measurement of exposure, blinding of outcome assessments, incomplete outcome data, and selective outcome reporting).

Data Extraction

Adjusted hazard ratios (HRs) with their confidence interval (CI) of CAD incidence/mortality for more versus the least frequent egg consumption were extracted from each study. These composed of HRs for the third/second versus first tertile frequency, the fourth/third/second versus first quartile frequency, and the fifth/fourth/third/second versus first quintile frequency of egg consumption. Data including study quality, design, and participants as well as the abovementioned HRs were identified and extracted by 2 co-authors (Y.H. and K.N.), then confirmed and saved in Microsoft Excel worksheets by another co-author (T.K.), and used to generate tables.

Statistical Analysis

Study-specific estimates (HRs) were pooled in the random-effects model (using inverse variance-weighted averages of logarithmic HRs). The primary meta-analysis pooled all HRs for the most versus least frequent egg consumption. These consisted of HRs for the third versus first tertile frequency, the fourth versus first quartile frequency, and the fifth versus first quintile frequency. The secondary meta-analyses separately ([1]-[6]) combined the following HRs: HRs for [1] the third versus first tertile frequency, [2] the fourth versus first quartile frequency, [3] the third versus first quartile frequency, [4] the fifth versus first quintile frequency, [5] the fourth versus first quintile frequency, and [6] the third versus first quintile frequency of egg consumption.

The following sensitivity analyses for the primary meta-analysis were performed: sensitivity analysis I combining all studies in the fixed-effect model, sensitivity analysis II combining epidemiological observational studies (excluding randomized controlled trials) in the random-effects model, sensitivity analysis III combining studies reporting CAD incidence (excluding studies reporting only CAD mortality) in the random-effects model, sensitivity analysis IV combining studies enrolling general population in the random-effects model, sensitivity analysis V combining studies enrolling ≥10 000 participants in the random-effects model, sensitivity analysis VI combining studies enrolling participants aged mean ≥50 years in the random-effects model, and sensitivity analysis VII combining HRs (excluding rate ratios) in the random-effects model. Funnel plot asymmetry (inferring the existence of publication bias) for the primary meta-analysis was statistically evaluated using the rank correlation and linear regression tests.

All analyses were conducted using Review Manager version 5.3 (http://tech.cochrane.org/revman) and ProMeta version 3.0 (https://idostatistics.com/prometa3/).

Results

Search Results and Qualitative Findings

As shown in Figure 1, 16 eligible studies[1,2,7,8,10-21] with a total of 1 285 505 participants (Table 1) were identified and included in the present meta-analysis. Only one study[10] was a large (>20 000 participants) randomized, double-blind, placebo-controlled trial to study low-dose aspirin and β-carotene for the primary prevention of CVD and cancer, whereas the others were epidemiological observational studies. Egg consumption was categorized into tertiles in 5 studies,[1,16,19-21] quartiles in 3 studies,[14,15,18] and quintiles in 8 studies[2,7,8,10-13,17] (Table 2). The quality (risk of bias) of the studies was illustrated in Figure 2.

Quantitative Findings

Extracted and calculated adjusted HRs were summarized in Table 2. The primary meta-analysis pooling all HRs for the most versus least frequent (the third vs first tertile, the fourth vs first quartile, and the fifth vs first quintile) egg consumption demonstrated that egg consumption was associated with significantly low CAD incidence (pooled HR: 0.93; 95% CI: 0.89-0.98; $P = .006$; $I^2 = 9\%$; Figure 2). In the secondary meta-analyses separately combining HRs for the third versus first tertile, the fourth versus first quartile, the third versus first quartile (Figure 3), the fifth versus first quintile, the fourth versus first quintile, and the third versus first quintile egg consumption (Figure 4), the fifth (vs first) quintile egg consumption was only associated with significantly low CAD incidence (pooled HR: 0.90; 95% CI: 0.86-0.94; $P < .00001$; $I^2 = 0\%$; Figure 4).

Sensitivity Analyses

All the sensitivity analyses for the primary meta-analysis (sensitivity analysis I in the fixed-effect model, sensitivity analysis II excluding 1 randomized controlled trial,[10] sensitivity analysis III excluding studies reporting only CAD mortality,[1,2,16,17,20] sensitivity analysis IV combining studies enrolling general population,[1,2,7,8,11-13,15-21] sensitivity

