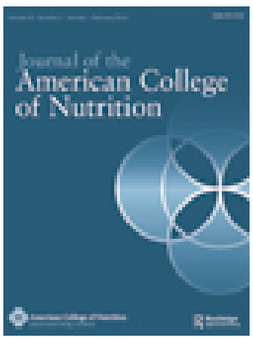

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Egg Consumption and Risk of Total and Cause-Specific Mortality: An Individual-Based Cohort Study and Pooling Prospective Studies on Behalf of the Lipid and Blood Pressure Meta-analysis Collaboration (LBPMC) Group

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ABSTRACT

The associations of egg consumption with total, coronary heart disease (CHD), and stroke mortality are poorly understood. We prospectively evaluated the link between total, CHD, and stroke mortality with egg consumption using a randomly selected sample of U.S. adults. Next we validated these results within a meta-analysis and systematic review of all available prospective results. We assessed the mean of cardiometabolic risk factors across the intake of eggs. We made the analysis based on data from the National Health and Nutrition Examination Surveys (NHANES; 1999–2010). In NHANES, vital status through December 31, 2011, was ascertained. Cox proportional hazard regression models were used to relate baseline egg consumption with all-cause and cause-specific mortality. PubMed, Scopus, Web of Science, and Google Scholar databases were also searched (up to December 2017). The DerSimonian-Laird method and generic inverse variance methods were used for quantitative data synthesis. Overall, 23,524 participants from NHANES were included (mean age of 47.7 years; 48.7% were men). Across increasing the intake of eggs, adjusted mean levels of cardiometabolic risk factors worsened. Adjusted logistic regression showed that participants in the highest category of egg intake had a greater risk of diabetes (T2DM; 30%) and hypertension (HTN; 48%). With regard to total and CHD mortality, multivariable Cox regression in a fully adjusted model showed no link in males and females. In males, egg intake had a reverse (66%) association with stroke mortality, while this link was not significant among females. The results of pooling data from published prospective studies also showed no link between CHD and total mortality with egg consumption, whereas we observed a reverse (28%) association between egg intake and stroke mortality. These findings were robust after sensitivity analysis. According to our findings, egg intake had no association with CHD and total mortality, whereas was associated with lower risk of mortality from stroke. Egg consumption was associated with T2DM, HTN, C-reactive protein, and markers of glucose/insulin homeostasis. If confirmed in clinical trials (causation), this information may have applications for population-wide health measures.

Key teaching points

- No link between total and CHD mortality with eggs intake in males and females.
- In males, egg intake had a reverse association with stroke mortality, while this link was not significant among females.
- The results of pooling data from published prospective studies also showed no link between CHD and total mortality with egg consumption, whereas we observed a reverse association between egg intake and stroke mortality.

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Egg; coronary heart disease; stroke; mortality; diabetes; hypertension

Introduction

Cardiovascular disease (CVD) is still the leading cause of mortality worldwide, with an essential social and economic toll globally. Currently it accounts for more than 17.3 million deaths annually, with almost 900,000 deaths in the United States only, a figure that is predicted to rise to more than 23.6 million by 2030 (1,2).

There is little controversy regarding the beneficial/detrimental effect of the diet on CVD development and progression (1,3–6). Diet is an important determinant

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Supplemental data for this article can be accessed here.

of serum cholesterol, but dietary cholesterol only makes a modest contribution to plasma concentrations of low-density lipoprotein cholesterol (LDL-C) (7). Among the known risk factors for CVD, LDL-C has attracted particular attention (8). To minimize the elevation of blood cholesterol and reduce the risk of CVD, the American Heart Association (AHA) has recommended that the public should consume <300 mg/d of cholesterol (9). Some available studies (10,11) showed that dietary cholesterol intake had only a little effect on the change in the ratio of LDL-C to high-density lipoprotein cholesterol (HDL-C). On the basis of two relatively old meta-analyses (from 1997) (12,13), a 100-mg dietary cholesterol intake would increase plasma total cholesterol by 2.2 to 2.5 mg/dL, LDL-C by 1.9 mg/dL, and HDL-C by 0.4 mg/dL.

Eggs are one of the main sources of dietary cholesterol. A medium egg contains around 225 mg cholesterol (14). Egg yolks are high in cholesterol, and thus reducing egg intake used to be recommended to lower serum cholesterol levels and help prevent coronary heart disease (CHD) (15). A meta-analysis of clinical trials (16) found that the addition of 100 mg dietary cholesterol from eggs increased the ratio of total cholesterol (TC) to HDL-C by 0.02 units as well as plasma TC by 2.2 mg/dL and HDL-C by 0.3 mg/dL. Due to the fact that a large egg contains about 210 mg of cholesterol, or about 70% of the corresponding recommended daily value, the AHA recommends restricting egg consumption unless dietary cholesterol intake from other sources is limited (17). However, on the other hand, eggs are also an important source of many other nutrients, including minerals, vitamins, proteins, and unsaturated fatty acids, which could lower the risk of mortality (14). In addition, in populations following a carbohydrate-restricted diet, dietary cholesterol from eggs increases plasma HDL-C concentrations (18), which might protect against vascular disease (19,20). In the same line, randomized controlled trials (RCTs) reported that egg intake did not appreciably alter plasma TC, LDL-C (21,22), HDL-C (21,22), or the ratio of TC to HDL-C (21–24). Therefore, most preventive scientific societies suggest that reducing egg intake might not be important for healthy people with normal blood cholesterol levels (8). The AHA guidelines are inconsistent with other recommendations on this issue. The British Heart Foundation has recently removed their advice to limit egg consumption to 3/wk, and there is currently no restriction on egg consumption (25); the Food Standards Agency suggests eggs as a good choice in a balanced diet (25), while Australian dietary recommendations limit cholesterol-rich foods but state that eggs are a good choice for healthy individuals with normal blood cholesterol levels (26). In addition, some available country-specific Food and Agriculture Organization food-based dietary guidelines recommend eating eggs regularly (or every day) as part of a healthy diet (27). Several prospective cohort studies have examined the association between egg consumption and risk of total mortality, CHD, and stroke (25,28–34). However, the relation between egg intake and mortality remains controversial. For example, Gou et al. (n = 2512, men, aged 45–59 years) reported a neutral impact of egg consumption on all-cause death (28), whereas both Nakamura et al. (n = 4,686, female, aged ≥30 years) and Djoussé et al. reported detrimental effects of egg intake on total mortality (29,30). Similar results have been found in other studies (31,32). Stroke mortality data are also controversial. For example, Sauvaget et al. and Scrafford et al. (25,34) observed a link between egg consumption and stroke mortality, whereas other studies reported no such association (31,33).

