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dose-response meta-analysis of prospective cohort studies**

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(Article begins on next page)

RESEARCH

Egg consumption and risk of coronary heart disease and stroke: dose-response meta-analysis of prospective cohort studies

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Abstract

Objective To investigate and quantify the potential dose-response association between egg consumption and risk of coronary heart disease and stroke.

Design Dose-response meta-analysis of prospective cohort studies.

Data sources PubMed and Embase prior to June 2012 and references of relevant original papers and review articles.

Eligibility criteria for selecting studies Prospective cohort studies with relative risks and 95% confidence intervals of coronary heart disease or stroke for three or more categories of egg consumption.

Results Eight articles with 17 reports (nine for coronary heart disease, eight for stroke) were eligible for inclusion in the meta-analysis (3 081 269 person years and 5847 incident cases for coronary heart disease, and 4 148 095 person years and 7579 incident cases for stroke). No evidence of a curve linear association was seen between egg consumption and risk of coronary heart disease or stroke ($P=0.67$ and $P=0.27$ for non-linearity, respectively). The summary relative risk of coronary heart disease for an increase of one egg consumed per day was 0.99 (95% confidence interval 0.85 to 1.15; $P=0.88$ for linear trend) without heterogeneity among studies ($P=0.97$, $I^2=0\%$). For stroke, the combined relative risk for an increase of one egg consumed per day was 0.91 (0.81 to 1.02; $P=0.10$ for linear trend) without heterogeneity among studies ($P=0.46$, $I^2=0\%$). In a subgroup analysis of diabetic populations, the relative risk of coronary heart disease comparing the highest with the lowest egg consumption was 1.54 (1.14 to 2.09; $P=0.01$). In addition, people with higher egg consumption had a 25% (0.57 to 0.99; $P=0.04$) lower risk of developing hemorrhagic stroke.

Conclusions Higher consumption of eggs (up to one egg per day) is not associated with increased risk of coronary heart disease or stroke. The increased risk of coronary heart disease among diabetic patients and reduced risk of hemorrhagic stroke associated with higher egg consumption in subgroup analyses warrant further studies.

Introduction

Cardiovascular disease is now a public health crisis, affecting millions of people in both developed and developing countries. Although the rate of death attributable to the disease has declined in developed countries in the past several decades, it is still the leading cause of death and extorts a heavy social and economic toll globally.^{1,3} In low and middle income countries, the prevalence of cardiovascular disease has increased dramatically. By 2020, the disease is forecasted to be the major cause of morbidity and mortality in most developing nations.⁴

In recent decades, concern has mounted regarding the high prevalence and costs associated with cardiovascular disease, with growing interest in altering risk factors and reversing this global epidemic. Among the known risk factors for cardiovascular disease, levels of low density lipoprotein (LDL) cholesterol have aroused particular attention. In the Women's Health Study, after a mean follow-up of eight years, participants with the highest levels of LDL cholesterol showed a notably higher risk of cardiovascular events than those with the lowest levels.⁵ In addition, several meta-analyses of observational studies and randomized controlled trials have found that a reduction in concentrations of LDL cholesterol could significantly reduce the risk of coronary heart disease and stroke

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Web appendix: Web tables

incidence and mortality.⁶⁻⁹ Diet is an important determinant of serum cholesterol, but dietary cholesterol has only a modest contribution to plasma concentrations of LDL cholesterol.¹⁰ On the other hand, dietary cholesterol may prompt the oxidation of LDL and increase postprandial lipemia, which could raise the risk of vascular disease.¹¹ To minimize the elevation of blood cholesterol and reduce the risk of cardiovascular disease, the American Heart Association (AHA) has recommended the public to consume less than 300 mg/day of cholesterol.^{12 13}

Since eggs are a major source of dietary cholesterol, with one large egg containing almost 210 mg of cholesterol, the public has been recommended to limit egg consumption unless the intake of other foods high in cholesterol is restricted.¹⁴ However, eggs are also an inexpensive and low calorie source of many other nutrients, including minerals, proteins, and unsaturated fatty acids, which could lower the risk of cardiovascular disease.¹⁵ Additionally, in populations following a carbohydrate restricted diet, dietary cholesterol from eggs could increase plasma concentrations of high density lipoprotein (HDL) cholesterol,¹⁶ which has been suggested to protect against vascular disease.^{17 18} Therefore, some organizations have recommended that reducing egg intake might not be important for healthy people with normal levels of cholesterol in the blood.¹⁹ Food based dietary guidelines from countries including Nepal, Thailand, and South Africa recommend consuming eggs every day or regularly as part of a healthy diet.²⁰

Several prospective cohort studies have examined the association between egg consumption and risk of coronary heart disease and stroke. However, the relation between egg consumption and risk of cardiovascular disease remains controversial. Therefore, we conducted a dose-response meta-analysis of prospective cohort studies to quantify the association between egg consumption and risk of coronary heart disease and stroke.

