


Egg consumption and risks of all-cause and cause-specific mortality: a dose–response meta-analysis of prospective cohort studies

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Context: Current dietary guidelines recommend eggs as a part of a healthy diet. However, whether egg consumption is associated with risk of mortality remains controversial. Moreover, the dose-response association of egg consumption with risk of mortality has not been determined. **Objective:** To determine the potential dose-response association of egg consumption with risk of mortality in the general population. **Data Sources:** The PubMed and Embase databases were searched for publications meeting eligibility criteria through November 2021. **Data Extraction:** Required data were extracted by 1 reviewer and then checked for accuracy by another reviewer. A random-effects dose-response meta-regression model was used to calculate the pooled risk estimates. A restricted cubic spline model was used to test nonlinearity. The certainty of evidence was assessed using the GRADE system. **Data Analysis:** Nineteen prospective cohort studies, involving 1 737 893 participants, were included. The pooled hazard ratios for an increase of 1 egg/d were 1.08 (95%CI, 1.01–1.15) for all-cause mortality, 1.07 (95%CI, 0.97–1.18) for cardiovascular disease–caused mortality, and 1.16 (95%CI, 1.04–1.30) for cancer-caused mortality. The certainty of evidence for these observations was rated as very low. Nonlinear dose-response associations were found for egg consumption and all-cause, cardiovascular disease–caused, and cancer-caused mortality. Moreover, the positive association between egg consumption and all-cause mortality was more pronounced in studies with adjustment for blood cholesterol-related covariates than those without ($P_{interaction} = 0.011$). **Conclusions:** Greater amount of egg consumption confers higher risks of death from all causes, cardiovascular disease, and cancer in a nonlinear dose-response pattern. These findings should be treated with caution and need to be confirmed by future studies.

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Key words: cancer, cardiovascular disease, dose-response meta-analysis, egg consumption, mortality.

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INTRODUCTION

Eggs are a common and inexpensive food in daily life and are rich in high-quality proteins and micronutrients (eg, vitamins and minerals).¹ Eggs also contain a high amount of cholesterol (~186 mg cholesterol/egg)¹; increasing cholesterol intake is traditionally considered a risk factor for cardiovascular disease.^{2,3} Hence, people have been advised to limit egg consumption, especially yolks, for decades. However, updated dietary guidelines from several countries, including the United States, Japan, and Mexico, have recommended eggs as a part of a healthy diet,^{4,5} because the current evidence does not support a positive association between egg consumption and the risk of cardiovascular disease.^{6–8}

Extensive observational studies have explored the association of egg consumption with risk of mortality, but they have yielded inconclusive results. For example, some studies showed a positive association between egg consumption and risk of all-cause mortality,^{9–14} whereas others revealed no association^{15–19} or even an inverse association.^{20,21} Several meta-analyses have compared the risk of mortality with the highest vs the lowest amount of egg consumption. However, their results are conflicting, with 1 meta-analysis showing a positive association²² and others showing a null association^{8,18,23}; moreover, these meta-analyses included limited studies and lacked detailed subgroup analyses. In addition, the dose-response relationship between egg consumption and risk of mortality has not been determined previously, to our knowledge.

Since the publication of the aforementioned meta-analyses,^{8,18,22,23} the number of original studies on the association of egg consumption and risk of mortality has doubled, indicating the necessity of performing an updated meta-analysis. A better understanding of this association can help the public make choices about and inform guideline makers to formulate recommendations for egg consumption. Hence, with the most up-to-date evidence, we performed this study to determine whether egg consumption is associated with risks of all-cause and cause-specific mortality in the general population.

METHODS

The results of this study were reported following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.²⁴

Search strategy

An electronic search of PubMed and Embase was conducted from the inception dates to November 7, 2021, to identify the potentially eligible studies, with language

restricted to English and Chinese. The search strategies developed by 2 reviewers (P.-F.Y. and W.-P.S.) and a trained librarian (P.Z.) are reported in [Table S1](#) in the Supporting Information online. In addition, the reference lists of relevant articles were scrutinized to identify additional eligible studies. The authors of several studies^{9–11} were contacted to obtain additional data.

Study selection

Prospective cohort studies (including case-cohort studies) on the association between egg consumption and risks of mortality from all causes, cardiovascular disease, cancer, stroke, and/or coronary heart disease in the general population were included if they provided the required data for the dose-response meta-analysis (deaths, person-years, and adjusted risk estimates and 95% CIs for at least 3 categories of egg consumption) ([Table 1](#)). When multiple reports originated from the identical study cohort,^{15,23,25} the report with the longest follow-up length was selected.¹⁵ On the basis of the above eligibility criteria, 2 reviewers (P.-F.Y. and W.-P.S.) first scrutinized title and abstract to exclude apparently irrelevant studies, and then carefully read the full text to further exclude ineligible studies. Any discrepancies were settled by discussion.

Data extraction

The following data were extracted from each eligible study: first author's family name, publication year, study location, study setting, mean age, the number of death, sample size, follow-up length, egg consumption assessment, death assessment, adjustment factors, and the aforementioned data for the dose-response meta-analysis. Data were extracted by 1 reviewer (Y.P.) with a standardized data collection form, and then checked for accuracy by another reviewer (C.-R.W.). Any discrepancies were resolved by discussion.

Risk-of-bias assessment

The risk of bias of included studies was assessed independently by 2 reviewers (Y.P. and C.-R.W.) using the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) tool.²⁶ Briefly, this tool is composed of the following domains: (1) bias due to confounding; (2) bias due to selection of participants; (3) bias due to exposure assessment; (4) bias due to misclassification during follow-up; (5) bias due to missing data; (6) bias due to outcome assessment; and (7) bias due to selective reporting. For each domain, the reviewer's judgments were ranked as low risk, moderate risk, serious risk,

Table 1 PICOS criteria for inclusion of studies

Parameter	Inclusion criterion
Participants	The general population
Intervention/exposure	Egg consumption
Comparison	Extreme quantiles
Outcome	Mortality from all causes, cardiovascular disease, cancer, stroke, and/or coronary heart disease
Study design	Prospective cohort study (including case-cohort study)

critical risk, and no information. Any discrepancies were handled by discussion.

Certainty-of-evidence assessment

The certainty of evidence for each outcome was assessed independently by 2 reviewers (Y.P. and C.-R.W.) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.²⁷ Observational studies were categorized first as being of low certainty, due to their inherent limitations, and then were upgraded or downgraded on the basis of predefined criteria (upgrade criteria: large effect, plausible confounding that would change the effect, and dose-response gradient; downgrade criteria: risk of bias, inconsistency, indirectness, imprecision, and publication bias). The assessment of certainty of evidence was conducted using GRADEpro software (version 3.6; GRADEpro.org). Any discrepancies were resolved by discussion.