Therefore, given the paucity of data, controversial results, and clinical importance of the issue with CHD and stroke being leading causes of death, we prospectively examined the relationship between egg consumption and all-cause and cause-specific (CHD and stroke) mortality in a large and nationally representative cohort in the United States. Furthermore, we performed a comprehensive systematic review and meta-analysis to examine associations of egg intake with all-cause and cause-specific mortality (CHD and stroke) by using existing prospective cohort studies.

Methods

Original data

Population

This was a prospective cohort study using data from the U.S. National Health and Nutrition Examination Survey (NHANES). The National Center for Health Statistics Research Ethics Review Board approved the underlying protocol, and written informed consent was obtained from all participants. The current study is based on the analysis of data for two 2-year NHANES survey cycles between 1999 and 2010, restricted to participants aged ≥ 20 years. Details on NHANES Laboratory/Medical Technologists Procedures and Anthropometry Procedures are described elsewhere (35,36).

A digital scale was used to measure weight to the nearest 100 g and a fixed stadiometer to measure height to the nearest mm. Body mass index (BMI) was calculated as weight in kg divided by the square of height in m. Waist circumference (WC) was measured at the iliac crest to the nearest mm, using a steel tape (37).

A blood specimen was drawn from the participant's antecubital vein. Glycated hemoglobin (HbA_{1c}) was measured using a Tosoh A1C 2.2 Plus Glycohemoglobin Analyzer (Tosoh Bioscience). Fasting blood glucose (FBG) was measured by a hexokinase method using a Roche/Hitachi 911 Analyzer and Roche Modular P Chemistry Analyzer. Insulin was measured using an enzyme-linked immunosorbent assay (Mercodia) (38). Other laboratory test details are available in the NHANES Laboratory/Medical Technologists Procedures Manual (39). The homeostatic model assessment of insulin resistance (HOMA-IR) was calculated as [FBG (mg/dL) * insulin (mU/mL) / 22.5] using fasting values (40). Details on C-reactive protein (CRP) measurement are available elsewhere (37). The anthropometrically predicted visceral adipose tissue was predicted with gender-specific validated equations that included age, BMI, WC, and thigh

circumference (41). The equation for men was 6 * WC – 4.41 * proximal thigh circumference + 1.19 * age – 213.65, and the equation for women was 2.15 * WC – 3.63 * proximal thigh + 1.46 * age +6:22 * BMI −92.713 (41). Triglyceride (TG) to HDL-C ratio was calculated as the ratio of TG (mg/dL) to HDL-C (mg/dL). In addition, we used the National Cholesterol Education Program's Adult Treatment Panel III report criteria to define metabolic syndrome (MetS) (42), which is a cluster of cardiometabolic risk factors. A participant with ≥3 of the following 5 criteria was classified as having MetS: (1) WC ≥102 cm for men or ≥88 cm for women; (2) TG ≥150 mg/dL; (3) HDL-C < 40 mg/dL for men or <50 mg/dL for women; (4) systolic blood pressure (SBP) ≥ 130 or diastolic blood pressure (DBP) ≥ 85 mmHg; and (5) FBG ≥100 mg/dL. Hypertension (HTN) was diagnosed in individuals with SBP ≥140 mm Hg and/or DBP ≥90 mm Hg and in participants on antihypertension medications (43). Type 2 diabetes (T2DM) was defined as a self-reported history of diabetes or FBG ≥126 mg/dL (44).

Dietary intake was assessed via 24-hour recall obtained by a trained interviewer, with the use of a computer-assisted dietary interview system with standardized probes, i.e., the United States Department of Agriculture Automated Multiple-Pass Method (AMPM) (45,46). Briefly, the type and quantity of all foods and beverages consumed in a single 24-hour period before the dietary interview (from midnight to midnight) were collected using the AMPM. The AMPM is designed to enhance complete and accurate data collection while reducing respondent burden (46,47). Egg consumption was defined as consumption of foods primarily composed of whole eggs (eggs used in baking were not included). The USDA Food and Nutrient Databases for Dietary Studies (versions 2.0, 3.0, and 4.0) were used to identify 73 food codes that contained whole eggs (food codes 31101010–32202200).

Mortality

The anonymized data of NHANES 1999–2010 participants were linked to longitudinal Medicare and mortality data using the NHANES assigned sequence number. Mortality follow-up data are available from the date of survey participation until December 31, 2011. We examined all-cause mortality, as well as mortality due to CHD (I00–I09, I11, I13, I20–I51) and cerebrovascular disease (I60–I69). Cause of death was determined using the 10th revision of the International Classification of Diseases.