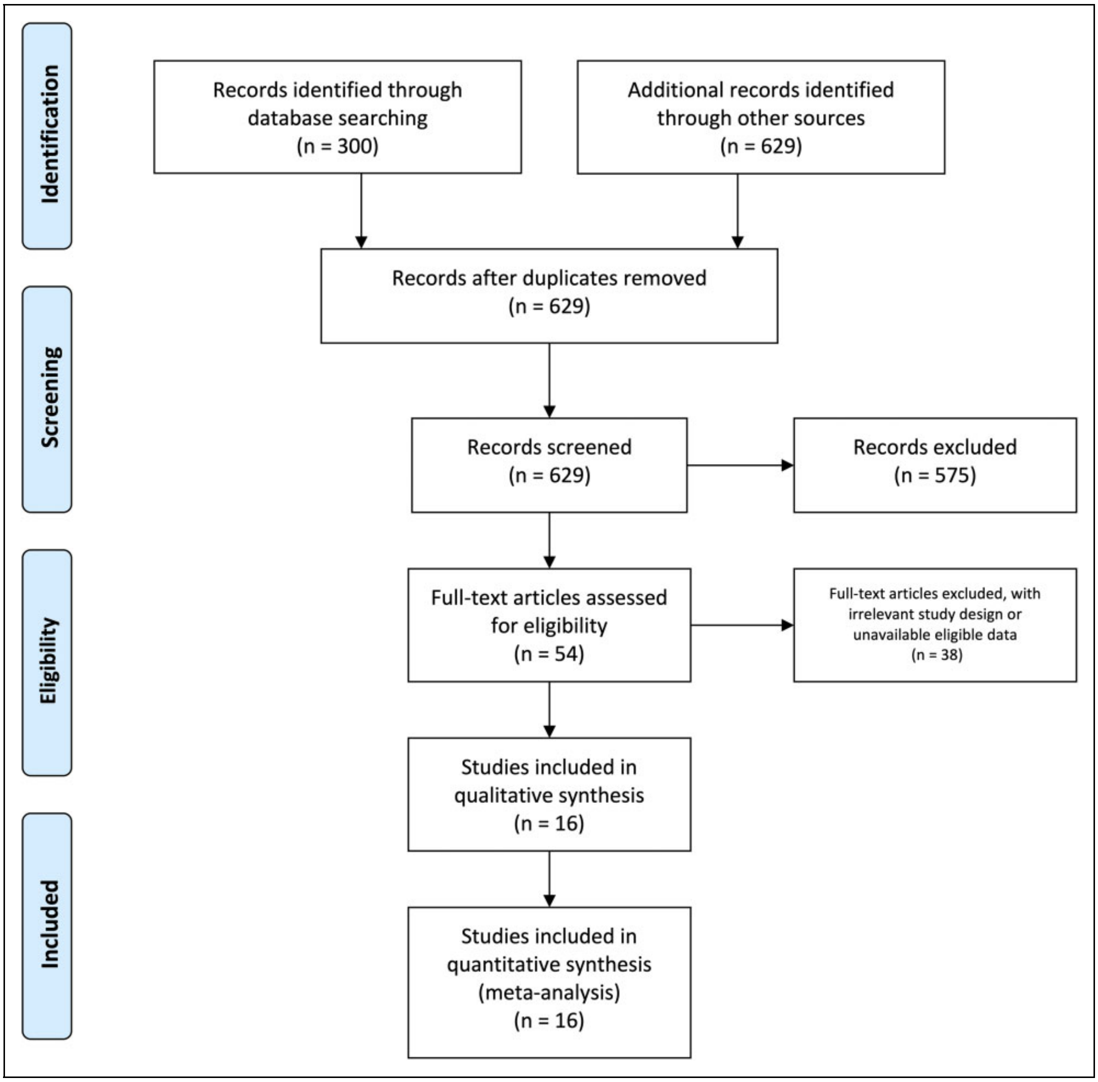

Figure 1. Flow diagram for the meta-analysis.

analysis V combining studies enrolling ≥10 000 participants,[1,2,7,8,10,13-16,18,20] sensitivity analysis VI combining studies enrolling participants aged mean ≥50 years,[2,7,8,10-15,17,18,21] and sensitivity analysis VII excluding 1 rate ratio[16]) demonstrated a still significant benefit of the most (vs least) frequent egg consumption for CAD incidence (Table 3).

Publication Bias

Significant funnel plot asymmetry for the primary meta-analysis was detected ($P = .040$ by the linear regression test despite $P = .791$ by the rank correlation test; Figure 5), which inferred the existence of publication bias. Hence, another sensitivity analysis was performed using the trim and fill method,[22] which conservatively imputes hypothetical negative unpublished studies to mirror the positive identified published studies causing funnel plot asymmetry. The imputed hypothetical studies synthesized symmetrical funnel plot, and the integrating both the identified published and hypothetical unpublished studies continued to demonstrate an association of egg consumption with significantly low CAD incidence (pooled HR: 0.93; 95% CI: 0.87-1.00 [0.996]; $P = .038$; Figure 5).

Discussion

The present meta-analysis of 16 prospective cohort studies with >1 280 000 participants suggests that egg consumption is independently associated with low CAD incidence (including mortality), which was robust in sensitivity analyses and after adjustment of publication bias. The association may be derived from the comparisons of the fifth versus first quintile egg consumption. Statistical heterogeneity, which indicates that effects of egg consumption are more different from each other than expected random error alone, was not identified in the primary meta-analysis ($I^2 = 9\%$) and the secondary meta-analysis for the fifth versus first quintile egg consumption ($I^2 = 0\%$).

Although eggs are a major dietary source of cholesterol, the quantity of egg consumption may not affect CVD risk factors

Table 1. Study Design and Participants.

Study	Reference	Region	Database	Follow-Up (Years)	End Point		Participant			
						Definition	Inclusion Criteria	Number	Age (Years)	Men (%)
Djoussé 2008[a]	10	United States	PHS I	Mean 20	MI incidence (including mortality)	World Health Organization criteria modified to use cardiac enzyme tests	Physicians (men) aged 40 to 85 years	21 327	53.7 ± 9.5	100
Goldberg 2014	11	United States	NOMAS	11 ± 5	MI incidence (including mortality)	*ICD-9*	General population aged >40 years	2669	68.8 ± 10.3	36
Guo 2018	12	United Kingdom	CAPS	Mean 22.8	MI incidence (including mortality)	*ICD-10* codes I21-I25	General population-based men aged 45 to 59 years	1781	61.7	100
Haring 2014	13	United States	ARIC	Median 22	CHD incidence (including mortality)	Information from study visits, yearly telephone follow-up calls, review of hospital discharge lists and medical charts, death certificates, next-of-kin interviews, physician completed questionnaires	General population aged 45 to 64 years	12 066	53.8	44.2
Hu 1999	14	United States	HPFS	8	CHD incidence (including mortality)	Biennial questionnaire, reported by next of kin, coworkers, postal authorities, or the National Death Index	Health professional men aged 40 to 75 years	37 851	53.3	100
			NHS	14	Ditto	Ditto	Nurses (women) aged 30 to 55 years	80 082	45.8	0
Key 2019	7	10 European countries	EPIC	Mean 12.6	IHD incidence (including mortality)	*ICD-10* codes I21, I20-I25	General population	409 885	51.7	26.0
Larsson 2015	15	Sweden	Swedish Men	13	MI incidence (including mortality)	*ICD-10* code I21	General population-based men	37,766	59	100
			SMC	Ditto	Ditto	Ditto	General population-based women	32 805	61	0
Mann 1997	16	United Kingdom	Not denominated	Men 13.3	IHD mortality	*ICD-9*	Vegetarians and their friend/relative nonvegetarians aged ≥16 years	10 802	33	38.0
Mazidi 2019	1	United States	NHANES (1999-2010)	Until December 2011	CHD mortality	*ICD-10* codes I00-I09, I11, I13, I20-I51	General population aged ≥20 years	23 524	47.7	48.7
Nakamura 2004	17	Japan	NIPPON DATA80	14	IHD mortality	National Vital Statistics	General population aged ≥30 years	9263	50.5	56.0

(continued)

Table 1. (continued)