Methods

Search strategy

We conducted a literature search of PubMed (Medline) and Embase from January 1966 through June 2012 for prospective cohort studies examining the association between egg consumption and risk of CHD and stroke. PubMed search terms were “Cardiovascular Diseases”[MeSH] or “Stroke”[MeSH] or “Coronary Disease”[MeSH] or “myocardial infarction”[MeSH] or CHD) and egg. Similar search terms were used for Embase. In addition, we scrutinized references from relevant original papers and review articles to identify further pertinent studies. No language restrictions were imposed. We followed the standard criteria for conducting meta-analyses of observational studies and reporting the results.²¹

Study selection

Studies were included in this meta-analysis if they satisfied the following criteria: the study design was prospective, the exposure of interest was egg consumption, the outcome was coronary heart disease or stroke, and the investigators reported relative risks with 95% confidence intervals for at least three quantitative categories of egg intake. Additionally, we excluded reviews, editorials, non-human studies, and letters without sufficient data. Studies of other exposures and diseases were also excluded. If study populations were reported more than once, we used the result with the longest follow-up time.

Data extraction

Data extraction was carried out independently by two authors (YR and LC) using a standard extraction form. We extracted the following information from each study: authors, year of publication, study name, study location, years of follow-up, sample size (number of participants and incident cases), participants' characteristics (age and sex), endpoints (coronary heart disease, stroke, or both), outcomes ascertainment, egg consumption categories, covariates adjusted in the multivariable analysis, and relative risks (95% confidence intervals) for all categories of egg consumption.

Quality assessment was performed according to the Newcastle-Ottawa quality assessment scale,²² which is a validated scale for non-randomised studies in meta-analyses. This scale awards a maximum of nine points to each study: four for selection of participants and measurement of exposure, two for comparability of cohorts on the basis of the design or analysis, and three for assessment of outcomes and adequacy of follow-up. We assigned scores of 0-3, 3.5-6, and 6.5-9 for low, moderate, and high quality of studies, respectively. When studies had several adjustment models, we extracted those that reflected the maximum extent of adjustment for potentially confounding variables.

For studies that reported egg intake as servings per week or day, we assumed that each serving was equivalent to one egg. For studies that lacked the unit of consumption, the categories were estimated by multiplying the frequency of consumption from the food frequency questionnaires with an average portion size according to the mean intake derived from the 24 h diaries. We contacted the authors if the data of interest were not directly shown in the publications. To resolve discrepancies, we used group consensus and consulted a third reviewer.

Statistical analysis

In this meta-analysis, the relative risks and 95% confidence intervals were considered as the effect size for all studies, and the hazard ratios were deemed equivalent to relative risks. Any results stratified by sex were treated as two separate reports. Those articles reporting both coronary heart disease and stroke were also treated as two separate reports. Owing to the distinct cut-off points for categories in different articles, we computed a relative risk with 95% confidence interval for an increased intake of one egg per day for each report. The method described by Greenland and Longnecker²³ and Orsini and colleagues²⁴ was used to calculate the trend from the correlated estimates for log relative risk across categories of egg consumption. The amount of egg consumption, distributions of cases and person years, and relative risks and 95% confidence intervals were extracted according to this method.

The median or mean egg consumption in each category was used as the corresponding dose of consumption. The midpoint of the upper and lower boundaries was considered the dose of each category if the median or mean intake per category was not available. If the highest category was open ended, the midpoint of the category was set at 1.5 times the lower boundary. If the number of cases and person years were not available, we used the relative risks comparing the highest versus lowest categories of egg intake to obtain a summary estimate.

In addition, we evaluated a potential curve linear association between egg consumption and risk of coronary heart disease and stroke, using restricted cubic splines with three knots at percentiles 10%, 50%, and 90% of the distribution.²⁵ A P value for curve linearity or non-linearity was calculated by testing the

null hypothesis that the coefficient of the second spline is equal to zero.

The heterogeneity among studies was estimated by the Cochran Q test and I^2 statistic.²⁶ Heterogeneity was confirmed with a significance level of $P \leq 0.10$. The I^2 statistic describes the percentage of total variation in point estimates that can be attributed to heterogeneity. For the I^2 metric, we considered low, moderate, and high I^2 values to be 25%, 50%, and 75%, respectively.^{26 27} We used a fixed effect model (Mantel-Haenszel method) when heterogeneity was negligible, and a random effect model (DerSimonian and Laird method) when heterogeneity was significant.²⁸ Forest plots and funnel plots were used to examine the overall effect and assess the publication bias, respectively.