Statistical analysis

Hazard ratio (HR) was used as a common measure of the association between egg consumption and risk of mortality. Relative risk was regarded an equivalent to HR in this study.²⁸ In addition, absolute risk difference (ARD) in mortality rate per 10 000 person-years was calculated using the method described previously.²⁹ The Hedges Q statistic ($P < 0.10$ indicates the presence of statistical heterogeneity) and the I^2 statistic ($I^2 > 75.0\%$, 50.0% – 75.0% , and $< 50\%$ suggests high, moderate, and low heterogeneity, respectively) were used to assess statistical heterogeneity qualitatively and quantitatively, respectively. Risk estimates were reported for men and women separately in 1 study,³⁰ so that study was regarded as having 2 independent cohorts. In another 1 study, risk estimates were reported by sex-specific quartiles,¹⁷ so egg consumption for participants in each quartile was estimated on the basis of the data reported for men and women.

We used a random-effects dose-response meta-regression model³¹ to calculate HRs and 95% CIs for an

increase of 1 egg/d, regardless of between-study statistical heterogeneity. This model is based on the amount of egg consumption, the distribution of cases and person-years, and adjusted HRs with 95% CIs for at least 3 quantitative categories. When egg consumption was reported as an interval, the midpoint of lower and upper boundaries was used as the assigned dose for each category. If the highest category was open ended, it was assumed to have the same width as the preceding interval; if the lowest category was open ended, the lower boundary of the category was assumed to be zero. When person-years were not provided by egg consumption category, these data were estimated by multiplying the number of participants in each category with mean or median follow-up duration.^{9,10,14,16,17,19,28,32} When the reference category was not the lowest category,^{13,30,33} the method proposed by Hamling et al³⁴ was used to convert risk estimates. For studies that reported egg consumption in servings or grams, the unit was converted into 1 whole egg with the assumption that 1 whole egg was equivalent to 1 serving size or weighed 50 g. For 1 study that did not report deaths for each quintile,⁹ these values were approximated by dividing the total number of deaths by the number of quintiles (ie, 5).^{22,35} For 1 case-cohort study³⁶ in which only person-years in a subcohort were reported, we estimated person-years for the whole study population on the basis of the available data to meet the requirement of the methodology.

A restricted cubic spline model was used to investigate the potential dose-response association between egg consumption and risk of mortality.³⁷ The number of knots was determined on the basis of the Akaike's information criterion,³⁸ with the lowest value indicating the best fitted model (for all-cause and cancer-caused mortality: 4 knots at the 5th, 35th, 65th, and 95th percentiles; for cardiovascular disease-caused mortality: 3 knots at the 10th, 50th, and 90th percentiles). A probability value for nonlinearity was calculated by testing the hypothesis that the regression coefficient of the second spline equals zero (for models with 3 knots) or the regression coefficients of the second and third splines equal zero (for models with 4 knots).

To identify potential sources of the observed heterogeneity, predefined subgroup analyses were conducted after stratifying for mean age (≥ 60 vs < 60 years), sex (male vs female), study setting (multi-center center vs single center), study location (United States vs Europe vs Asia), risk of bias (moderate vs serious), number of participants ($\geq 10\,000$ vs $< 10\,000$), number of deaths (≥ 5000 vs < 5000), repeated egg-consumption assessment (yes vs no), and adjustment for blood cholesterol, dyslipidemia, or dyslipidemia therapy (yes vs no). A probability value for the interaction

between stratification factors and egg consumption was calculated through meta-regression prior to conducting the subgroup analyses, to avoid spurious subgroup effects. To examine the stability of the pooled results, several sensitivity analyses were conducted, including repeating meta-analysis with a fixed-effects model, omitting 1 study in turn, and using various eligibility criteria.

The Egger linear regression test³⁹ and Begg rank correlation test⁴⁰ were used to evaluate the potential publication bias if there were ≥ 10 included studies. All data analyses were performed with STATA software (version 12.0; StataCorp, College Station, TX). A statistical significance level of $P < 0.05$ was applied to 2-sided tests unless otherwise specified.

RESULTS

Literature search

The electronic search identified 7789 and 8342 records from PubMed and Embase, respectively. After removing duplicates, a total of 9465 records remained. After reading titles and abstracts, an additional 9416 records were excluded, resulting in that 49 records thought to be potentially eligible. Thirty records were excluded after checking the full text (Table S2 in the Supporting Information online provides the primary reason for exclusion). Finally, a total of 19 studies were included (Figure 1).

Study characteristics and quality assessment

The publication year of included studies ranged from 2004 to 2021. Eight studies were performed in the Asia,^{13,18,20,21,28,30,33,41} 6 in the United States,^{9–11,14,15,32} 4 in Europe,^{12,17,19,36} and the remaining 1 in multiple countries.¹⁶ Of 19 included studies, 13^{9–11,13–17,20,30,32,33,41} and 6^{12,18,19,21,28,36} were multicenter and single-center studies, respectively. The mean age of participants varied from 42.9²⁰ to 66.5 years.¹⁶ The sample size of included studies ranged from 2512¹⁹ to 521 120,¹⁰ with a total of 1 737 893 participants. A food frequency questionnaire was used in 14 studies^{9–12,14,16–19,21,28,32,33,36} and 24-h dietary recalls to assess egg consumption were used in 2^{15,20} included studies. The method of outcome assessment mainly included National Death Index, household member reports, death certificates, and medical records. The main characteristics of included studies are summarized in Table 2.^{9–21,28,30,32,33,36,41} On the basis of the risk-of-bias assessment, 6 included studies^{14,17,30,33,36} were judged to be at a serious risk of bias; the remaining

studies were judged to be at a moderate risk of bias (Figure S1 in the Supporting Information online).

Egg consumption and risk of all-cause mortality

Seventeen studies ($n = 19$ cohorts),^{9–21,28,30,33,36} involving 1 179 849 participants and 214 073 all-cause deaths ($n = 16 021 692.2$ person-years), were included in this dose-response meta-analysis. The pooled HR of all-cause mortality for an increase of 1 egg/d was 1.08 (95%CI, 1.01–1.15), with high heterogeneity ($I^2 = 91.3\%$; $P_{\text{heterogeneity}} < 0.001$) (Figure S2 in the Supporting Information online). The corresponding ARD in all-cause mortality rate per 10 000 person-years was 9.90 (95%CI, 1.32–7.43). The restricted cubic spline model revealed a significant nonlinear dose-response association of egg consumption with risk of all-cause mortality ($P_{\text{nonlinearity}} = 0.011$) (Figure 2).