Study	Reference	Region	Database	Follow-Up (Years)	End Point		Participant			
						Definition	Inclusion Criteria	Number	Age (Years)	Men (%)
Nakamura 2006	18	Japan	Japan Public Health Center	Mean 10.2	CHD incidence (including mortality)	Follow-up questionnaire, *ICD-9/10*	General population aged 40 to 59 years in cohort I and aged 40 to 59 years in cohort II	90 735	52.6	47.7
Qin 2018	8	China	CKB	Median 8.9 (IQR 2.15)	IHD incidence (including mortality), IHD mortality, MCE incidence (including mortality)	*ICD-10* codes I20-I25	General population aged 30 to 79 years	461 213	50.7	41.0
Qureshi 2007	19	United States	NHANES I (1971-1975)	15.9 ± 5.6	CAD incidence (including mortality)	*ICD-9* codes 410-414	General population aged 25 to 74 years	9734	49.2	38.6
Scrafford 2011	20	United States	NHANES III (1988-1994)	Mean 8.8 (range 0.1-12.2) in men and mean 8.9 (range 0.2-12.2) in women	CHD mortality	*ICD-10* codes I20-I25	General population ages ≥17 years	14 946	NA	45.7
Virtanen 2016	21	Eastern Finland	KIHD	20.8 ± 6.5	CAD incidence (including mortality)	*ICD-9* codes 410-414, *ICD-10* codes I20-I25	General population-based men aged 42, 48, 54, or 60 years	1032	51.8	100
Xu 2019	2	Southern China	GBCS	Mean 9.8	IHD mortality	*ICD-10*	General population	28 024	61.8	27.2

Abbreviations: ARIC, Atherosclerosis Risk in Communities Study; CAD, coronary artery disease; CHD, coronary heart disease; CKB, China Kadoorie Biobank; EPIC, European Prospective Investigation Into Cancer and Nutrition; GBCS, Guangzhou Biobank Cohort Study; HPFS, Health Professionals Follow-up Study; *ICD-9*, *International Classification of Diseases*, *Ninth revision*; *ICD-10*, *International Classification of Diseases, Tenth revision*; IHD, ischemic heart disease; IQR, interquartile range; KIHD, Kuopio Ischaemic Heart Disease Risk Factor Study; MCE, major coronary events (including ischemic heart disease mortality and nonfatal myocardial infarction); MI, myocardial infarction; NA, not available; NHANES, National Health and Nutrition Examination Survey; NHS, Nurses' Health Study; NIPPON DATA80, National Integrated Project for Prospective Observation of Non-communicable Disease And its Trends in the Aged, 1980; NOMAS, Northern Manhattan Study; PHS: Physicians' Health Study; SMC, Swedish Mammography Cohort.

[a]Randomized, double-blind, placebo-controlled trial using a 2 × 2 factorial design to study low-dose aspirin and β-carotene for the primary prevention of cardiovascular disease and cancer.

Table 2. Hazards Ratios of the End Point for More Versus Least Frequent Egg Consumption (EC).

Study	Reference	Adjusted Covariate	End Point	HR of End Point (95% CI) for More Versus Least Frequent EC			
Djoussé 2008	10	Age, BMI, smoking, HT, vitamin intake, alcohol consumption, vegetable consumption, breakfast cereal, physical activity, treatment arm, AF, DM, HC, parental history of premature MI	MI incidence	1.12 (0.96-1.31) for 1 vs <1 time/wk	1.16 (1.00-1.36) for 2-4 vs <1 time/wk	1.18 (0.93-1.49) for 5-6 vs <1 time/wk	0.90 (0.72-1.14) for ≥7 vs <1 time/wk[a]
Goldberg 2014	11	Age, sex, race/ethnicity, BMI, DM, HT, LDL, HDL, TG, cholesterol-lowering medication, moderate alcohol use, moderate-heavy physical activity, smoking, high school completion, family history of stroke in siblings, family history of MI in siblings, daily consumption of saturated fat, unsaturated fat, carbohydrates, and protein	MI incidence	0.83 (0.57-1.22) for 1 vs <1 egg/mon	0.66 (0.40-1.06) for 2-3 vs <1 egg/mon	1.09 (0.77-1.55) for 1/wk vs <1 egg/mon	0.81 (0.34-1.93) for ≥2/wk vs <1 egg/mon[a]
Guo 2018	12	Age, BMI, total energy intake, alcohol consumption, smoking, energy expenditure, social class, family history of MI, DM, sugar intake, fruit consumption, red meat consumption, fiber	MI incidence	0.97 (0.72-1.31) for >1-≤2 vs ≥0-≤1 egg/wk	1.14 (0.85-1.52] for >2-≤3 vs ≥0-≤1 egg/wk	1.01 (0.72-1.40) for >3-<5 vs ≥0-≤1 egg/wk	0.91 (0.64-1.31) for ≥5 vs ≥0-≤1 egg/wk[a]
Haring 2014	13	Age, sex, race, study center, total energy intake, smoking, education, SBP, use of antihypertensive medication, HDL, TC, use of lipid-lowering medication, BMI, WHR, alcohol intake, sports-related physical activity, leisure-related physical activity, carbohydrate intake, fiber intake, magnesium intake	CHD incidence	0.92 (0.76-1.12) for second vs first quintile EC	0.88 (0.73-1.06) for third vs first quintile EC	0.83 (0.69-0.99) for fourth vs first quintile EC	0.96 (0.77, 1.19) for fifth vs first quintile EC[a]
Hu 1999, HPFS	14	Age, BMI, 2-year time periods, cigarette smoking, parental history of MI, multivitamin supplement use, vitamin E supplement use, alcohol consumption, menopausal status and postmenopausal hormone use (women), HT, physical activity, total energy intake	CHD incidence	1.06 (0.88-1.27) for 1 vs <1 egg/wk	1.12 (0.95-1.33) for 2-4 vs <1 egg/wk	0.90 (0.63-1.27) for 5-6 vs <1 egg/wk[a]	
Hu 1999, NHS	14	Ditto	Ditto	0.82 (0.67-1.00) for 1 vs <1 egg/wk	0.99 (0.82-1.18) for 2-4 vs <1 egg/wk	0.95 (0.70-1.29) for 5-6 vs <1 egg/wk[a]	
Key 2019	7	Age, smoking status and number of cigarettes per day, DM, HT, HL, Cambridge physical activity index, employment status, level of education completed, BMI, current alcohol consumption, observed intakes of energy, fruit and vegetables combined, sugars, fiber from cereals, stratified by sex and EPIC center	IHD incidence	0.96 (0.89-1.04) for second vs first quintile EC	0.97 (0.90-1.05) for third vs first quintile EC	1.02 (0.94-1.09) for fourth vs first quintile EC	0.93 (0.86-1.01) for fifth vs first quintile EC[a]
Larsson 2015	15	Age, includes education, family history of MI before 60 years of age, smoking status and pack-years of smoking, aspirin use, walking/bicycling, exercise, BMI, history of HT, HC, and DM, intakes of total energy, alcohol, fruit and vegetables, and processed meat	MI incidence	0.96 (0.90-1.02) for 1-2 egg/wk vs ≤3 egg/mon	0.96 (0.87-1.07) for 3-6 egg/wk vs ≤3 egg/mon	0.98 (0.82-1.17) for ≥1 egg/d vs ≤3 egg/mon	
Larsson 2015, Swedish Men	15	Ditto	Ditto	0.98 (0.90-1.05) for 1-2 egg/wk vs ≤3 egg/mon	0.95 (0.84-1.08) for 3-6 egg/wk vs ≤3 egg/mon	1.03 (0.84-1.27) for ≥1 egg/d vs ≤3 egg/mon[a]	