We also conducted analyses stratified by sex, study location, number of cases and participants, duration of follow-up, repeated egg consumption measurements, study quality, and whether diet variables or cholesterol levels were controlled for in models. All statistical analyses were performed with Stata version 11 (Stata Corp), and all tests were two sided with a significance level of 0.05.

Results

Literature search

Figure 1 shows the results of literature research and selection. We identified 616 articles from PubMed and 824 articles from Embase prior to 20 June 2012. After exclusion of duplicates and studies that did not fulfill the inclusion criteria, 16 remaining articles seemed to be relevant for this meta-analysis. After evaluating the full texts of these 16 publications, we excluded eight articles as follows. Two articles^{29 30} were excluded owing to lack of sufficient data for estimation of relative risks. Another two articles^{31 32} were excluded because they did not separately report the relative risks and 95% confidence intervals for coronary heart disease or stroke. We also excluded one report³³ because it was the meeting abstract of the study by Scrafford and colleagues.³⁴ A study by He and colleagues³⁵ was excluded because it reported the intermediate follow-up results of Health Professionals Follow-up Study. The final meta-analysis included eight articles, of which four^{34 36-38} examined men and women separately. For the study by Scrafford and colleagues,³⁴ the estimate of the association between egg consumption and stroke mortality among men was imprecise because of sparse data, and thus for this report we included only data for women. In total, our meta-analysis included eight articles with 17 independent reports.

Study characteristics

Tables 1 and 2 show the information extracted from the included studies, all of which had prospective cohort designs and participants with no prior diagnoses of cardiovascular disease at baseline. The meta-analysis consisted of 263 938 participants with 3 081 269 person years of follow-up for coronary heart disease, and 210 404 patients with 4 148 095 person years of follow-up for stroke. Among the participants, we documented 5847 cases of coronary heart disease during follow-up periods ranging from eight to 20 years, and 7579 cases of stroke during a follow-up ranging from 8.8 to 22 years. Three cohorts^{37 39 40} were among Asians (Japan), and the others^{34 36 38 41 42} were conducted in the United States. Egg consumption was measured by food frequency questionnaires in all studies. Four studies^{36 38 40 42} used repeated measurements to update dietary information to more accurately reflect the dietary intakes over follow-up. Results of study quality

assessment (score 0-9) yielded a score of 6.5 or above (high quality) for all studies, with an average score of 7.6 (web appendix, tables A and B).

Association between egg consumption and risk of coronary heart disease

Six articles^{34 36 37 40-42} with nine reports were included in the dose-response analysis of egg consumption and risk of coronary heart disease. Using a restricted cubic splines model, we found no evidence of a curve linear association between egg consumption and risk of coronary heart disease ($P=0.67$ for non-linearity; fig 2). The summary relative risk of coronary heart disease for an increase of one egg per day was 0.99 (95% confidence interval 0.85 to 1.15; $P=0.88$ for linear trend). We saw no heterogeneity among studies ($P=0.97$, $I^2=0\%$; fig 3). Additionally, Begg and Egger regression tests provided no evidence of substantial publication bias ($P>0.05$ for both tests). Among the included studies, two articles^{34 37} (four total reports) examined the relation between egg consumption and risk of coronary heart disease in populations with diabetes. Owing to the lack of data for person years in diabetic populations, we obtained the summary relative risk comparing the highest with the lowest egg consumption for coronary heart disease in diabetic patients (relative risk 1.54 (1.14 to 2.09); $P=0.01$; table 3; web appendix, table C).

Association between egg consumption and risk of stroke

This dose-response analysis involved six articles^{34 37-39 41 42} with eight reports on egg consumption and stroke risk. We did not find a curve linear association between egg consumption and risk of stroke ($P=0.27$ for non-linearity; fig 4). The combined relative risk of stroke for an increment of one egg consumed per day was 0.91 (95% confidence interval 0.81 to 1.02; $P=0.10$ for linear trend; fig 5). No heterogeneity of effect estimates on relative risks was observed ($P=0.46$, $I^2=0\%$). Neither the Begg test nor the Egger test for publication bias reached significance ($P>0.05$ for both tests). In addition, three articles^{34 37 39} with four reports provided information on fatal stroke (pooled relative risk 0.94 (0.80 to 1.10); $P=0.46$; table 3). Moreover, four articles^{38 39 41 42} reported results for different types of stroke, and three articles^{34 41 42} provided results for stroke in those with diabetes. For these studies, the combined relative risks comparing the highest versus lowest egg intake were 0.75 (0.57 to 0.99) for hemorrhagic stroke, 0.91 (0.82 to 1.01) for ischemic stroke, and 0.80 (0.29 to 2.15) for total stroke among people with diabetes (table 3; web appendix, table D).