From the subgroup analyses we found that the observed association was not modified by mean age, sex, study setting, study location, risk of bias, number of participants, number of deaths, and repeated egg-consumption assessment (all $P_{\text{interaction}} > 0.05$) (Table 3); however, the positive association of egg consumption with risk of all-cause mortality was significantly more pronounced in studies with adjustment for blood cholesterol, dyslipidemia, or dyslipidemia therapy than those without ($P_{\text{interaction}} = 0.001$). Repeating the analysis with a fixed-effects model (HR, 1.15; 95%CI, 1.13–1.16) and applying various eligibility criteria did not alter the initial association substantially (Table S3 in the Supporting Information online). Also, ignoring 1 study in turn did not materially change the observed association of egg consumption with risk of all-cause mortality, with the pooled HRs ranging from 1.07 (95%CI, 1.00–1.14)¹⁰ to 1.10 (95%CI, 1.03–1.17)²⁰ (Figure S3 in the Supporting Information online). The certainty of evidence for this association was rated as very low (Table S4 in the Supporting Information online). No evidence of publication bias was found using the Begg test and Egger tests (all $P > 0.05$).

Egg consumption and risk of cardiovascular disease-caused mortality

Nine studies ($n = 10$ cohorts)^{10,12,13,16–18,21,32,36} were included in this dose-response meta-analysis, with 56 550 cardiovascular deaths observed in 943 827 participants ($n = 13 412 396.8$ person-years). The summary HR of cardiovascular disease-caused mortality for an increase of 1 egg/d was 1.07 (95%CI, 0.97–1.18), with high heterogeneity ($I^2 = 75.8\%$; $P_{\text{heterogeneity}} < 0.001$) (Figure S4 in the Supporting Information online). The corresponding ARD in cardiovascular disease-caused mortality rate

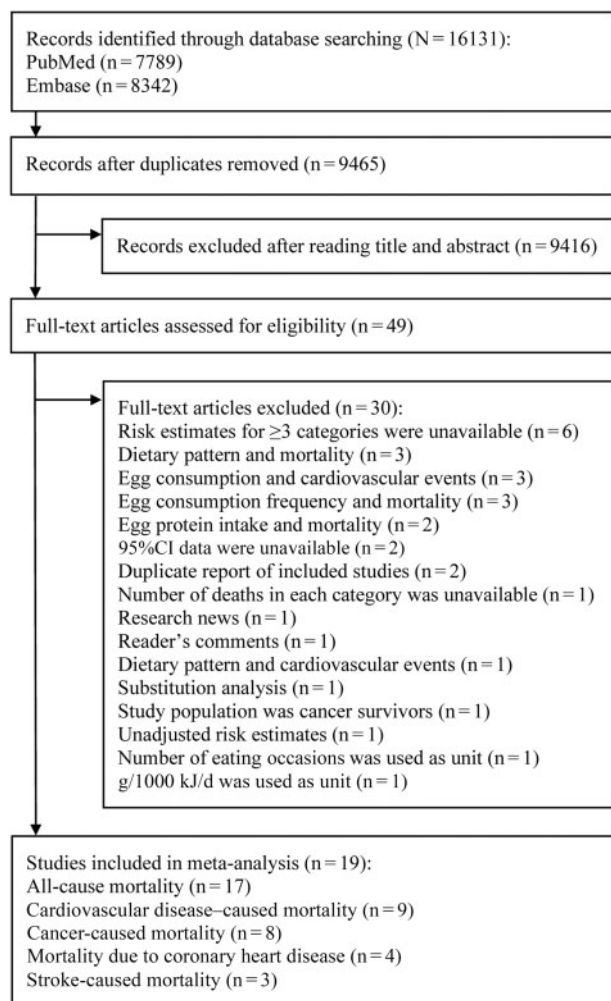


Figure 1 The flow chart of the literature search and identification of included studies.

per 10 000 person-years was 2.76 (95%CI, -1.31 to 6.44). A marginally significant nonlinear dose-response association was found for egg consumption and risk of cardiovascular disease-caused mortality using the restricted cubic spline model ($P_{\text{nonlinearity}} = 0.063$) (Figure 3). Based on limited studies, subgroup analyses showed that the observed association of egg consumption with risk of cardiovascular disease-caused mortality was not significantly modified by the prespecified stratification factors (all $P_{\text{interaction}} > 0.05$) (Table S5 in the Supporting Information online). Moreover, the observed association did not alter materially in sensitivity analyses (Table S6 and Figure S5 in the Supporting Information online).

We also investigated the association between egg consumption and the risk of mortality from stroke and coronary heart disease. Based on 3 studies ($n = 79\,690$ participants and 1067 stroke deaths),^{18,21,30} a significant association between egg consumption and risk of stroke mortality (HR for an increase of 1 egg/d 0.95 [95%CI,

0.84 – 1.06]; ARD in stroke mortality rate per 10 000 person-years, -0.76 [95%CI, -2.76 to 0.82]) (Figure S6 in the Supporting Information online) was not found. Likewise, on the basis of findings from 4 studies ($n = 12\,0311$ participants and 1546 coronary heart disease-caused deaths), a significant association for egg consumption and risk of coronary heart disease-caused mortality (HR for an increase of 1 egg/d 0.90 [95%CI 0.75 – 1.09]; ARD in coronary heart disease mortality rate per 10 000 person-years, -1.16 [95%CI -3.47 to 0.86]) was not found (Figure S7 in the Supporting Information online).^{17,18,21,30} The certainty of evidence for the observed associations of egg consumption with the risk of mortality resulting from cardiovascular disease, stroke, and coronary heart disease was rated as very low (Table S4 in the Supporting Information online).

Egg consumption and risk of cancer-caused mortality

Eight studies ($n = 9$ cohorts)^{10,12,13,17,21,30,32,36} involving 747 511 participants and 59 381 cancer deaths ($n = 11\,725\,075.7$ person-years) were included in this dose-response meta-analysis. The pooled HR of cancer-caused mortality for an increase of 1 egg/d was 1.16 (95%CI, 1.04 – 1.30), with high heterogeneity ($I^2 = 75.9\%$; $P_{\text{heterogeneity}} < 0.001$) (Figure S8 in the Supporting Information online). The corresponding ARD in cancer-caused mortality rate per 10 000 person-years was 6.98 (95%CI, 1.95 – 11.68).