(continued)

Table 2. (continued)

Study	Reference	Adjusted Covariate	End Point	HR of End Point (95% CI) for More Versus Least Frequent EC			
Larsson 2015, SMC	15	Ditto	Ditto	0.94 (0.84-1.05) for 1-2 egg/wk vs ≤3 egg /mon	1.03 (0.86-1.24) for 3-6 egg/wk vs ≤3 egg/mon	0.85 (0.59-1.23) for ≥1 egg/d vs ≤3 egg/mon[a]	
Mann 1997	16	Age, sex, smoking habit, social class	IHD mortality	Rate ratio 1.28 (0.59-2.79) for 1-5 vs <1 egg/wk	Rate ratio 2.68 (1.19-6.02) for ≥6 vs <1 egg/wk[a]		
Mazidi 2019	1	Age, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, intake of fiber and meat, BMI, HT, DM	CHD mortality in men	1.10 (0.58-2.13) for second vs first tertile EC	1.03 (0.50-2.16) for third vs first tertile EC		
		Ditto	CHD mortality in women	1.05 (0.55-2.01) for second vs first tertile EC	1.23 (0.38-3.91) for third vs first tertile EC		
		Ditto	CHD mortality in both men and women	1.08 (0.68-1.71) for second vs first tertile EC[b]	1.09 (0.59-2.02) for third vs first tertile EC[a,b]		
Nakamura 2004	17	Age, serum creatinine, TC, blood glucose, BMI, S/DBP, use of blood pressure-lowering drugs, cigarette smoking, alcohol intake	IHD mortality in men	1.44 (0.26-7.98) for 1-2 egg/wk vs seldom[c]	1.25 (0.22-7.12) for 0.5 egg/d vs seldom[c]	0.84 (0.18-3.85) for 1 egg/d vs seldom[c]	NA
		Ditto	IHD mortality in women	0.45 (0.13-1.54) for 1-2 egg/week vs seldom[d]	0.56 (0.16-1.95) for 0.5 egg/day vs seldom[d]	0.70 (0.28-1.79) for 1 egg/day vs seldom[d]	0.88 (0.09-8.42) for ≥2 egg/day vs seldom[d]
		Ditto	IHD mortality in both men and women	0.68 (0.23-2.09) for 1-2 egg/week vs seldom[b]	0.74 (0.27-2.02) for 0.5 egg/day vs seldom[b]	0.74 (0.33-1.63) for 1 egg/day vs seldom[a,b]	NA
Nakamura 2006	18	Age, sex, BMI, HT, DMs, use of cholesterol-lowering drugs, smoking, alcohol drinking, whether or not intended to avoid cholesterol-rich diets, consumption frequencies of meat, fish, vegetables, and fruits, cohort effects	CHD incidence	0.84 (0.56-1.28) for 1-2 vs <1 d/wk[e]	0.84 (0.56-1.25) for 3-4 vs <1 d/wk[e]	0.84 (0.61-1.16) for almost daily vs <1 d/wk[a,e]	
Qin 2018	8	Age at recruitment, sex, education level, household income, marital status, alcohol consumption, tobacco smoking, physical activity in MET-hours/d, BMI, WHR, HT, use of aspirin, family history of CVD, intake of multivitamin supplementation, dietary pattern	IHD incidence	0.95 (0.91-0.99) for 1-3 d/mon vs never/rarely	0.92 (0.88-0.96) for 1-3 d/wk vs never/rarely	0.86 (0.81-0.91) for 4-6 d/wk vs never/rarely	0.88 (0.84-0.93) for 7 d/wk vs never/rarely[a]
		Ditto	IHD mortality	0.90 (0.79-1.02) for 1-3 d/mon vs never/rarely	0.94 (0.83-1.05) for 1-3 d/wk vs never/rarely	0.85 (0.73-0.99) for 4-6 d/wk vs never/rarely	0.88 (0.77-1.02) for 7 d/wk vs never/rarely
		Ditto	MCE incidence	0.93 (0.84-1.04) for 1-3 d/mon vs never/rarely	0.93 (0.85-1.03) for 1-3 d/wk vs never/rarely	0.83 (0.73-0.94) for 4-6 d/wk vs never/rarely	0.86 (0.76-0.97) for 7 d/wk vs never/rarely
Qureshi 2007	19	Age, gender, race/ethnicity, SBP, DM, serum cholesterol, cigarette smoking, BMI, educational status	CAD incidence	1.0 (0.9-1.1) for 1-6 vs <1 egg/wk	1.1 (0.9-1.3) for >6 vs <1 egg/wk[a]		

(continued)

Table 2. (continued)

Study	Reference	Adjusted Covariate	End Point	HR of End Point (95% CI) for More Versus Least Frequent EC			
Scrafford 2011	20	Age, energy, marital status, race/ethnicity, BMI, DM, HT, alcohol intake	CHD mortality in men	1.38 (0.85-2.24) for ≥1-<7 vs <1 occasion/wk	1.38 (0.84-2.26) for ≥7 vs <1 occasion/wk		
		Age, energy, marital status, educational status, race/ethnicity, WHR, DM, HT, vitamin E	CHD mortality in women	1.06 (0.67-1.68) for ≥1-<7 vs <1 occasion/wk	0.78 (0.26-2.30) for ≥7 vs <1 occasion/wk		
		Age, energy, marital status, race/ethnicity, DM, HT	CHD mortality in both men and women	1.20 (0.86-1.68) for ≥1-<7 vs <1 occasion/wk[b]	1.25 (0.80-1.96) for ≥7 vs <1 occasion/wk[a,b]		
Virtanen 2016	21	Age, examination year, energy intake, smoking, BMI, DM, HT, leisure-time physical activity, CAD history in close relatives, education, intakes of alcohol, fruit, berries, vegetables, fiber, PUFAs, and SFAs	CAD incidence	0.96 (0.69-1.34) for second vs first tertile EC	1.18 (0.85-1.66) for third vs first tertile EC[a]		
Xu 2019	2	Sex, age, education, occupation, family income, smoking status, physical activity, alcohol drinking, self-rated health and chronic disease history (DM, HT, and DL)	IHD mortality	0.86 (0.66-1.13) for 1-2 vs <1 egg/wk	1.03 (0.79-1.34) for 3-4 vs <1 egg/wk	0.75 (0.44-1.27) for 5-6 vs <1 egg/wk	0.92 (0.63, 1.36) for ≥7 vs <1 egg/wk[a]