Statistical analysis

Analyses were conducted according to the guidelines set by the Centers for Disease Control and Prevention for analysis of the NHANES data set, accounting for the masked variance and using their suggested weighting methodology (48). Continuous and categorical demographic variables were compared across egg consumption using analysis of variance and Chi-square tests, respectively. We compared adjusted (for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, and intake of fiber and meat) mean of cardiometabolic factors across egg intake categories using the analysis of covariance. Adjusted (for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, and intake of fiber and meat) logistic regression was used to determine the risk of HTN, T2DM, and MetS across egg consumption categories and results were expressed as odds ratio (OR) and 95% confidence intervals (95% CIs).

Multivariable Cox proportional hazards were applied to determine the hazard ratios (HRs) and 95% CIs of mortality (total, CHD, and cerebrovascular) for egg consumption; the first tertile (T1) was always used as reference. To derive the HR and 95% CI we performed two different models: Model 1 adjusted for age, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, intake of fiber and meat, and Model 2 adjusted for age, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, intake of fiber and meat, BMI, HTN, and T2DM. A two-sided $p < 0.05$ was used to characterize significant results. Data were analyzed using the SPSS complex sample module version 22.0 (IBM Corp).

Systematic review, meta-analysis

Literature search and study selection

This meta-analysis was designed, conducted, and reported according to Meta-analysis of Observational Studies in Epidemiology guidelines (49). The primary exposure of interest was egg consumption, whereas the primary outcome of interest was changes in total and cause-specific mortality subsequent to egg intake. Prospective cohort studies published up to December 2017 (without language restriction) were searched using PubMed, Embase, and Scopus databases. The query syntax of searching is shown in the Supplemental Methods (Supplementary Table 1). This was complemented by hand searches of the reference list of eligible articles and email correspondence with authors for additional relevant data.

After excluding duplicates and based on titles and abstracts, we excluded studies on animals, those with baseline age ≥18 years, or those with populations with prior CHD, T2DM, or any other chronic disease. Eligible studies were selected by using predefined inclusion criteria of prospective cohort studies, healthy populations, and original articles on the association of egg consumption and all-cause and cause-specific mortality (CHD and cerebrovascular). In addition, supplementary hand searching of reference lists of previous reviews or meta-analyses was conducted. Of 18 eligible full articles, 7 articles met the inclusion criteria (Figure 1).

Study Selection

Study selection started with the removal of duplicates, followed by screening of titles and abstracts by two reviewers (MM and NK). To avoid bias, the reviewers were blinded to

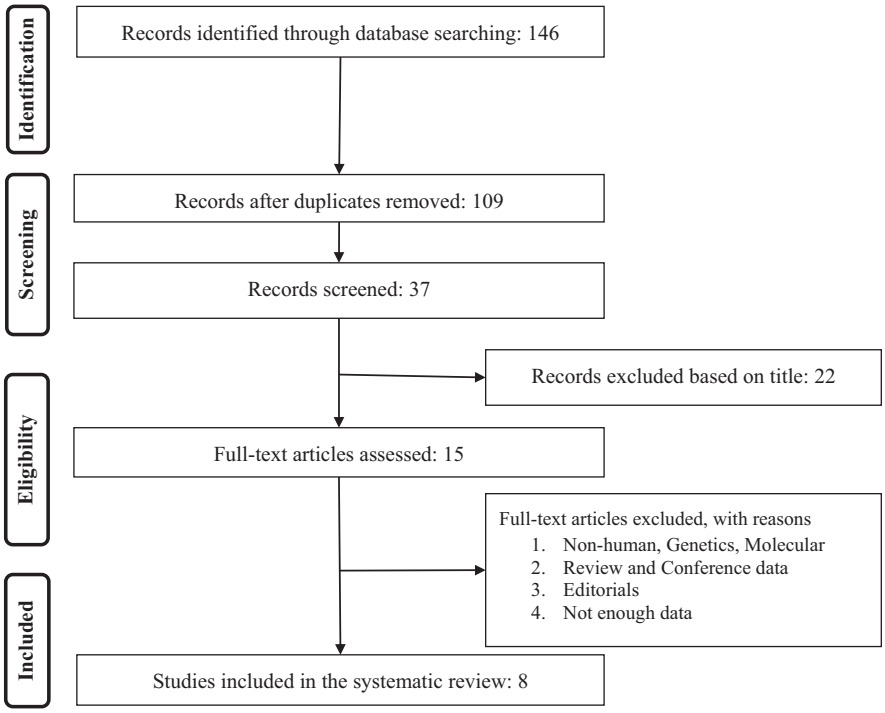

Figure 1. Flowchart of literature search for meta-analysis on egg intake with total and cause-specific mortality for the studies selection.

the names, qualifications, or institutional affiliations of the study authors. The agreement between the reviewers was excellent (Kappa index: 0.90; $p < 0.001$). Disagreements were resolved at a meeting between reviewers and third reviewer (MB) prior to selected articles being retrieved (a flowchart is available in Figure 1). We included studies if they met all the following criteria: (1) evaluated dairy product intake, (2) were population-based cohort studies and reported mortality data, and (3) relative risk (RR), HR, or OR estimates with 95% CIs adjusted for multivariable factors were available or could be calculated. Studies were excluded according to the following criteria: (1) reviews, letters, unpublished data or comments, (2) those published in languages other than English, (3) not population-based cohort studies, and (4) RR, HR, or OR estimates with 95% CI were not available or could not be calculated. Narrative reviews, comments, opinion pieces, editorials, letters, or any other publications lacking primary data and/or explicit method descriptions were also excluded.