Subgroup analyses

Subgroup analyses were conducted to examine the stability of the primary results (table 3). The associations between egg consumption and risk of coronary heart disease and stroke were similar in subgroup analyses, which were defined by sex, study location, number of cases or participants, duration of follow-up, repeated egg consumption measurements, study quality, and whether diet variables or cholesterol levels were controlled for in models. An increment of one egg consumed per day did not significantly increase risk of coronary heart disease or stroke in any of the categories.

Discussion

This meta-analysis identified no significant association between egg consumption and risk of coronary heart disease or stroke. Higher intake of eggs (up to one egg per day) was not associated

with risk of coronary heart disease or stroke. Similar results were obtained in subgroup analyses. However, among diabetic participants, higher egg consumption was associated with a significantly elevated risk of coronary heart disease. On the other hand, higher egg intake was associated with a lower risk of hemorrhagic stroke. These subgroup results should be interpreted with caution, because only a few studies focused on diabetic participants and particular stroke subtypes.

Results in relation to other studies

To date, the majority of prospective studies have found no significant association between egg consumption and risk of coronary heart disease or stroke. However, Burke and colleagues⁴³ analyzed data from 514 Western Australian aborigines with almost 14 years of follow-up and found that risk of coronary heart disease increased in participants consuming eggs more than twice per week. But this study was small and analyzed multiple dietary and lifestyle exposures.

Some studies have found an inverse association between egg consumption and stroke risk. For example, an analysis of the Third National Health and Nutrition Examination Survey 1988-1994 (NHANES III) dataset found a significant inverse association between higher egg consumption and stroke mortality among men.³⁴ A cohort study from Japan found that increased consumption of animal products (including eggs) was associated with reduced risk of total and hemorrhagic stroke death.³⁹

We considered several potential reasons for the lack of an overall association between egg consumption and coronary heart disease or stroke. Although dietary cholesterol influences plasma concentrations of serum cholesterol, the effects are relatively small.¹⁰ In addition, epidemiologic studies have found weak or little association between dietary cholesterol intake and cardiovascular disease risk.¹⁰ Apart from dietary cholesterol, saturated fat and dietary patterns might also influence blood cholesterol levels,⁴⁴⁻⁴⁶ suggesting that compliance with general dietary recommendations instead of simply reducing egg consumption could have a greater effect on the risk of cardiovascular disease. Additionally, individual differences in response to dietary cholesterol vary greatly, which could affect the association between egg consumption and risk of coronary heart disease and stroke. Moreover, several studies have shown that egg consumption favors the formation of larger LDL and HDL particles, which might enhance protection against atherosclerosis.^{47 48}

Other than cholesterol, eggs are a good source of other nutrients such as high quality protein and vitamin D. In the Diet, Obesity, and Gene (Diogenes) Project, increased protein consumption together with a modest reduction in glycemic index was beneficial for weight control.⁴⁹ Substituting protein for carbohydrate also partly resulted in lower blood pressure, improved lipids levels, and concomitantly reduced cardiovascular risk.⁵⁰ Higher vitamin D intake might have beneficial effects on the reduction of visceral adipose tissue⁵¹ and other cardiovascular risk factors⁵².

Another possibility is that lifestyle factors associated with egg consumption might have obscured a positive association between egg consumption and risk of coronary heart disease and stroke. However, regular egg consumption tends to be associated with unhealthy lifestyle factors such as smoking and physical inactivity.^{34 36 53} Higher consumption of eggs is also likely to be associated with increased consumption of red and processed meats.³⁶ These confounding factors tend to exaggerate rather than mask the association between egg consumption and

cardiovascular disease risk. One study found that participants with high levels of cholesterol in the blood were more likely to reduce their egg consumption than others.⁴⁰ However, our subgroup analysis showed that the association between egg consumption and coronary heart disease was similar in the models, with or without adjustment for cholesterol levels.

Recently, a cross sectional study assessed the total plaque area in patients attending Canadian vascular prevention clinics to determine whether the atherosclerosis burden was related to dietary egg intake.⁵⁴ The study found a strong positive association between the number of egg yolks and the degree of atherosclerosis measured by plaque areas. However, the study did not assess or adjust for other dietary or lifestyle factors and did not examine hard cardiovascular disease endpoints. The cross sectional nature of the study also limited causal interpretation of the data. Therefore, the results from this cross sectional analysis should be interpreted with caution.⁵⁵ The findings from our meta-analyses of prospective cohort studies do not support a positive association between egg consumption and cardiovascular disease outcomes in the general population.