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CAD, coronary artery disease; C: confidence interval; CVD, cardiovascular disease; DL, dyslipidemia; DM, diabetes mellitus; EPIC, European Prospective Investigation Into Cancer and Nutrition; TG, triglyceride; HC, hypercholesterolemia; HDL, high-density lipoprotein; HL, hyperlipidemia; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; HT, hypertension; IHD, ischemic heart disease; LDL, low-density lipoprotein; MCE, major coronary events; MET, metabolic equivalent task; MI, myocardial infarction; NHS, Nurses' Health Study; PUFAs, polyunsaturated fatty acids; S/DBP, systolic/diastolic blood pressure; SFAs, saturated fatty acids; SMC, Swedish Mammography Cohort; TC, total cholesterol; WHR, waist to hip ratio.

[a] Combined in the primary meta-analysis.

[b] Calculated by HRs in both men and women.

[c] Calculated by HRs for 0.5 egg/d, 1 to 2 egg/wk, and seldom versus 1 egg/d.

[d] Calculated by HRs for ≥2 egg/d, 0.5 egg/d, 1 to 2 egg/wk, and seldom versus 1 egg/d.

[e] Calculated by HRs for <1, 1 to 2, and 3 to 4 d/wk versus almost daily.

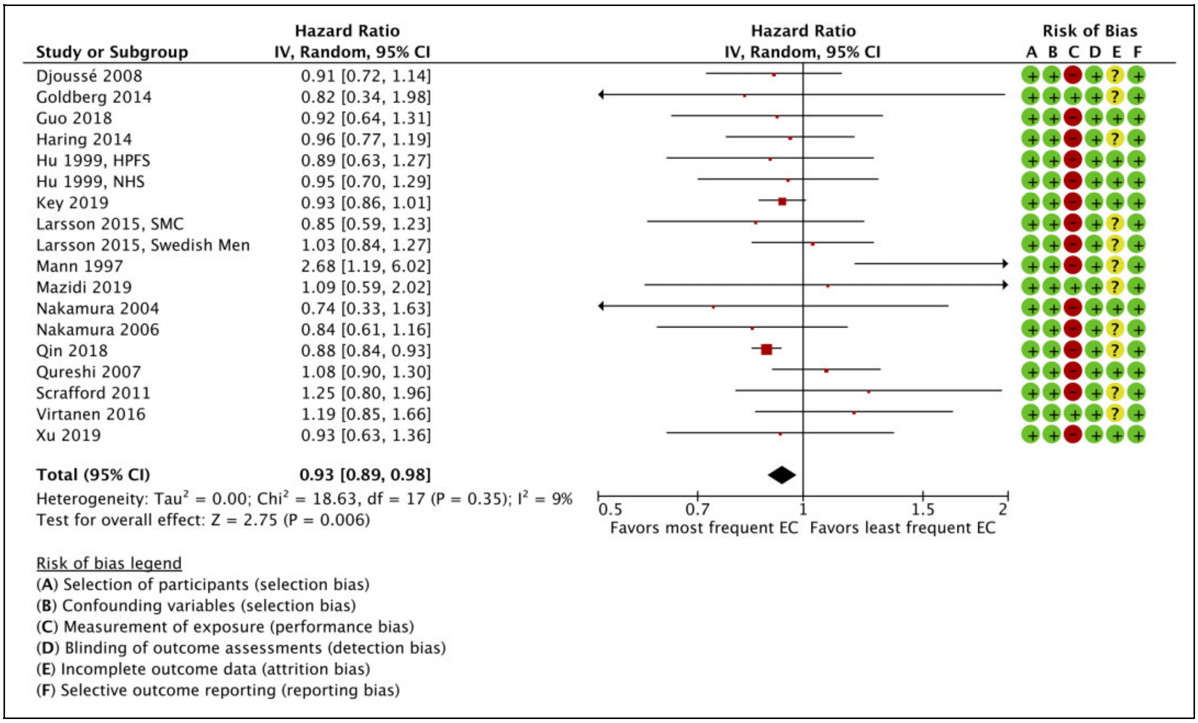

Figure 2. Primary meta-analysis pooling all hazard ratios for the most versus least frequent (the third vs first tertile, the fourth vs first quartile, and the fifth vs first quintile) egg consumption. + indicates low risk of bias;?, unclear risk of bias; −, high risk of bias; CI, confidence interval; HPFS, Health Professionals Follow-up Study; IV, inverse variance; NHS, Nurses' Health Study; SMC, Swedish Mammography Cohort.