Data extraction and management

The full text of studies meeting inclusion criteria was retrieved and screened to determine eligibility by two reviewers (MM and PR). The study quality assessment was performed according to the Newcastle-Ottawa Scale (NOS, Supplementary Table 2) (50). By evaluation of selection, comparability, and outcome, the rating system scores studies from 0 (highest degree of bias) to 9 (lowest degree of bias). In addition, we investigated the funding sources of the eligible studies. Following assessment of methodological quality, the two reviewers extracted data using a purpose-designed data extraction form and independent summaries of what they consider to be the most important results from each study. These summaries were compared and any differences of opinion were resolved by discussion and consultation with a third reviewer (MB). Any further calculations on study data considered necessary were conducted by the first reviewer and checked by the second reviewer. Information extracted from each eligible study included the following items: author, year and references, country, study name, men (%), age, follow-up time (years), number of cases, number of participants, exposure categories, outcome, and main confounders (Table 1).

Data synthesis and statistical analyses

For studies that reported results from different multivariable-adjusted models, the model with the most confounding factors was extracted for the meta-analysis. The random-effect model was applied to calculate pooled RRs, 95% CI, and p value for heterogeneity. RRs comparing the highest score category with the lowest category were combined across studies to generate the summary associations. The extent of heterogeneity across studies was examined using the I^2 test (51–53); an $I^2 > 50\%$ together with a two-sided $p < 0.05$ indicated significant heterogeneity (51–53).

Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation, and Egger's weighted regression tests. Duval and Tweedie 'trim method was used to adjust the analysis for the effects of publication bias (54). Meta-analysis was conducted using the Comprehensive Meta-Analysis V3 software (Biostat) (55).

Table 1. Characteristics of the Prospective Cohort Studies Included in the Present Meta-Analysis.

Author, Year, and Reference	Country, Region/Cohort	Men (%)	Age	Follow-Up Time (Years)	No. of Cases	No. of Participants	Exposure Categories	Outcome	Main Confounders
Mann et al., 1997 (1)	UK	38.0	16–79	13.3	64	10,802	$<$ 1/wk, 1–5/wk, $\geq$ 6/wk	Total death	Age, sex, smoking, and all-cause social class
Sauvaget et al., 2003 (2)	Life Span Study, Japan	38.3	34–103	16.0	1462	37,130	Never, $\leq$ 1/wk, 2–4/wk, almost daily	Stroke death	Hazard ratios stratified by sex and birth cohort and adjusted for city, radiation dose, body mass index (BMI), smoking status, alcohol habits, education level, history of diabetes (T2DM), or hypertension
Nakamura et al., 2004 (3)	NIPPON DATA80, Japan	100	50.3	13.0	39,112	4077	$<$ 1/wk, 1–2/wk, 0.5/d, 1/d	Coronary heart disease (CHD) death, stroke death	Age, serum creatinine, total cholesterol, blood glucose, BMI, systolic and diastolic blood pressure (BP), use of BP-lowering drugs, cigarette smoking, and alcohol intake
Nakamura et al., 2004 (3)	National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged 80, Japan	0	50.7	13.3	41,107	5186	$<$ 1/wk, 1–2/wk, 0.5/d, 1/d	CHD death, stroke death	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 (4)	National Health and Nutrition Examination Survey–I, USA	38.6	25–74	16.6	3,117,655	9734	$<$ 1/wk, 1–6/wk, $\geq$ 7/wk	Total death, stroke death	Age, sex, race-ethnicity, systolic BP, T2DM, serum cholesterol, cigarette smoking, BMI, and education status
Djousse et al., 2008 (5)	Physicians' Health Study, USA	100	40–86	20.0	5169	21,327	$<$ 1/wk,1/wk, 2–4/wk, 5–6/wk, $\geq$ 7/wk	Total death	Age, BMI, smoking, history of hypertension, vitamin intake, alcohol consumption, vegetable consumption, breakfast cereal, physical activity, treatment arm a-fib, T2DM, hypercholesterolemia, and parental history of premature myocardial infarction
Scrafford et al., 2010 (6)	National Health and Nutrition Examination Survey III, USA	100	$>$17	8.8	198, 63	6833	$<$ 1/wk, 1–6/wk, $\geq$ 7/wk	CHD death, stroke death	Age, energy, marital status, education status, race-ethnicity, BMI, T2DM, hypertension, and alcohol intake
Scrafford et al., 2010 (6)	National Health and Nutrition Examination Survey III, USA	0	$>$17	8.9	168, 74	8113	$<$ 1/wk, 1–6/wk, $\geq$ 7/wk	CHD death, stroke death	Age, energy, marital status, education status, race-ethnicity, BMI, diabetes, hypertension, and alcohol intake
Nakamura et al., 2017 (7)	National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged 90, Japan	0	52.8	15.0	599	4686	$>$ 1/w, 1–2/w, 0.5/d, 1/d, $\geq$ 2/d	Total mortality	Age, BMI, hypertension, diabetes, cigarette smoking, alcohol drinking, dyslipidemia therapy, and intake of fiber, meat, and sodium
Guo et al., 2017(8)	Caerphilly prospective cohort study, UK	100	45–59	22.8	1028	2512	$0 \leq n \leq 1$, $1 < n \leq 2$, $2 < n \leq 3$, $3 < n < 5$, $n \geq 5$ eggs/wk	Total mortality	Age, BMI, total energy intake, alcohol consumption, smoking, energy expenditure, social class, family history of myocardial infarction, T2DM, sugar intake , fruit consumption, red meat consumption and fiber intake

Table 2. Characteristics of the Study Participants Based on Egg Consumption.