On the basis of the restricted cubic spline model, a significant nonlinear dose-response association was found for egg consumption and risk of cancer-caused mortality ($P_{\text{nonlinearity}} = 0.001$) (Figure 4). No significant interactions between egg consumption and the predefined stratification variables were detected by subgroup analyses (all $P_{\text{interaction}} > 0.05$) (Table S7 in the Supporting Information online). In addition, the positive association between egg consumption and risk of cancer-caused mortality remained in sensitivity analyses (Table S8 and Figure S9 in the Supporting Information online). The certainty of evidence for this association was rated as very low (Table S4 in the Supporting Information online).

DISCUSSION

From this dose-response meta-analysis, we found that a high amount of egg consumption was associated with an increased risk of death from all causes, cardiovascular disease, and cancer in a nonlinear, dose-response manner. These observed associations persisted in sensitivity analyses, indicating the robustness of the results. Subgroup analysis further revealed that the positive

Table 2 Main characteristics of included studies of egg consumption and risk of mortality

Reference; study location; study setting; cohort name	Mean age (y)	Follow-up* (y)	Sample size	Deaths	Exposure assessment	Outcome assessment	Adjustment factors
Zhuang et al (2021) ¹⁰ ; United States; multicenter; NIH-AARP Study	62.2	16.0	T: 521 120; M: 306 419; W: 214 701	All-cause: 129 328; CVD: 38 747; cancer: 45 783	FFQ	National Death Index Plus	Age; sex; race; BMI; educational level; marital status; household income; smoking; alcohol drinking; vigorous physical activity; usual activity at work; history of hypertension, hypercholesterolemia, history of heart disease, stroke, diabetes, and cancer at baseline; total energy intake; egg whites/substitutes; and Healthy Eating Index-2015
Sun et al (2021) ¹¹ ; United States; multicenter; Women's Health Initiative Study	62.8	18.1	T: 102 521; W: 102 521	All-cause: 25 976	FFQ	Death certificate, medical record, autopsy report, or National Death Index	Age, race, educational level, income, study group, unopposed estrogen use, estrogen and progesterone use, smoking status, BMI, physical activity, alcohol intake, total energy intake, baseline diabetes mellitus status, baseline high blood cholesterol status, family history of heart attack or stroke, whole-grain consumption, vegetable consumption, fruit consumption, sugar-sweetened beverage consumption, and mutual adjustment for other protein sources
Ruggiero et al (2021) ¹² ; Italy; single center; Moli-Sani Study	54.0	8.3	T: 20 562; M: 9657; W: 10 905	All-cause: 838; CVD: 271; cancer: 334	FFQ	Death registry	Age; sex; energy intake; educational level; household income; residence; smoking status; BMI; leisure-time physical activity; baseline diabetes, hypertension, and hyperlipidemia; and Mediterranean diet score
Liu et al (2021) ²⁸ ; China; single center; cohort study in Anhui	51.7	14.0	T: 9444; M: 5271; W: 4173	All-cause: 814	FFQ	Telephone or face-to-face interviews with family members, neighbors, or village doctors	Age, sex, smoking, alcohol drinking, systolic blood pressure, diastolic blood pressure, heart rate, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, BMI, education level, fruit consumption, vegetable consumption, milk

(continued)

Table 2 Continued

Reference; study location; study setting; cohort name	Mean age (y)	Follow-up* (y)	Sample size	Deaths	Exposure assessment	Outcome assessment	Adjustment factors
Chen et al (2021) ³² ; United States; multicenter; Women's Health Initiative Study	63.0	18.9 [†]	T: 96 831; W: 96 831	CVD: 5589; cancer: 6228	FFQ	Death certificate, medical record, autopsy report, or National Death Index	consumption, and meat consumption Age; region; race; study group; educational level; annual family income; health insurance; smoking status; pack-years of smoking; alcohol intake; quitting smoking/drinking owing to health problems; recreational physical activity; total energy intake; using fat to deep fry, pan fry, or saute; aspirin use; use of nonsteroidal anti-inflammatory drugs; hormone use; self-rated health status; waist circumference; diabetes; systolic and diastolic blood pressure; anti-hypertensive drug use; dyslipidemia; and food groups
Zhuang et al (2020) ²⁰ ; China; multicenter; China Health and Nutrition Survey	42.9	14.6 [†]	T: 18 914; M: 8822; W: 10 092	All-cause: 1429	24-h dietary recalls	Household member report	Age; sex; nationality; marital status; BMI; household income; urbanization index; educational level; physical activity; smoking status; alcohol-drinking status; history of CVD, cancer, diabetes, or hypertension; total energy intake; consumption of cereals, potatoes, dairy products, nuts or legumes, red meat, white meat, sugar-sweetened beverages, vegetables, and fruit
Xia et al (2020) ³³ ; China; multicenter; China-PAR	51.5	7.6	T: 102 136; M: 41 140; W: 60 996	All-cause: 5511	FFQ	Death certificate, proxy report, and hospital record	Age, sex, BMI, urban or rural resident, household income, education attainment, tobacco smoking, alcohol consumption, family history of CVD, physical activity, and intakes of red meat, fresh fruit, and vegetable
Xia et al (2020) ¹⁵ ; United States; multicenter; National Health and Nutrition Examination Survey 1999–2014	50.2	7.8	T: 37 121; M: 18 263; W: 18 858	All-cause: 4991	24-h dietary recalls	National Death Index	Age, sex, race, educational level, BMI, family income poverty ratio, marital status, National Health and Nutrition Examination Survey cycles, total energy intake,

(continued)