Subgroup analyses have suggested a positive association between egg consumption and coronary heart disease risk in diabetic patients. Among diabetic populations, decreased plasma levels of apolipoprotein E, together with increased levels of apolipoprotein C-III could lead to abnormal cholesterol transport, which might increase the risk of coronary heart disease.^{56 57} The adverse effect of egg consumption on lipoprotein profile and glycemic control could contribute to the elevated risk of coronary heart disease in diabetic populations.

In addition, insulin sensitivity could influence HDL metabolism and cholesterol transport.^{58 59} Riemens and colleagues⁶⁰ found that people with lower insulin sensitivity had increased levels of plasma cholesterol, very low density lipoprotein cholesterol, and LDL cholesterol, compared with those with higher insulin sensitivity. Activities of plasma lecithin, cholesterol acyl transferase, phospholipid transfer protein, and hepatic lipase were negatively correlated with insulin sensitivity, which could have enhanced reverse cholesterol transport.⁶⁰ These findings suggest a biological mechanism for possible adverse effects of insulin resistance on risk of coronary heart disease in diabetic populations through cholesterol metabolism. Nonetheless, this subgroup finding of a positive association between egg consumption and coronary heart disease risk was based on a small number of studies and thus needs to be replicated in further studies.

Several prospective cohort studies showed that hemorrhagic stroke had an inverse association with serum levels of cholesterol.⁶¹⁻⁶⁴ In particular, the result of a meta-analysis including 13 cohorts from China and Japan showed that decreased cholesterol concentrations conferred an increased risk of hemorrhagic stroke.⁶⁵ It has been suggested that low cholesterol levels promote necrosis of medial muscle cells and reduce platelet aggregability, which could lead to plasmatic arterionecrosis and the incidence of hemorrhagic stroke.^{66 67} It is unclear whether the inverse association between egg consumption and hemorrhagic stroke is mediated through low levels of serum cholesterol or other mechanisms. Since this subgroup finding was based on a small number of studies, the results should be interpreted with caution.

Strengths and limitations

Our study has several strengths. Our meta-analysis included prospective cohort studies with large sample size and long duration of follow-up, which significantly increased the

statistical power to detect potential associations. We investigated a dose-response relation between egg consumption and risk of coronary heart disease and stroke, allowing us to examine the shape of this possible association. Linear and non-linear relations were also tested to quantify the associations. In addition, we used models adjusting for most established risk factors and did stratified analyses to explore whether some factors could explain the results.

Several limitations of our study should also be acknowledged. Firstly, errors in measurement of egg intake and other dietary habits could have attenuated individual study results and led to the null association between egg consumption and risk of coronary heart disease and stroke. All the studies in our analysis assessed egg consumption using food frequency questionnaires, several of which have been validated with reasonable reproducibility and validity of self reported egg intake. However, misreporting of intake was still inevitable.⁶⁸⁻⁷⁰

The cooking methods of eggs and the amount of salt added to eggs were not available in most of the included studies. The nutrient contents of eggs could alter depending on different cooking methods or feeding methods of chicken. In addition, we could not uniformly quantify the size of eggs in each study. Moreover, participants with higher egg intake consumed more dietary cholesterol and protein but fewer carbohydrates and were more likely to have lower levels of education than those with lower egg intake.³⁴⁻³⁶ Several studies adjusted for those confounding factors. To reduce this bias, we conducted a stratified analysis and found the results to be robust in different strata of covariates.

Secondly, during the long follow-up, participants may have changed their diets. However, in our meta-analysis, nearly half the included studies updated the diet information from food frequency questionnaires. Stratified analysis indicated that the associations between egg consumption and risk of coronary heart disease and stroke were similar, regardless of whether repeated egg consumption measurements were considered.

Thirdly, some studies considered the intake of foods in which egg was the main ingredient. However, the results suggested that the amount of eggs estimated in other foods was relatively small and was unlikely to affect the aforementioned associations. Finally, the statistical power was limited in subgroup analyses of diabetic patients or subtypes of stroke.

Conclusions

In summary, results from our meta-analysis do not support that higher egg consumption is associated with elevated risk of coronary heart disease and stroke. Subgroup analyses suggest a positive association between higher egg intake and risk of coronary heart disease in diabetic patients, and an inverse association between higher egg consumption and incidence of hemorrhagic stroke. Studies with larger sample sizes and longer follow-up times are warranted to confirm these subgroup results.