		Egg Consumption			
		T1 (n = 8,756)	T2 (n = 7,489)	T3 (n = 7,261)	*p* Value
Age (years)		46.7 ± 0.2	47.6 ± 0.2	48.1 ± 0.2	< 0.001
Gender	**Men** (%)	46.7	46.5	59.2	< 0.001
	Women (%)	53.3	53.5	47.1	
Race/ethnicity	**Mexican-American** (%)	19.4	16.5	21.2	< 0.001
	Non-Hispanic White (%)	47.6	42.3	44.6	
	Non-Hispanic Black (%)	18.3	22.3	22.3	
Marital status	**Married** (%)	48.8	51.2	54.2	< 0.001
	Widowed (%)	8.4	8.4	8.5	
	Divorced (%)	10.5	10.5	9.8	
Education status	**Less than high school** (%)	27.4	26.6	27.1	< 0.001
	Completed high school (%)	24.1	24.7	22.9	
	More than high school (%)	45.2	48.5	47.6	

Groups across the quartiles were compared by either chi-square or analysis of variance. Values expressed as mean ± standard error of mean or %.

Table 3. Age, Gender, Race, Education, Marital Status, Poverty to Income Ratio, Total Energy Intake, Physical Activity, Smoking, Alcohol Consumption, Intake of Fiber and Meat Adjusted Characteristics of the Study Participants by Egg Consumption.

	Egg Consumption			
	T1 (n = 8756)	T2 (n = 7489)	T3 (n = 7261)	Trend *p* Value
Body mass index (kg/m^2)	28.9 ± 0.1	28.8 ± 0.1	29.0 ± 0.1	0.235
Waist circumference (cm)	98.5 ± 0.4	98.7 ± 0.3	97.6 ± 0.4	0.425
apVAT	182.3 ± 3.4	181.5 ± 2.5	18.9 ± 2.6	0.341
Systolic blood pressure (mm Hg)	122.2 ± 0.3	123.0 ± 0.4	123.8 ± 0.3	< 0.001
Diastolic blood pressure (mm Hg)	68.3 ± 0.4	68.5 ± 0.39	69.8 ± 0.3	< 0.001
Triglycerides (mg/dl)	155.2 ± 3.5	156.8 ± 2.7	156.3 ± 4.1	0.246
High-density lipoprotein cholesterol (mg/dl)	51.9 ± 0.4	52.0 ± 0.4	51.8 ± 0.3	0.328
TG to HDL	3.74 ± 0.1	3.65 ± 0.09	3.68 ± 0.1	0.418
Fasting blood glucose (mg/dl)	99.3 ± 0.6	99.8 ± 0.7	100.1 ± 0.8	0.038
Insulin	13.1 ± 0.2	13.5 ± 0.2	13.9 ± 0.3	< 0.001
HOMA-IR	0.74 ± 0.03	0.89 ± 0.03	1.11 ± 0.02	< 0.001
HbA1c (%)	5.52 ± 0.02	5.67 ± 0.02	5.72 ± 0.02	0.022
CRP (mg/dl)	0.38 ± 0.01	0.40 ± 0.01	0.43 ± 0.01	0.037

Note. Adjusted means were compared across egg consumption by using analysis of covariance.
HOMA-IR = homeostatic model assessment of insulin resistance; apVAT = anthropometrically predicted visceral adipose tissue; TG to HDL = triglycerides to high-density lipoprotein; CRP = C-reactive protein; HbA1c = glycated hemoglobin.

Results

Original data

Overall, 23,524 participants were included, with a mean age of 47.7 years; 48.7% were men. Their demographic characteristics are shown in Table 2. Participants with a higher intake of eggs were significantly older than the lower egg consumption category (46.7 vs. 48.1 years, $p < 0.001$, Table 2). For the lowest and medium category of egg consumption, females were the majority, while males were the majority in the highest category (male: 59.2 vs. female: 47.1, $p < 0.001$).

Across increasing intake of egg, adjusted (for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, and intake of fiber and meat) mean levels of cardiometabolic risk factors were worsening. For example, SBP and DBP rose with increasing egg intake (highest vs. lowest intake: SBP = 123.8 vs. 122.2 mm Hg and DBP = 69.8 vs. 68.3 mm Hg, $p < 0.001$, Table 2). Markers of glucose/insulin homeostasis such as FBG, insulin, HOMA-IR, and HbA_{1c} were also worse for participants with the highest egg consumption compared with those with the lowest category ($p < 0.022$ for all comparisons, Table 2). For example, from the lowest to the highest category of egg intake, FBG and HbA_{1c} increased from 99.3 to 100.1 mg/dl and from 5.52% to 5.72%, respectively ($p < 0.022$ for both comparisons, Table 2). TG, HDL-C, and TG to HDL-C ratio did not change across egg consumption categories ($p > 0.246$). We also found that participants with a higher intake of eggs had higher CRP levels compared with the lowest category (0.43 vs. 0.38 mg/dL, $p = 0.037$, Table 2).

By applying on multiple logistic regressions (adjusted for age, gender, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, and intake of fiber and meat), we found that, compared with participants in the lowest egg consumption category, those with the highest egg consumption (T3) had a greater risk of T2DM (T2: OR = 1.17; 95% CI, 0.99–1.60; T3: OR = 1.30; 95% CI, 1.05–1.62; $p = 0.029$) and HTN (T2: OR = 1.20; 95% CI, 1.07–1.35; T3: OR = 1.48; 95% CI, 1.16–1.93; $p < 0.001$). No link was found between categories of egg consumption and risk of MetS ($p = 0.112$).