Table 2 Continued

Reference; study location; study setting; cohort name	Mean age (y)	Follow-up* (y)	Sample size	Deaths	Exposure assessment	Outcome assessment	Adjustment factors
Dehghan et al (2020) ¹⁶ ; 21 countries; multicenter; Prospective Urban Rural Epidemiology Study	50.6	9.5	T: 146 011; M: 61 178; W: 84 833	All-cause: 8932; CVD: 3410	FFQ	Death certificate, autopsy report, medical record, and household interview	cigarette smoking, alcohol drinking, physical activity, hypertension, diabetes, CVD, cancer, and hypercholesterolemia Age; sex; smoking; location; education; physical activity; history of diabetes; blood cholesterol; daily intakes of fruits, vegetables, dairy, red meat, poultry, and fish; percentage energy from carbohydrate; total daily energy; and center as random effect
Dehghan et al (2020) ¹⁶ ; 40 countries; multicenter; ONTARGET and TRANSCEND	66.5	4.7 [†]	T: 31 544; M: 22 168; W: 9376	All-cause: 3769; CVD: 2264	FFQ	Evaluation by a blinded central committee	Age; sex; smoking; location; BMI; education; physical activity; history of diabetes, myocardial infarction, stroke, medication use; trial allocation; daily intakes of fruit, vegetables, red meat, poultry, fish, and dairy; and regions as a random effect
Zhong et al (2019) ⁹ ; United States; multicenter; Lifetime Risk Pooling Project	51.6	17.7	T: 29 615; M: 13 299; W: 163 16	All-cause: 6132	FFQ and dietary history survey method	(Not available)	Age, sex, ethnicity, education, total energy, smoking status, smoking pack-years, cohort-specific physical activity z-score, alcohol consumption, use of hormone replacement therapy, BMI, diabetes status, systolic blood pressure, use of antihypertensive drugs, high-density lipoprotein cholesterol, non-high-density lipoprotein cholesterol, and use of lipid-lowering drugs
Zamora-Ros et al (2019) ¹⁷ ; Spain; multicenter; European Prospective Investigation into Cancer and Nutrition Study	49.3	18.4	T: 40 621; M: 15 323; W: 25 298	All-cause: 3561; CVD: 761; cancer: 1694; CHD: 314	Dietary history questionnaire	Record linkage with Spanish National Statistics Institute	Smoking intensity, BMI, lifetime alcohol intake, educational level, physical activity, energy intake, and adherence to Mediterranean diet
Xu et al (2019) ¹⁸ ; China; single center;	62.0	9.8	T: 28 024; M: 7630; W: 20 394	All-cause: 2680; CVD: 873; Stroke: 341; CHD: 388	FFQ	Death certificate, autopsy report, and medical record	Age; sex; educational level; occupation; family income; smoking status; physical activity; alcohol

(continued)

Table 2 Continued

Reference; study location; study setting; cohort name	Mean age (y)	Follow-up* (y)	Sample size	Deaths	Exposure assessment	Outcome assessment	Adjustment factors
Guangzhou Biobank Cohort Study							drinking; self-rated health status; history of diabetes, hypertension or dyslipidemia; total energy intake; and intakes of vegetable, fruit, milk and nuts
van den Brandt (2019) ³⁶ ; Netherland; single center; Netherlands Cohort Study	62.7	9.5	T: 12 025; M: 7332; W: 4693	All-cause: 8823; CVD: 2985; cancer: 3917	FFQ	Linkage with the Dutch Central Bureau of Genealogy and Statistics Netherlands	Age, sex, smoking status, number of cigarettes smoked/d, years of smoking, history of physician-diagnosed hypertension and diabetes, body height, BMI, nonoccupational physical activity, highest level of education, alcohol intake, vegetables and fruit consumption, energy intake, use of nutritional supplement, and postmenopausal hormone replacement therapy (only for women)
Qin et al (2018) ⁴¹ ; China; multicenter; China Kadoorie Biobank Study	50.7	9.1	T: 461 213; M: 189 097; W: 272 116	CVD: 9985	A laptop-based questionnaire	Death registries and residential records	Age, sex, education level, household income, marital status, alcohol consumption, tobacco smoking, physical activity, BMI, waist to hip ratio, prevalent hypertension, use of aspirin, family history of CVD, intake of multivitamin supplementation, and dietary pattern
Nakamura et al (2018) ¹³ ; Japan; multicenter; NIPPON DATA90	52.8	13.8	T: 4686; W: 4686	All-cause: 599; CVD: 183; cancer: 210	Food frequency method	National Vital Statistics	Age, BMI, history of hypertension or diabetes, cigarette smoking, alcohol drinking, dyslipidemia therapy, intakes of fiber, meat, and sodium
Guo et al (2018); United Kingdom ¹⁹ ; single center; Caerphilly Prospective Cohort Study	61.7	22.8	T: 2512; M: 2512	All-cause: 1028	FFQ	Death certificate	Age, BMI, total energy intake, alcohol consumption, smoking status, energy expenditure, social class, family history of myocardial infarction, diabetes mellitus, sugar intake, fruit consumption, red meat consumption, and fiber intake
Farvid et al (2017) ²¹ ; Iran; single center; Golestan Cohort Study	53.1	8.0	T: 42 403; M: 15 688; W: 26715	All-cause: 3291; CVD: 1467; cancer: 859; stroke: 507; CHD: 764	FFQ	Report from family member, friend, or local health worker,	Age, sex, ethnicity, education level, marital status, resident location, smoking status, opium use, alcohol drinking, BMI, systolic blood

(continued)

Table 2 Continued

Reference; study location; study setting; cohort name	Mean age (y)	Follow-up* (y)	Sample size	Deaths	Exposure assessment	Outcome assessment	Adjustment factors
Djousse et al (2008) ¹⁴ ; United States; multicenter; Physicians' Health Study I	53.7	20.0	T: 21 327; M: 21 327	All-cause: 5169	FFQ	Death certificate, report from the next of kin, and medical record	pressure, occupational physical activity, family history of cancer, wealth score, medication use, and energy intake Age, BMI, smoking status, history of hypertension, vitamin intake, alcohol consumption, vegetable consumption, breakfast cereal, physical activity, treatment arm, atrial fibrillation, diabetes mellitus, hypercholesterolemia, and parental history of premature myocardial infarction
Nakamura et al (2004) ³⁰ ; Japan; multicenter; NIPPON DATA80	50.5	13.2	T: 9263; M: 4077; W: 5186	All-cause: 1202; cancer: 356; stroke: 219; CHD: 80	Self-administered questionnaire	National Vital Statistics	Age, serum creatinine, total cholesterol, blood glucose, BMI, systolic and diastolic blood pressures, use of blood pressure-lowering drugs, cigarette smoking, and alcohol intake

*Mean value unless otherwise specified.

[†]Median value.

Abbreviations: BMI, body mass index; CHD, coronary heart disease; China-PAR, Prediction for Atherosclerotic Cardiovascular Disease Risk in China; CVD, cardiovascular disease; FFQ, food frequency questionnaire; M, men; NIH-AARP, National Institutes of Health-AARP; NIPPON DATA, National Integrated Project for Prospective Observation of Noncommunicable Disease and its Trends in the Aged; ONTARGET, Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial; T, total; TC, total cholesterol; TRANSCEND, Telmisartan Randomized Assessment Study in ACEI Intolerant Subjects with Cardiovascular Disease; W, women.