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Contributors: YR and LL conceived the study. YR and LC searched the databases and checked them according to the eligible criteria and exclusion criteria. LL helped develop search strategies. TZ gave advice on meta-analysis methodology. YS helped extract quantitative data from some papers. YS, MY, and ZS analyzed the data. YR wrote the draft of the paper. LC, TZ, YS, MY, ZS, AS, FBH, and LL contributed to writing, reviewing, or revising the paper. LL is the guarantor.

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Ethical approval: Ethical approval not needed.

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What is already known on this topic

Cardiovascular disease affects millions of people in both developed and developing countries

As a major source of dietary cholesterol, eggs have been investigated by several epidemiologic studies in relation to risk of coronary heart disease and stroke

However, whether egg consumption increases the future risk of coronary heart disease and stroke remains unclear

What this study adds

Consumption of up to one egg per day was not associated with increased risk of coronary heart disease or stroke

Subgroup analysis suggested that consumption of up to one egg per day was associated with a significantly elevated risk of coronary heart disease in diabetic populations, and a reduced risk of hemorrhagic stroke

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Tables

Table 1 | Characteristics of participants and follow-up in included studies of egg consumption in relation to risk of coronary heart disease and stroke

Author	Publication year	Study name	Country	Sex of population	Age at baseline (years)	No of participants	Mean length of follow-up (years)	Endpoints (No of cases)
Hu et al ³⁶	1999	Health Professionals Follow-up Study	USA	Male	40-75	37 851	8	Coronary heart disease (866)
Hu et al ³⁶	1999	Nurses' Health Study	USA	Female	34-59	80 082	14	Coronary heart disease (939)
Sauvagat et al ³⁹	2003	Hiroshima/Nagasaki Life Span Study	Japan	Male and female	34-103	34 807	16-17	Stroke mortality (1259)
Nakamura et al ³⁷	2004	NIPPON DATA80	Japan	Male	30+	4077	14	Ischemic heart disease mortality (39), stroke mortality (112)
Nakamura et al ³⁷	2004	NIPPON DATA80	Japan	Female	30+	5186	14	Ischemic heart disease mortality (41), stroke mortality (107)
Nakamura et al ⁴⁰	2006	Japan Public Health Center-based prospective study	Japan	Male and female	40-69	90 735	10.2	Coronary heart disease (462)
Qureshi et al ⁴¹	2007	NHANES-I	USA	Male and female	25-74	9734	20	Coronary artery disease (1584), stroke (655)
Djousse et al ⁴²	2008	Physicians' Health Study I	USA	Male	40-85	21 327	20	Myocardial infarction (1550), stroke (1342)
Scrafford et al ³⁴	2011	NHANES III	USA	Male	17+	6833	8.8	Coronary heart disease mortality (198), stroke mortality (63)
Scrafford et al ³⁴	2011	NHANES III	USA	Female	17+	8113	8.9	Coronary heart disease mortality (168), stroke mortality (74)
Bernstein et al ³⁸	2012	Health Professionals Follow-Up Study	USA	Male	40-75	43 150	22	Stroke (1397)
Bernstein et al ³⁸	2012	Nurses' Health Study	USA	Female	30-55	84 010	26	Stroke (2633)

NHANES-I=First National Health and Nutrition Examination Survey; NHANES III=Third National Health and Nutrition Examination Survey; NIPPON DATA80=National Integrated Project for Prospective Observation of Non-communicable Disease and its Trends in the Aged, 1980.

Table 2 | Outcomes and covariates of included studies of egg consumption in relation to risk of coronary heart disease and stroke