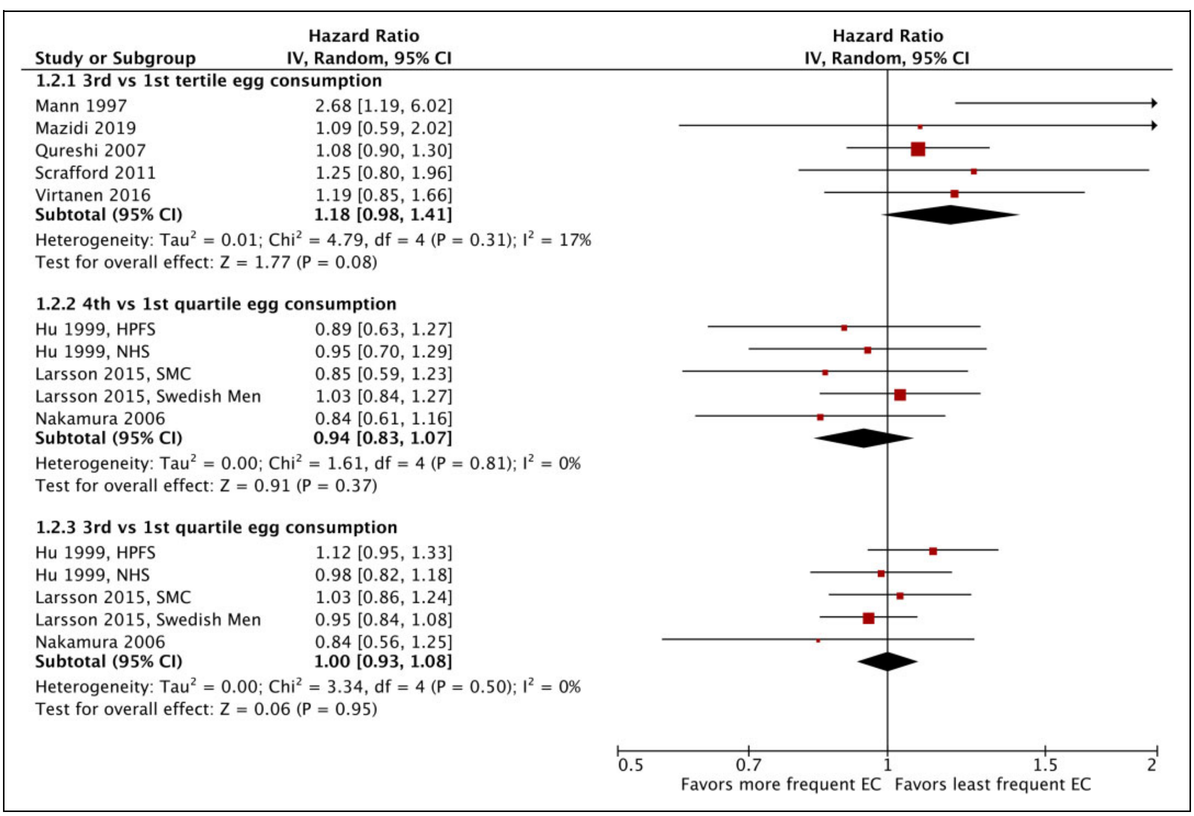

Figure 3. Secondary meta-analyses separately combining hazard ratios for the third versus first tertile, the fourth versus first quartile, and the third versus first quartile egg consumption. CI indicates confidence interval; HPFS, Health Professionals Follow-up Study; IV, inverse variance; NHS, Nurses' Health Study; SMC, Swedish Mammography Cohort.

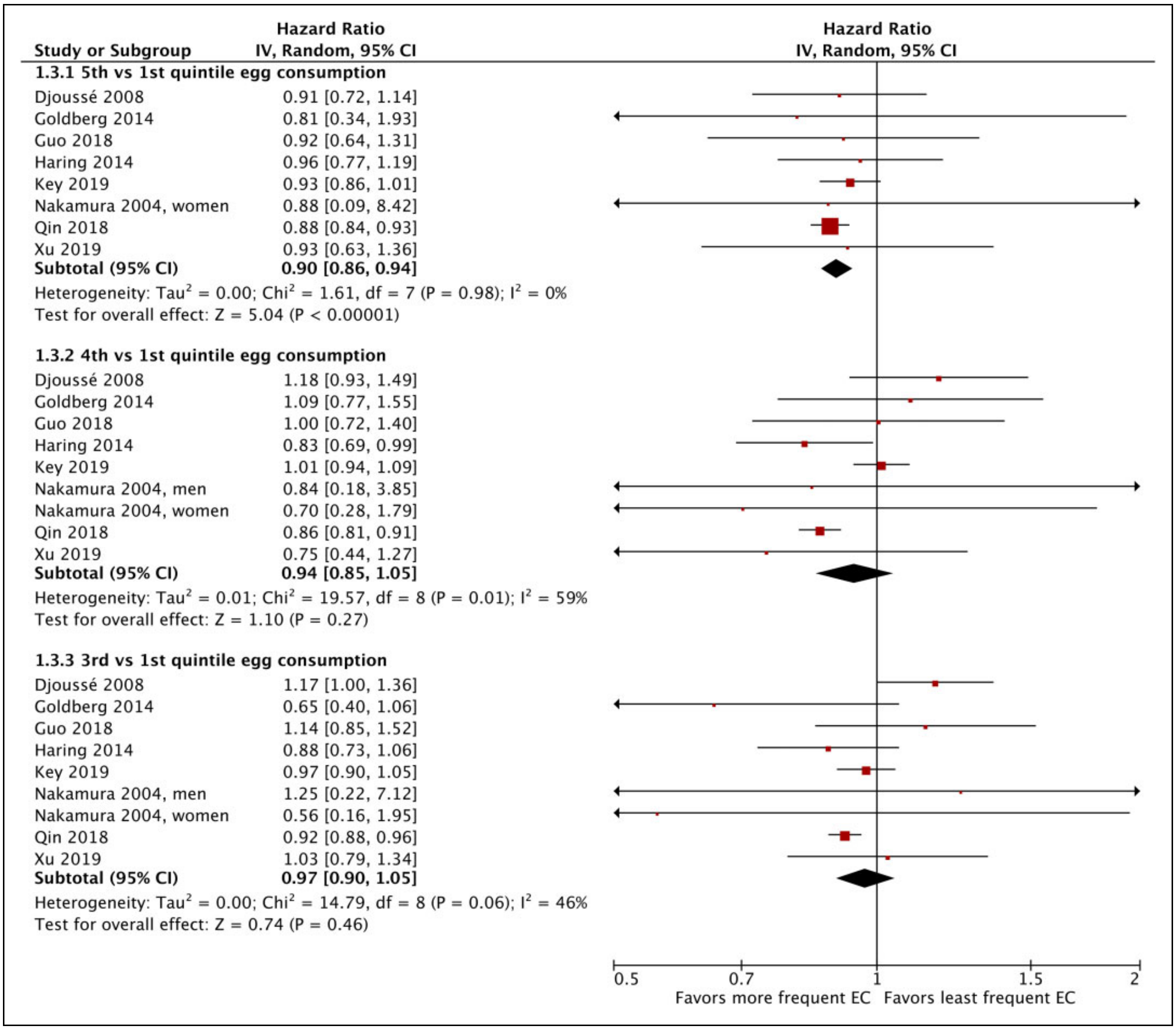

Figure 4. Secondary meta-analyses separately combining hazard ratios for the fifth versus first quintile, the fourth versus first quintile, and the third versus first quintile egg consumption. CI indicates confidence interval; IV, inverse variance.