Results from multivariable Cox regression models for risk of death (total, CHD, and stroke) across egg consumption categories are shown in Table 3. With regard to total mortality, in Model 1, males with the highest egg consumption had a 42% greater risk of mortality (HR = 1.42; 95% CI, 1.27–1.96); this link disappeared in Model 2 (HR = 1.06; 95% CI, 0.71–1.57; $p = 0.245$; Table 3). Furthermore, we found no significant association between egg intake and total mortality in females (Model 2: HR = 1.12; 95% CI,

Table 4. Gender-Stratified Multivariable-Adjusted Hazard Ratios (95% Confidence Intervals) for Mortality Across Groups of Egg Consumption.

		Egg Consumption							
		Male			*p* Value	Female			*p* Value
Total mortality	**Model 1**	*1 (Reference)*	1.23 (1.11–1.43)	1.42 (1.27–1.96)	< 0.001	*1 (Reference)*	1.10 (0.98–1.42)	1.22 (0.95–1.63)	0.069
	Model 2	*1 (Reference)*	0.88 (0.35–2.61)	1.06 (0.71–1.57)	0.245	*1 (Reference)*	1.06 (0.62–1.49)	1.12 (0.72–1.76)	0.087
Coronary heart disease mortality	**Model 1**	*1 (Reference)*	1.12 (0.52–1.35)	1.22 (0.31–3.60)	0.152	*1 (Reference)*	0.98 (0.50–1.90)	1.03 (0.25–4.22)	0.421
	Model 2	*1 (Reference)*	1.10 (0.58–2.13)	1.03 (0.50–2.16)	0.327	*1 (Reference)*	1.05 (0.55–2.01)	1.23 (0.38–3.91)	0.362
Cerebrovascular disease mortality	**Model 1**	*1 (Reference)*	0.99 (0.51–2.49)	0.28 (0.10–0.75)	< 0.001	*1 (Reference)*	0.95 (0.49–1.96)	0.98 (0.52–2.11)	0.128
	Model 2	*1 (Reference)*	1.05 (0.45–2.23)	0.34 (0.13–0.85)	< 0.001	*1 (Reference)*	1.02 (0.29–3.96)	0.96 (0.40–2.13)	0.249

Note. Model 1 = adjusted for age, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, and intake of fiber, meat, and sodium.
Model 2 = adjusted for age, race, education, marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, intake of fiber and meat, body mass index, hypertension, and diabetes.

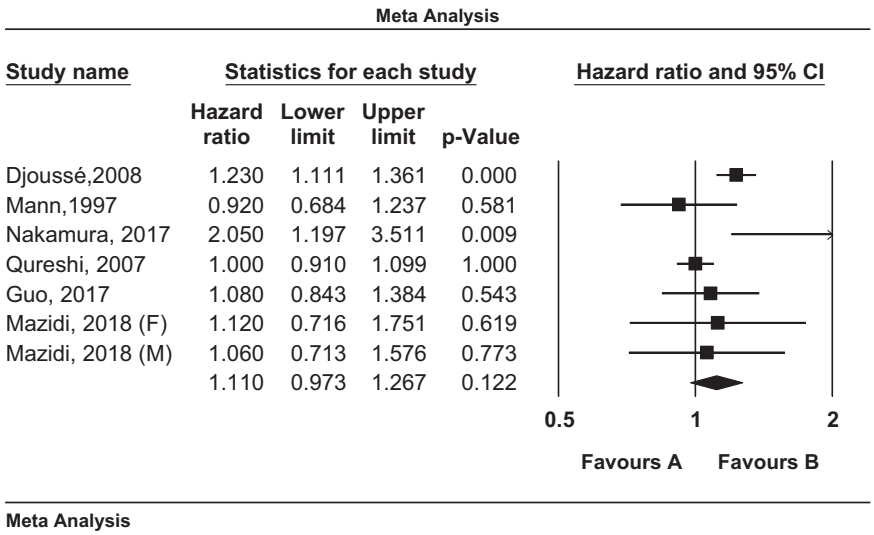

Figure 2. Forest plot of egg consumption and risk of total mortality.

0.72–1.76; $p = 0.087$; Table 3). Egg consumption could not predict CHD mortality in both males and females ($p < 0.125$), as well as cerebrovascular disease mortality in females (Model 2: HR = 0.96; 95% CI, 0.40–2.13; $p = 0.249$; Table 3). In males, egg intake had a reverse and significant association with cerebrovascular disease mortality; for example, in Model 2, participants with the highest egg intake had a 66% lower risk of cerebrovascular disease mortality (HR = 0.34; 95% CI, 0.13–0.85; Table 3).

We have evaluated the HR of the total, CHD, and cerebrovascular disease mortality for the participants with T2DM (Model 2), and it turns out that those with T2DM have 16.5% higher risk of total and CHD mortality. However, there was a reverse and significant link between cerebrovascular disease mortality and egg consumption (−23%).

Systematic review and meta-analysis

An overview of key characteristics of the 10 prospective cohort studies is shown in Table 1. A total of 110,400 participants, with 12,896 mortality cases, were included in the analysis. A total of five studies presented gender-specific results (25,28–30,33). The duration of follow-up ranged from 8.8 to 22.8 years, with a mean follow-up of 15.6 years. Results of quality assessment are shown in the Supplemental Table 2, with five studies scoring 8 and three scoring 9.

Egg Consumption and total and cause-specific mortality

The results of pooling data from published prospective studies that evaluated the link between egg consumption and total and cause-specific mortality are shown in Figures 2–4. We found a positive but nonsignificant association between egg consumption and total mortality (HR = 1.11; 95% CI, 0.97–1.26; $p = 0.122$; n = 7 studies; Figure 2), with no chance of heterogeneity ($I^2 = 15.1$, $p = 0.849$). The results from pooling data showed that egg intake could not predict CHD mortality (HR = 1.23; 95% CI, 0.88–1.77; $p = 0.214$; n = 6 studies; Figure 3; $I^2 = 10.3$, $p = 0.895$), whereas we observed a reverse and significant association between egg intake and stroke mortality, with no chance of heterogeneity (HR = 0.72; 95% CI, 0.54–0.96; $p = 0.026$; n = 8 studies; Figure 4; $I^2 = 9.6$; $p = 0.922$).