Study	Endpoints	Case ascertainment	Dietary category and relative risk (95% CI)	Covariates in fully adjusted model
Hu et al, 1999 ³⁶ (men)	Coronary heart disease	Self reported diagnosis or confirmed by medical records or autopsy	<1 egg/week, 1.0 (reference); 1, 1.06 (0.88 to 1.27); 2-4, 1.12 (0.95 to 1.33); 5-6, 0.90 (0.63 to 1.27); ≥7, 1.08 (0.79 to 1.48)	Age, body mass index, two year time periods, smoking, parental history of myocardial infarction, multivitamin supplement use, alcohol consumption, menopausal status and postmenopausal hormone use (women), history of hypertension, physical activity, and total energy intake
Hu et al, 1999 ³⁶ (women)	Coronary heart disease	Same as above	<1 egg/week, 1.0 (reference); 1, 0.82 (0.67 to 1.00); 2-4, 0.99 (0.82 to 1.18); 5-6, 0.95 (0.70 to 1.29); ≥7, 0.82 (0.60 to 1.13)	
Sauvaget et al, 2003 ³⁹	Stroke mortality	Confirmed by nationwide family registration system	Never, 1.0 (reference); ≤1 egg/week*, 0.74 (0.55 to 1.00); 2-4 eggs/week, 0.78 (0.59 to 1.04); almost daily, 0.72 (0.54 to 0.97)	Age, sex, birth cohort, city, radiation dose, body mass index, smoking, alcohol habits, education level, history of diabetes, or hypertension
Nakamura et al, 2004 ³⁷ (men)	Ischemic heart disease mortality, stroke mortality	Confirmed by National Vital Statistics	Ischemic heart disease mortality: seldom, 1.18 (0.26 to 5.42); 1-2 eggs/week, 1.71 (0.78 to 3.76); 0.5 eggs/day, 1.49 (0.63 to 3.48); 1 egg/day, 1.0 (reference) Stroke mortality: seldom, 0.93 (0.36 to 2.40); 1-2 eggs/week, 1.09 (0.69 to 1.72); 0.5 eggs/day, 1.10 (0.68 to 1.76); 1 egg/day, 1.0 (reference); ≥2 eggs/day, 0.25 (0.03 to 1.81)	Age, serum creatinine, total cholesterol, blood glucose, body mass index, blood pressures, use of blood pressure lowering drugs, smoking, and alcohol intake
Nakamura et al, 2004 ³⁷ (women)	Ischemic heart disease mortality, stroke mortality	Same as above	Ischemic heart disease mortality: seldom, 1.42 (0.56 to 3.62); 1-2 eggs/week, 0.64 (0.28 to 1.44); 0.5 eggs/day, 0.78 (0.35 to 1.82); 1 egg/day, 1.0 (reference); ≥2 eggs/day, 1.27 (0.16 to 9.80) Stroke mortality: seldom, 0.78 (0.35 to 1.73); 1-2 eggs/week, 0.79 (0.47 to 1.33); 0.5 eggs/day, 1.46 (0.89 to 2.4); 1 egg/day, 1.0 (reference); ≥2 eggs/day, 1.22 (0.29 to 5.17)	
Nakamura et al, 2006 ⁴⁰	Coronary heart disease	Confirmed by medical records, letter, telephone or death certificate	<1 egg/week*, 1.19 (0.86 to 1.64); 1-2 eggs/week, 1.00 (0.77 to 1.30); 3-4 eggs/week, 1.00 (0.79 to 1.26); almost daily, 1.0 (reference)	Age; sex; body mass index; hypertension; diabetes; use of cholesterol lowering drugs; smoking; alcohol drinking; whether participants intended to avoid cholesterol rich diets; consumption frequencies of meat, fish, vegetables, and fruits; and cohort effects
Qureshi et al, 2007 ⁴¹	Coronary artery disease, stroke	Confirmed by medical records or death certificate	Coronary artery disease: <1 egg/week, 1.0 (reference); 1-6, 1.0 (0.9 to 1.1); >6, 1.1 (0.9 to 1.3) Stroke: <1 egg/week, 1.0 (reference); 1-6, 0.9 (0.7 to 1.0); >6, 0.9 (0.7 to 1.1)	Age, sex, race or ethnicity, systolic blood pressure, diabetes mellitus, serum cholesterol, smoking, body mass index, and educational status
Djousse et al, 2008 ⁴²	Myocardial infarction, stroke	Confirmed by physicians or medical records	Myocardial infarction: <1 egg/week, 1.0 (reference); 1, 1.12 (0.96 to 1.31); 2-4, 1.16 (1.00 to 1.36); 5-6, 1.18 (0.93 to 1.49); ≥7, 0.90 (0.72 to 1.14) Stroke: <1 egg/week, 1.0 (reference); 1, 0.96 (0.82 to 1.13); 2-4, 1.06 (0.91 to 1.24); 5-6, 1.13 (0.89 to 1.42); ≥7, 0.99 (0.80 to 1.23)	Age, body mass index, smoking, 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
Scrafford et al, 2011 ³⁴ (men)	Coronary heart disease mortality, stroke mortality	Not applicable	Coronary heart disease mortality: <1 egg/week, 1.0 (reference); 1-6, 1.26 (0.79 to 2.00); >6, 1.13 (0.61 to 2.11) Stroke mortality: <1 egg/week, 1.0 (reference); 1-6, 1.00 (0.49 to 2.02); >6, 0.27 (0.10 to 0.73)	Age, energy, marital status, educational status, race or ethnicity, smoking, body mass index, waist to hip ratio, diabetes, hypertension, and dietary variables
Scrafford et al, 2011 ³⁴ (women)	Coronary heart disease mortality, stroke mortality	Not applicable	Coronary heart disease mortality: <1 egg/week, 1.0 (reference); 1-6, 1.12 (0.66 to 1.89); >6, 0.92 (0.27 to 3.11) Stroke mortality: <1 egg/week, 1.0 (reference); 1-6, 0.93 (0.46 to 1.90); >6, 1.03 (0.25 to 4.22)	
Bernstein et al, 2012 ³⁸ (men)	Stroke	Confirmed by medical records or autopsy report	0.14 eggs/week†, 1.0 (reference); 0.49, 0.80 (0.66 to 0.97); 1.19, 0.88 (0.73 to 1.05); 3.01, 0.80 (0.66 to 0.96); 5.53, 0.84 (0.68 to 1.04)	Age, time period, body mass index, smoking, physical exercise, parental history of early myocardial infarction, menopausal status in women, multivitamin use, vitamin E supplement use, aspirin use at least once per week, total energy, cereal fiber, alcohol, trans fat, fruit and vegetables, and other protein sources
Bernstein et al, 2012 ³⁸ (women)	Stroke	Same as above	0.49 eggs/week†, 1.0 (reference); 1.26, 0.90 (0.80 to 1.01); 2.17, 0.94 (0.83 to 1.05); 3.01, 0.86 (0.76 to 0.99); 4.69, 0.91 (0.80 to 1.04)	