such as blood pressure, lipids, and lipoproteins. A meta-analysis[23] of 8 randomized controlled trials reported no difference in changes of systolic/diastolic blood pressure, and triglyceride, total cholesterol, and high-/low-density lipoprotein cholesterol concentrations between >4 and ≤4 whole egg/week consumption. Furthermore, another meta-analysis[24] of 36 studies (17 cohorts and 19 trials) showed that dietary cholesterol was associated with increased serum high-density lipoprotein concentrations (pooled mean difference for 650-900 mg/d, 2.7 mg/dL; 95% CI: 0.7-4.7 mg/dL) despite associations with increased serum total cholesterol and low-density lipoprotein concentrations. Egg components other than cholesterol may favorably influence risk of CVD.[25-29] Dietary supplementation of egg yolk increases plasma carotenoids such as lutein and zeaxanthin,[25] which are related to low risk of atherosclerosis via their antioxidant and anti-inflammatory effects.[26] The bioavailability of lutein from lutein-enriched eggs is greater compared to that from lutein supplements, lutein ester supplements, and spinach,[27] and cooked whole egg consumption is efficacious to augment absorption of lutein and zeaxanthin from other carotenoid-rich foods such as a raw mixed-vegetable salad.[28] Egg phospholipid consumption is also associated with beneficial impacts on pathways in relation to cholesterol metabolism and high-density lipoprotein function.[29] Moreover, egg consumption for breakfast induces greater satiety, suppresses postprandial glycemic, insulinemic, and ghrelin responses and decreases succeeding food/energy intake.[30,31] The abovementioned findings may partially explain the association of egg consumption with low CAD incidence demonstrated in the present meta-analysis.

Egg consumption may be associated with low stroke mortality. In a meta-analysis of 5 studies, Mazidi et al[1] reported that egg consumption was associated with significantly low stroke mortality (pooled HR: 0.72; 95% CI: 0.54-0.91; P = .026). However, an association of egg consumption with stroke incidence has been still controversial.[2,4] In their meta-analysis of 9 studies, Xu et al[2] showed an association of egg

Table 3. Sensitivity Analyses of the Primary Meta-Analysis.[a]

Study	Reference	Primary Meta-Analysis	Sensitivity Analysis						
			I	II	III	IV	V	VI	VII
Djoussé 2008	10	√	√	Excluded	√	Excluded	√	√	√
Goldberg 2014	11	√	√	√	√	√	Excluded	√	√
Guo 2018	12	√	√	√	√	√	Excluded	√	√
Haring 2014	13	√	√	√	√	√	√	√	√
Hu 1999, HPFS	14	√	√	√	√	Excluded	√	√	√
Hu 1999, NHS	14	√	√	√	√	Excluded	√	Excluded	√
Key 2019	7	√	√	√	√	√	√	√	√
Larsson 2015, Swedish Men	15	√	√	√	√	√	√	√	√
Larsson 2015, SMC	15	√	√	√	√	√	√	√	√
Mann 1997	16	√	√	√	Excluded	Excluded	√	Excluded	Excluded
Mazidi 2019	1	√	√	√	Excluded	√	√	Excluded	√
Nakamura 2004	17	√	√	√	Excluded	√	Excluded	√	√
Nakamura 2006	18	√	√	√	√	√	√	√	√
Qin 2018	8	√	√	√	√	√	√	√	√
Qureshi 2007	19	√	√	√	√	√	Excluded	Excluded	√
Scrafford 2011	20	√	√	√	Excluded	√	√	Excluded	√
Virtanen 2016	21	√	√	√	√	√	Excluded	√	√
Xu 2019	2	√	√	√	Excluded	√	√	√	√
Pooled HR (95% CI)		0.93 (0.89-0.98)	0.92 (0.88-0.95)	0.94 (0.89-0.99)	0.91 (0.88-0.95)	0.92 (0.88-0.95)	0.92 (0.87-0.96)	0.91 (0.87-0.94)	0.92 (0.88-0.95)
P value		.006	<.00001	.03	<.00001	<.0001	.0002	<.00001	<.00001

Abbreviations: √, included; CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; NHS, Nurses' Health Study; SMC, Swedish Mammography Cohort.

[a]Primary meta-analysis combined all studies in the random-effects model. Sensitivity analysis I combined all studies in the fixed-effect model. Sensitivity analysis II combined prospective cohort studies (excluding one randomized controlled trial) in the random-effects model. Sensitivity analysis III combined studies reporting CAD incidence (excluding studies reporting only CAD mortality) in the random-effects model. Sensitivity analysis IV combined studies enrolling general population in the random-effects model. Sensitivity analysis V combined studies enrolling ≥10 000 participants in the random-effects model. Sensitivity analysis VI combined studies enrolling participants aged mean ≥50 years in the random-effects model. Sensitivity analysis VII combined HRs (excluding one rate ratio) in the random-effects model.

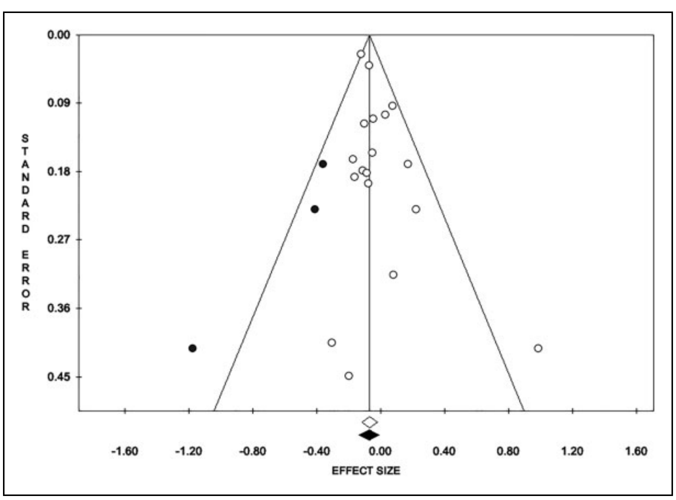

Figure 5. Funnel plot of the logarithm of effect size (hazard ratio) versus the standard error for the primary meta-analysis. Open and closed circles denote identified published and hypothetical unpublished studies, respectively. An open and closed lozenge denotes, respectively, an unadjusted summary estimate exclusively combining the identified published studies and an adjusted summary estimate integrating both the identified published and hypothetical unpublished studies.

consumption with significantly low stroke incidence (pooled HR: 0.91; 95% CI: 0.85-0.98). However, in their meta-analysis of 8 studies, Bechthold et al[4] reported that egg consumption was not associated with low stroke incidence (pooled relative risk, 0.99; 95% CI: 0.93-1.05; $P = .65$). Further investigations are required.

The present findings should be interpreted with caution owing to the following limitations. Notable qualitative heterogeneity was identified among the studies included in the present meta-analysis (Table 1). Cautious and respective elimination of ununiform studies in the sensitivity analyses, however, verified the association of egg consumption with low CAD incidence demonstrated in the primary meta-analysis. The statistical evaluation of the funnel plot revealed significant asymmetry (inferring the existence of publication bias), which suggests that the present results may be influenced by publication bias. Adjustment for the asymmetry using the trim and fill method,[22] however, ascertained the results of the primary meta-analysis.