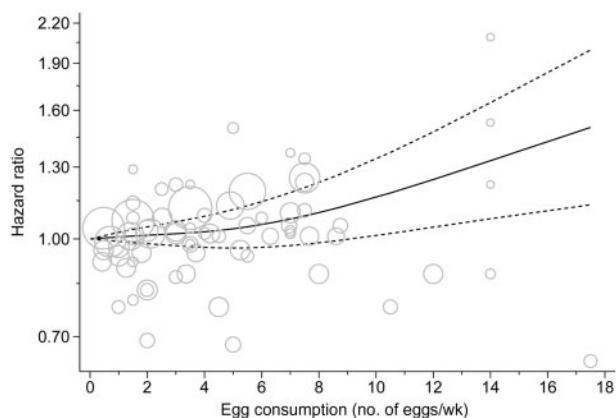


Figure 2 Nonlinear dose-response analysis of egg consumption and risk of all-cause mortality. The reference level was set at 0 eggs/week. The black solid line represents the fitted nonlinear trend, and the black, short, dashed line represents the 95%CI. The gray circles represent egg consumption-specific risk estimates, and their sizes are proportional to the precision (ie, inverse variance) of risk estimates

association of egg consumption with risk of all-cause mortality was significantly more pronounced in studies with adjustment for blood cholesterol, dyslipidemia, or dyslipidemia therapy than those without.

Meta-analyses have been used previously to investigate the association between egg consumption and risk of all-cause mortality.^{8,18,22,23} In a 2017 meta-analysis, involving 8 prospective studies and 30 352 all-cause deaths, authors found that the highest vs the lowest amount of egg consumption was associated with an increased risk of all-cause mortality (risk ratio 1.06; 95%CI, 1.00–1.12)²²; however, this positive association was not observed in other meta-analyses of highest vs lowest amount of egg consumption.^{8,18,23} The inconsistency may result from the differences in eligibility criteria, the number of included studies, and/or statistical methods. Given the different cutoff points for egg-consumption categories across included studies, we did not perform a similar meta-analysis in this study; instead, we used a dose-response meta-regression model to calculate risk estimates of mortality when consumption was increased by 1 egg/d.

Compared with the published meta-analyses,^{8,18,22,23} the present study has the following advantages. First, we investigated the dose-response associations between egg consumption and risk of mortality from all causes, cardiovascular disease, and cancer, and found that these associations were nonlinear. Second, we performed a series of predefined subgroup analyses to identify the potential effect modifiers and showed that whether adjustment for covariates related to blood cholesterol could significantly modify the association between egg consumption and risk of all-cause

mortality. Third, we included the latest studies on the association of egg consumption with risk of mortality; thus, this study represents the most up-to-date evidence in this field. Finally, we explored the associations between egg consumption and risks of cardiovascular disease-caused and cancer-caused mortality, which were not investigated in the previous meta-analyses.^{8,18,22,23}

Eggs are cooked by different methods in different countries (eg, in the United States, the most common cooking method for eggs is frying, whereas in China, boiling is most common¹⁵). Notably, nutrient content of eggs can be changed by changes in cooking method. For example, in a recent study, researchers found that the contents of fat and vitamins A and E were the highest in fried eggs, followed by microwaved eggs, and were the lowest in baked eggs.⁴² Therefore, cooking method should be considered when exploring the associations of egg consumption with health outcomes. However, of included studies, only 1 evaluated the associations of egg consumption with mortality by cooking method, which revealed similar positive associations for fried and nonfried eggs¹⁰; thus, subgroup analysis by cooking method could not be performed to clarify its potential impacts on the observed associations. More studies are needed to clarify whether the association of egg consumption with risk of mortality can be modified by cooking method.

In the present study, high heterogeneity across studies for the associations of egg consumption with mortality from all causes, cardiovascular disease, and cancer was observed. As suggested by subgroup analysis results, whether included studies adjusted for blood cholesterol, dyslipidemia, or dyslipidemia therapy explained the observed heterogeneity in part. Specifically, the positive associations observed in this review were more pronounced in studies with adjustment for those covariates than those without, indicating the potential interaction between egg consumption and blood cholesterol level. Indeed, a cross-sectional analysis showed that people who ate more eggs had a lower level of total cholesterol and were less likely to use cholesterol-lowering drugs.⁴³ These subgroup analysis results highlight the importance of adjustment for blood cholesterol in investigating the association of egg consumption with risk of mortality and indirectly suggest that heterogeneous results of included studies may be due to whether blood cholesterol is adjusted in their multivariable models. Importantly, the possibility that the modification effect by blood cholesterol level is a chance finding cannot be excluded according to the criteria proposed for credible subgroup differences.^{44,45} Therefore, subgroup analysis results from this study should be interpreted with caution and need to be verified by other studies. In addition, the sensitivity

Table 3 Subgroup analyses of egg consumption and risk of all-cause mortality

Subgroup	No.	HR (95%CI) ^a	I ² (%)	P ^b	P ^c
All cohorts	19	1.08 (1.01–1.15)	91.3	<0.001	–
Mean age (years)					
≥60	6	1.14 (1.06–1.22)	71.7	0.003	0.548
<60	13	1.07 (0.99–1.14)	83.8	<0.001	
Sex					
Male	3	1.14 (1.02–1.28)	38.6	0.196	0.460
Female	3	1.22 (1.15–1.28)	0.0	0.878	
Study setting					
Multicenter center	13	1.08 (1.01–1.17)	93.6	<0.001	0.824
Single center	6	1.07 (0.91–1.27)	67.9	0.008	
Study location					
United States	5	1.16 (1.09–1.24)	82.6	<0.001	0.383
Europe	4	1.11 (0.90–1.36)	64.7	0.037	
Asia	8	1.03 (0.94–1.13)	78.6	<0.001	
Risk of bias					
Moderate	12	1.08 (1.00–1.18)	92.1	<0.001	0.951
Serious	7	1.08 (0.98, 1.18)	77.8	<0.001	
No. of participants					
≥10,000	14	1.06 (0.98–1.15)	93.6	<0.001	0.254
<10,000	5	1.16 (1.07–1.27)	0.0	0.496	
No. of deaths					
≥5000	7	1.12 (1.03–1.23)	93.5	<0.001	0.265
<5000	12	1.05 (0.97–1.14)	74.1	<0.001	
Repeated egg-consumption assessment					
Yes	4	1.02 (0.86–1.21)	91.8	<0.001	0.339
No	15	1.10 (1.02–1.18)	89.5	<0.001	
Adjustment for blood cholesterol, dyslipidemia, or dyslipidemia therapy					
Yes	12	1.15 (1.09–1.21)	75.8	<0.001	0.001
No	7	0.95 (0.90–1.01)	47.8	0.074	

^aHRs refer to risk estimates for an increase of 1 egg/d.