Sensitivity analysis

In leave-one-out sensitivity analyses, the pooled effect estimates remained similar for the impact of egg consumption on total mortality (HR = 1.11; 95% CI, 0.97–1.26; $p = 0.122$), CHD mortality (HR = 1.23; 95% CI, 0.88–1.77; $p = 0.214$), and stroke mortality (HR = 0.72; 95% CI, 0.54–0.96; $p = 0.026$). This stability confirms that the significant difference between the studied groups is the overall effect of all included studies.

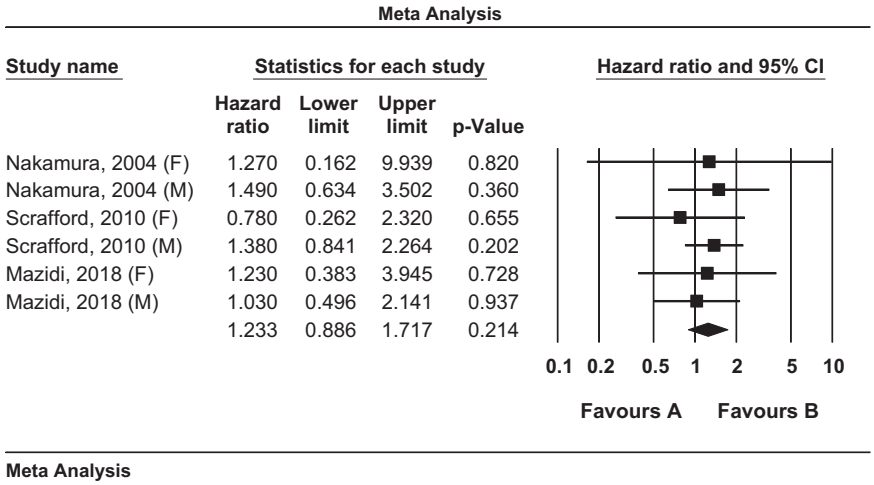

Figure 3. Forest plot of egg consumption and risk of coronary heart disease mortality.

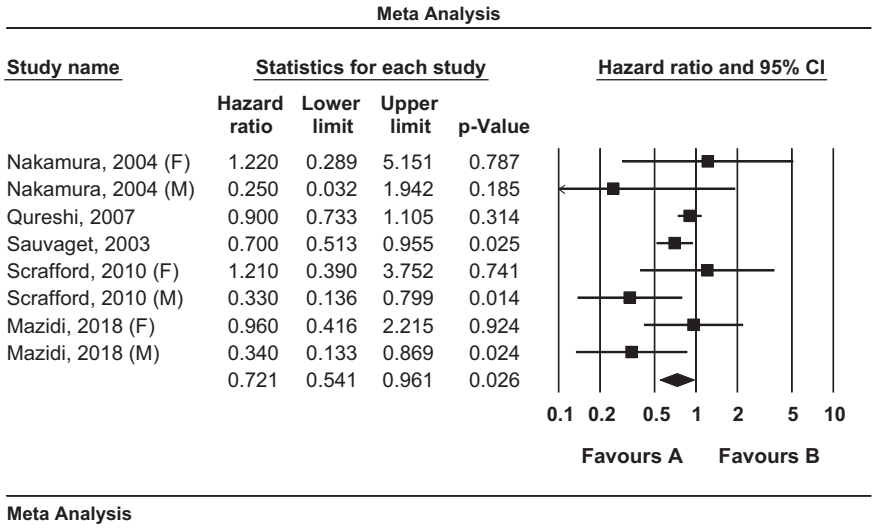

Figure 4. Forest plot of egg consumption and risk of stroke mortality.

Publication bias

Visual inspection of funnel plot symmetry suggested no potential publication bias for the comparison of egg consumption and total mortality (Figure supplementary 1). Furthermore, both Egger's linear regression (intercept = 0.461; 95% CI, −2.45 to 3.37; $p = 0.701$) and Begg's rank correlation test (Kendall's Tau with continuity correction = 0.285, z = 0.901, $p = 0.367$) were not indicative of publication bias. After adjustment of effect size for potential publication bias using the "trim and fill" correction, no potentially missing studies were imputed in the funnel plot (Figure supplementary 2). The "fail-safe N" test showed that 44 studies would be needed to bring the weighted mean difference down to a non-significant ($p \geq 0.05$) value.

Discussion

We used a large and nationally representative sample of U.S. adults and also pooled all published prospective studies to evaluate the impact of egg consumption on total and cause-specific mortality. The link between egg intake and total mortality in males disappeared after adjustment for more confounders. No associations between total mortality and egg consumption were observed in females or between CHD mortality and egg intake in either gender. Egg consumption was associated with a lower risk of stroke mortality only in males, which was further supported by pooling studies together. These results were more pronounced among those with T2DM. The results of pooling data from published prospective studies indicated a neutral effect of egg intake on total and CHD mortality. Furthermore, egg consumption was negatively related to FBG, HbA_{1c}, HOMA-IR, blood pressure, and CRP. These effects require long-term consideration and may, to some extent, contribute to the observed association between egg intake and the likelihood of T2DM and HTN. The association between egg intake and T2DM and HTN was robust after further adjustments.