In conclusion, egg consumption is independently associated with low CAD incidence (including mortality), which may be derived from the comparisons of the fifth versus first quintile egg consumption.

Authors' Note

All authors (1) contributed to conception and design, or acquisition of data, or analysis and interpretation of data; (2) participated in either drafting the article or revising it critically for important intellectual content; and (3) gave final approval of the version to be published.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iDs

Hisato Takagi https://orcid.org/0000-0002-5594-8072
Toshiki Kuno https://orcid.org/0000-0002-2487-8366

Supplementary Material

Supplemental material for this article is available online.

References

1. Mazidi M, Katsiki N, Mikhailidis DP, Pencina MJ, Banach M. Egg consumption and risk of total and cause-specific mortality: an individual-based cohort study and pooling prospective studies on behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group. *J Am Coll Nutr*. 2019:38:552-63.
2. Xu L, Lam TH, Jiang CQ, et al. Egg consumption and the risk of cardiovascular disease and all-cause mortality: Guangzhou biobank cohort study and meta-analyses. *Eur J Nutr*. 2019;58:785-96.
3. Shin JY, Xun P, Nakamura Y, He K. Egg consumption in relation to risk of cardiovascular disease and diabetes: a systematic review and meta-analysis. *Am J Clin Nutr*. 2013;98:146-59.
4. Bechthold A, Boeing H, Schwedhelm C, et al. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose–response meta-analysis of prospective studies. *Crit Rev Food Sci Nutr*. 2019;59:1071-90.
5. Alexander DD, Miller PE, Vargas AJ, Weed DL, Cohen SS. Meta-analysis of egg consumption and risk of coronary heart disease and stroke. *J Am Coll Nutr*. 2016;35:704-16.
6. Rong Y, Chen L, Zhu T, et al. Egg consumption and risk of coronary heart disease and stroke: dose–response meta-analysis of prospective cohort studies. *BMJ*. 2013;346:e8539.
7. Key TJ, Appleby PN, Bradbury KE, et al. Consumption of meat, fish, dairy products, and eggs and risk of ischemic heart disease. *Circulation*. 2019;139:2835-45.
8. Qin C, Lv J, Guo Y, et al; China Kadoorie Biobank Collaborative Group. Associations of egg consumption with cardiovascular disease in a cohort study of 0.5 million Chinese adults. *Heart*. 2018;104:1756-63.
9. Kim SY, Park JE, Lee YJ, et al. Testing a tool for assessing the risk of bias for nonrandomized studies showed moderate reliability and promising validity. *J Clin Epidemiol*. 2013;66:408-14.
10. 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.
11. Goldberg S, Gardener H, Tiozzo E, et al. Egg consumption and carotid atherosclerosis in the Northern Manhattan study. *Atherosclerosis*. 2014;235:273-80.
12. Guo J, Hobbs DA, Cockcroft JR, et al. Association between egg consumption and cardiovascular disease events, diabetes and all-cause mortality. *Eur J Nutr*. 2018;57:2943-52.
13. Haring B, Gronroos N, Nettleton JA, von Ballmoos MC, Selvin E, Alonso A. Dietary protein intake and coronary heart disease in a large community based cohort: results from the Atherosclerosis Risk in Communities (ARIC) study [corrected]. *PLoS One*. 2014;9:e109552. Erratum in: *PLoS One*. 2014;9:e114114.
14. Hu FB, Stampfer MJ, Rimm EB, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA*. 1999;281:1387-94.
15. Larsson SC, Åkesson A, Wolk A. Egg consumption and risk of heart failure, myocardial infarction, and stroke: results from 2 prospective cohorts. *Am J Clin Nutr*. 2015;102:1007-13.
16. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart*. 1997;78:450-55.
17. Nakamura Y, Okamura T, Tamaki S, et al. Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged, 1980 (NIPPON DATA80). *Am J Clin Nutr*. 2004;80:58-63.
18. Nakamura Y, Iso H, Kita Y, et al. 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.
19. 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.
20. 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.
21. Virtanen JK, Mursu J, Virtanen HE, et al. Associations of egg and cholesterol intakes with carotid intima-media thickness and risk of incident coronary artery disease according to apolipoprotein E phenotype in men: the Kuopio Ischaemic Heart Disease Risk Factor study. *Am J Clin Nutr*. 2016;103:895-901.
22. Duval S, Tweedie R. Trim and fill: a simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-63.
23. Wang MX, Wong CH, Kim JE. Impact of whole egg intake on blood pressure, lipids and lipoproteins in middle-aged and older population: a systematic review and meta-analysis of randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2019;29:653-64.
24. Berger S, Raman G, Vishwanathan R, Jacques PF, Johnson EJ. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr*. 2015;102:276-94.
25. Handelman GJ, Nightingale ZD, Lichtenstein AH, Schaefer EJ, Blumberg JB. Lutein and zeaxanthin concentrations in plasma

after dietary supplementation with egg yolk. *Am J Clin Nutr*. 1999;70:247-51.

26. Ciccone MM, Cortese F, Gesualdo M, et al. Dietary intake of carotenoids and their antioxidant and anti-inflammatory effects in cardiovascular care. *Mediators Inflamm*. 2013;2013:782137.
27. Chung HY, Rasmussen HM, Johnson EJ. Lutein bioavailability is higher from lutein-enriched eggs than from supplements and spinach in men. *J Nutr*. 2004;134:1887-93.
28. Kim JE, Gordon SL, Ferruzzi MG, Campbell WW. Effects of egg consumption on carotenoid absorption from co-consumed, raw vegetables. *Am J Clin Nutr*. 2015;102:75-83. Erratum in: *Am J Clin Nutr*. 2015;102:981.
29. Blesso CN. Egg phospholipids and cardiovascular health. *Nutrients*. 2015;7:2731-47.
30. Bonnema AL, Altschwager DK, Thomas W, Slavin JL. The effects of the combination of egg and fiber on appetite, glycemic response and food intake in normal weight adults—a randomized, controlled, crossover trial. *Int J Food Sci Nutr*. 2016;67:723-31.
31. Ratliff J, Leite JO, de Ogburn R, Puglisi MJ, VanHeest J, Fernandez ML. Consuming eggs for breakfast influences plasma glucose and ghrelin, while reducing energy intake during the next 24 hours in adult men. *Nutr Res*. 2010;30:96-103.