^bP for heterogeneity.

^cP for interaction between subgroups with meta-regression.

Abbreviation: HR, hazard ratio.

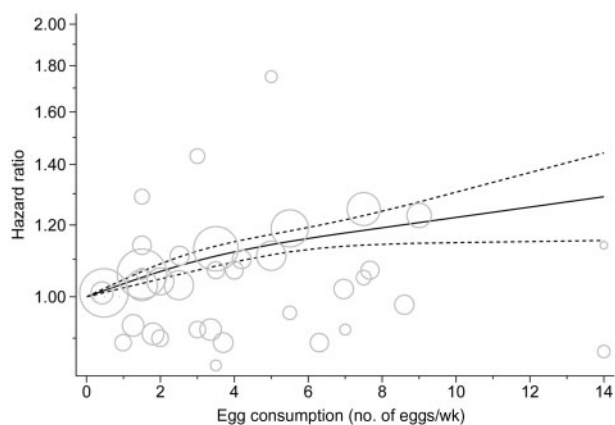


Figure 3 Nonlinear dose-response analysis of egg consumption and risk of cardiovascular disease-caused mortality. The reference level was set at 0 eggs/week. The black solid line represents the fitted nonlinear trend, and the black, short, dashed line represents the 95%CI. The gray circles represent egg consumption-specific risk estimates, and their sizes are proportional to the precision (ie, inverse variance) of risk estimates

analyses we performed for the present review showed that the observed heterogeneity was reduced markedly after excluding studies with a sample size of > 100 000,

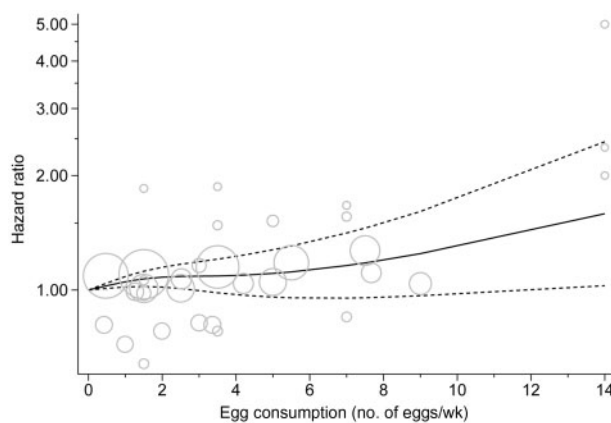


Figure 4 Nonlinear dose-response analysis of egg consumption and risk of cancer-caused mortality. The reference level was set at 0 eggs/week. The black solid line represents the fitted nonlinear trend, and the black, short, dashed line represents the 95%CI. The gray circles represent egg consumption-specific risk estimates, and their sizes are proportional to the precision (ie, inverse variance) of risk estimates

indicating that the difference in sample size across included studies also contributed to the observed heterogeneity to some extent. Commonly, large studies are

conducted with more rigorous methodology and observe more outcome events of interest than do small studies.⁴⁶

Several potential mechanisms may explain the harmful associations between egg consumption and risks of death from all causes, cardiovascular disease, and cancer. First, a straightforward explanation is the high cholesterol content of eggs.¹ A recent meta-analysis of 17 randomized controlled trials showed that egg consumption significantly increased low-density lipoprotein cholesterol level and the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol in healthy study participants.⁴⁷ Prospective studies have shown that high dietary cholesterol intake is associated with an increased risk of mortality^{10,15,32}; moreover, it is now well established that low-density lipoprotein cholesterol plays a causal role in the development of atherosclerotic cardiovascular disease.⁴⁸ In fact, in a recent mediation analysis, authors found that dietary intake of cholesterol explained 63.2%, 62.3%, and 49.6% of all-cause, cardiovascular disease-caused, and cancer-caused mortality in relation to egg consumption, respectively.¹⁰ However, this explanation seems not to be supported by the results of subgroup analysis in the present study, which showed that the observed association between egg consumption and mortality was more evident after adjustment for blood cholesterol-related covariates. In addition, eggs are also rich in saturated fatty acids (~1.563 g cholesterol/egg),¹ and their increased dietary intake confers an elevated risk of mortality,^{49,50} which may explain the observed associations to some degree. Second, individuals with high amount of egg consumption also had an increased consumption of red meat^{51,52} and a decreased consumption of fruits and vegetables,¹⁰ which are suggestive of their poor diet quality, a well-defined risk factor for premature death.⁵³ Likewise, a high amount of egg consumption was associated with smoking⁹ and physical inactivity,²⁰ all of which predict the increased mortality. Third, the unfavorable association of egg consumption with risk of mortality may be attributable to the role of metabolites of egg components. For example, egg consumption leads to an elevated level of trimethylamine-*N*-oxide, a metabolite of choline^{54,55} (eggs are a rich source of choline¹). Trimethylamine-*N*-oxide can increase low-density lipoprotein oxidation and exacerbate inflammation,⁵⁶ resulting in an increased risk of adverse cardiovascular events.⁵⁴

Interestingly, authors of a previous meta-analysis reported that egg consumption was related to an increased risk of cardiovascular disease in a diabetic population (HR, 1.69; 95%CI, 1.09–2.62) but not in the overall study population (HR, 0.96; 95%CI, 0.88–1.05).⁸ Likewise, in 2 studies included in this meta-analysis,

researchers also observed that the harmful association of egg consumption with risk of all-cause mortality was stronger in study participants with diabetes than those without.^{14,32} The biological mechanisms behind these observations are unclear. In a comparative study, mRNA expression level of *NPC1L1*, a gene playing an important role in the absorption of intestinal cholesterol,⁵⁷ was significantly higher in intestinal biopsy samples from patients with diabetes than in those from patients who did not have diabetes.⁵⁸ Thus, a possible explanation is that patients with diabetes have higher absorption efficiency for dietary cholesterol. Also, the observations may be due to the different shapes of the dose-response relationship between cholesterol levels and the risk of chronic disease in populations with diabetes (linear) and without diabetes (U shaped).⁵⁹ However, it should be noted that in 3 studies included in this study, the modification effect by diabetes status was not detected.^{9,15,33} The different reporting style among these studies^{9,14,15,32,33} precluded the attempt to perform a relevant subgroup analysis. Overall, it still remains unknown whether the association of egg consumption with risk of mortality can be modified by diabetes status. More studies are needed to disentangle this question.