A recent study (28) (n = 2512, United Kingdom, 22.8 years follow-up) reported no link between CVD mortality and egg intake, which is supported by previous meta-analyses and studies (8, 14, 56–58). Our findings either from individual data or pooling studies further supported the null association between egg consumption and CHD mortality. Conversely, the HR of heart failure was 1.33 (95% CI, 1.04–1.70) with egg

consumption ≥7/wk compared with that of <1/wk over 20 years of follow-up for physicians free of previous myocardial infarction as shown in the Physicians' Health Study (PHS) (30). In accordance with our findings, a recent study (n = 4686, Japan, 15.0 years follow-up) found that egg consumption was not associated with CVD mortality (29).

The PHS reported a significant positive relationship between egg consumption and all-cause mortality (30). We also found a significant and positive link between total mortality and egg intake (Model 1); however, this link disappeared after further adjustments (Model 2). The difference in the observed association of egg consumption and all-cause mortality between the current study and the PHS may be due to differences in participant characteristics. Briefly, the PHS study recruited physicians (30), whereas in the present study participants were randomly selected and represented a national sample of U.S. adults with different levels of education.

We have found that egg intake is associated with lower stroke mortality in males, but not females. This result is supported by some previous studies (25,28,31,34,59). A similar inverse association was observed in the Life Span Study that followed survivors of the Hiroshima/Nagasaki bombings between consumption of eggs and stroke (34). However, they found a significant reduction in stroke risk both in men and women (34). Conflicting results were also observed in previous prospective studies (30,31,57). They are some hypotheses of mechanism, within which eggs might decrease stroke risk. Eggs provide arginine, a precursor to nitric oxide, which plays a central role in endothelial function (60,61). Eggs are also a rich source of some beneficial dietary components such as vitamins, minerals, and carotenoids (62)—factors that may have protective effects on stroke mortality. The present study is consistent with earlier studies showing no adverse effects of egg consumption on the lipid profile (63,64). A recent study also reported no change in TC after egg intake (29). Findings from a 3-month RCT showed that there was no negative effect of higher egg consumption (>12 eggs/wk) on blood lipid profile compared with low egg intake (<2 eggs/wk) (65).

Our findings on blood pressure are similar to what was observed in two trials (66,67), although this needs confirmation in randomized controlled dietary intervention trials. We observed that egg intake increased the likelihood of T2DM. An earlier study also showed that higher egg consumption was associated with elevated FBG in 394 middle-aged healthy men (68). This was also supported by another cross-sectional analysis that observed significant positive relationships between egg consumption and FBG, insulin, or insulin resistance (30). Randomized trials with diets rich in egg consumption (2–3 eggs/d for 6–12 weeks) have generally found no change in FBG levels (65,69,70), postprandial response to glucose (70), HbA_{1c} (65,70) or fasting insulin levels (70). Several recent studies in European (71,72), Asian (73), and U.S. (74) populations reported no association or an inverse association between egg consumption and glucose homeostasis (75).

Our study may have public health implications. With regard to mortality, we found either a neutral or a beneficial impact of egg intake. Excluding eggs from diets of patients with CVD as per the current AHA dietary recommendations (17) could potentially lead to alternate choices high in starch and sugar, potentially associated with increased CVD morbidity and mortality. The protein content of eggs is associated with a high satiety index and, thus, eggs may be of benefit in obesity (62). Furthermore, eggs provide a relatively inexpensive source of amino acids and essential fatty acids (76).

Our study has important limitations, for example, lack of information on consumption of egg white, egg yolk, or both. Another limitation is that egg consumption as well as other dietary factors and covariates were assessed with a self-administered questionnaire at a single time point, which inevitably led to a degree of misclassification. Food preparation methods (e.g., boiled or fried eggs, whole eggs or only egg whites) are also important factors. Moreover, the observational design with regression adjustment means that we cannot exclude the possibility that our findings may be influenced by unmeasured or residual confounding. In addition, cooking methods and information on how eggs were consumed (i.e., with what other foods) was not recorded (77). Furthermore, the lack of standardization of eggs type is an important issue (e.g., the weight and cholesterol content of the eggs is largely variable depending on chicken type, breeding, and feeding). Although our analysis was corrected for several covariates, we still need to mention that it would be better for future studies to consider more variables or use a different study design to minimize the impact of other factors.

The strength of the present study is that the analysis was mainly based on long-term large population-based data originating from multiple nations and was performed with a high level of precision using a random-effect model method. Furthermore, we performed a meta-analysis, pooling all the published studies which could reinforce our results and their validity. Heterogeneity of the results of the component studies was low, which indicated that each result was consistent and most variation was attributable to chance alone. The availability of detailed data on covariates allowed us to better control for confounding. We used a validated food frequency questionnaire, and our data were collected by trained personnel in settings, which allows us to report health data accurately.

In conclusion, the present study highlighted the potential role of egg consumption on total and cause-specific mortality. According to our findings, egg intake was not associated with CHD and total mortality, whereas it was a associated with decreased risk of mortality from stroke. Furthermore, egg consumption was associated with T2DM, HTN, CRP, and markers of glucose/insulin homeostasis. If confirmed in clinical trials (causation), this knowledge may have application for both population-wide and high-risk approaches to mortality prevention and control.

Acknowledgments

The material presented in this article is original and has not been submitted for publication elsewhere.

Conflict of interest statement

NK has given talks, attended conferences, and participated in trials sponsored by Amgen, Angelini, AstraZeneca, Boehringer Ingelheim, MSD, Novartis, Novo Nordisk, Sanofi, and WinMedica. DPM has given talks and attended conferences sponsored by MSD, AstraZeneca, and Libytec. The other authors have no conflict of interest to declare.

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