The present study has several limitations. First, egg consumption was evaluated only at baseline in most included studies. The evaluation of dietary exposure at a single point may lead to nondifferential bias, because an individual's dietary habit can change with time. Nevertheless, subgroup analyses in this study revealed no significant difference in the risk of mortality between studies with and without repeated egg-consumption assessment. Moreover, the approaches using baseline diet only have been indicated to yield a weaker association than do those using the cumulative averages.⁶⁰ Second, in approximately half of the included studies, death certificates were used to identify the causes of mortality. However, the information from death certificates is not accurate in some conditions.⁶¹ Hence, findings from the present study on the association between egg consumption and risk of cause-specific mortality could be subject to misclassification bias. In addition, findings from this study were based on the study-level data, which do not permit us to perform a competing risk analysis to determine the potential impacts of competing risk bias on the results for cause-specific mortality. Third, high heterogeneity was observed for meta-analyses of egg consumption and risks of all-cause, cardiovascular disease-caused, and cancer-caused mortality, which raises some concerns about the reliability of the pooled results and the rationality of conducting a meta-analysis. Nonetheless, the sources of the observed heterogeneity had been identified by subgroup and

sensitivity analyses. Also, methodological and clinical heterogeneity always exist for all meta-analyses, especially meta-analysis of observational studies. Fourth, the most fully adjusted risk estimates were extracted for analyses, but results from the present study still could have been influenced by the residual confounding considering unmeasured or unrecognized confounders. Finally, findings from the present study on egg consumption and risk of cause-specific mortality (particularly for stroke and coronary heart disease-caused mortality) were derived from limited studies. Thus, these findings should be interpreted with caution and need to be validated by more studies.

CONCLUSIONS

A high amount of egg consumption is associated with increased risk of mortality from all causes, cardiovascular disease, and cancer in a nonlinear dose-response pattern. However, considering small effect sizes (especially for all-cause and cardiovascular disease-caused mortality), high between-study heterogeneity, and the observational nature of this study, these findings should be interpreted with caution and need to be validated by future studies.

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Authors' contributions. G.-C.Z. conceived the study idea and the other authors made useful suggestions for the study idea. P.-F.Y. and W.-P.S. performed the literature search and study selection. C.-R.W. and Y.P. performed data extraction and quality assessment of included studies. F.-B.H. performed all statistical analyses. G.-C.Z. and F.-B.H. interpreted the results of statistical analyses. C.-R.W. drafted the initial manuscript, and all authors made critical comments and revisions for the initial manuscript. P.-F.Y. and G.-C.Z. were responsible for manuscript revisions following reviewers' comments. G.-C.Z. had full access to original data. All authors approved the final version of the article, including the authorship list.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

[Table S1 Search strategies for PubMed and Embase databases](#)

[Table S2 Excluded studies after checking the full text and primary reason for exclusion](#)

[Table S3 Sensitivity analyses of egg consumption and risk of all-cause mortality](#)

[Table S4 GRADE evidence profile for prospective cohort studies of egg consumption and risk of mortality](#)

[Table S5 Subgroup analyses on egg consumption and risk of cardiovascular disease-caused mortality](#)

[Table S6 Sensitivity analyses of egg consumption and risk of cardiovascular disease-caused mortality](#)

[Table S7 Subgroup analyses on egg consumption and risk of cancer-caused mortality](#)

[Table S8 Sensitivity analyses of egg consumption and risk of cancer-caused mortality](#)

[Figure S1 Risk-of-bias assessment of included studies using the Risk of Bias in Nonrandomized Studies of Interventions \(ROBINS-I\) tool](#)

[Figure S2 Meta-analysis of egg consumption and risk of all-cause mortality.](#) The square represents a hazard ratio for an increase of 1 egg/d calculated from each individual study, with the area representing the weight assigned to the study. The horizontal line across each square represents the 95%CI. The diamond represents the combined hazard ratio for an increase of 1 egg/d, with width representing the 95%CI

[Figure S3 Sensitivity analyses of egg consumption and risk of all-cause mortality: omitting a single study in turn.](#) The study cited on the left is the 1 omitted in each turn. The circle represents the pooled risk estimates after omitting a single study, and the dotted line across each circle represents the 95%CI. The middle, vertical solid line represents the pooled risk estimates of all included studies, and left and right vertical solid lines represent lower and upper limits, respectively

[Figure S4 Meta-analysis of egg consumption and risk of cardiovascular disease-caused mortality.](#) The square represents a hazard ratio for an increase of 1 egg/d calculated from each individual study, with the area representing the weight assigned to the study. The horizontal line across each square represents the 95%CI. The diamond represents the combined hazard ratio for an increase of 1 egg/d, with width representing the 95%CI

[Figure S5 Sensitivity analyses of egg consumption and risk of cardiovascular disease-caused mortality: omitting a single study in turn.](#) The study cited on the left is the 1 omitted in each turn. The circle represents the pooled risk estimates after omitting a single study, and the dotted line across each circle represents the 95%CI. The middle, vertical solid line represents the pooled risk estimates of all included studies, and left and right vertical solid lines represent lower and upper limits, respectively

Figure S6 Meta-analysis of egg consumption and risk of stroke mortality. The square represents a hazard ratio for an increase of 1 egg/d calculated from each individual study, with the area representing the weight assigned to the study. The horizontal line across each square represents the 95%CI. The diamond represents the combined hazard ratio for an increase of 1 egg/d, with width representing the 95%CI

Figure S7 Meta-analysis of egg consumption and risk of coronary heart disease mortality. The square represents a hazard ratio for an increase of 1 egg/d calculated from each individual study, with the area representing the weight assigned to the study. The horizontal line across each square represents the 95%CI. The diamond represents the combined hazard ratio for an increase of 1 egg/d, with width representing the 95%CI

Figure S8 Meta-analysis of egg consumption and risk of cancer-caused mortality. The square represents a hazard ratio for an increase of 1 egg/d calculated from each individual study, with the area representing the weight assigned to the study. The horizontal line across each square represents the 95%CI. The diamond represents the combined hazard ratio for an increase of 1 egg/d, with width representing the 95%CI

Figure S9 Sensitivity analyses of egg consumption and risk of cancer-caused mortality: omitting a single study in turn. The study cited on the left is the 1 omitted in each turn. The circle represents the pooled risk estimates after omitting a single study, and the dotted line across each circle represents the 95%CI. The middle, vertical solid line represents the pooled risk estimates of all included studies, and left and right vertical solid lines represent lower and upper limits, respectively

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