Table 2 (continued)

Study	Endpoints	Case ascertainment	Dietary category and relative risk (95% CI)	Covariates in fully adjusted model
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*Unit of egg consumption was assumed.

†Servings per day converted to eggs consumed per week.

Table 3| Stratified analyses of relative risk of coronary heart disease and stroke

	No of reports*	Relative risk (95% CI)	P for heterogeneity	I ²	P for test
Coronary heart disease					
Total cases	9	0.99 (0.85 to 1.15)	0.97	0.0	0.88
Fatal cases	4	1.18 (0.71 to 1.96)	0.91	0.0	0.53
Coronary heart disease with diabetes†	5	1.54 (1.14 to 2.09)	0.59	0.0	0.01
Subgroup analyses for total coronary heart disease					
Sex					
Male	4	1.06 (0.89 to 1.25)	0.83	0.0	0.53
Female	3	0.99 (0.83 to 1.20)	0.99	0.0	0.95
Study location					
USA	6	1.01 (0.90 to 1.13)	0.96	0.0	0.89
Asia	3	0.95 (0.64 to 1.41)	0.76	0.0	0.79
No of participants					
>10 000	4	0.97 (0.81 to 1.15)	0.87	0.0	0.70
≤10 000	5	1.14 (0.83 to 1.56)	0.93	0.0	0.42
No of cases					
>500	4	1.00 (0.89 to 1.13)	0.79	0.0	0.94
≤500	5	0.96 (0.67 to 1.37)	0.93	0.0	0.83
Duration of follow-up					
>15 years	2	1.02 (0.89 to 1.16)	0.40	0.0	0.83
≤15 years	7	0.98 (0.81 to 1.19)	0.98	0.0	0.85
Repeated egg consumption measurements					
Yes	4	0.97 (0.81 to 1.15)	0.87	0.0	0.70
No	5	1.14 (0.83 to 1.56)	0.93	0.0	0.42
Study quality					
Score ≥8	5	0.97 (0.80 to 1.17)	0.93	0.0	0.74
Score <8	4	1.06 (0.88 to 1.28)	0.81	0.0	0.55
Controlling for other diet variables in models‡					
Yes	6	0.97 (0.82 to 1.15)	0.97	0.0	0.73
No	5	1.14 (0.84 to 1.55)	0.92	0.0	0.40
Controlling for serum cholesterol levels or use of cholesterol lowering drugs in models					
Yes	5	0.97 (0.75 to 1.26)	0.65	0.0	0.83
No	4	1.01 (0.86 to 1.18)	0.97	0.0	0.94
Stroke					
Total stroke	8	0.91 (0.81 to 1.02)	0.46	0.0	0.10
Fatal stroke	4	0.94 (0.81 to 1.10)	0.47	0.0	0.46
Hemorrhagic stroke†	3	0.75 (0.57 to 0.99)	0.21	36.8	0.04
Ischemic stroke†	4	0.91 (0.82 to 1.01)	0.79	0.0	0.08
Stroke with diabetes†	3	0.80 (0.29 to 2.15)	0.09	58.9	0.65
Subgroup analyses for total stroke					
Sex					
Male	4	0.89 (0.77 to 1.03)	<0.001	90.5	0.13
Female	4	0.91 (0.77 to 1.07)	0.24	29.0	0.25
Study location					
USA	5	0.90 (0.79 to 1.03)	0.38	4.9	0.13
Asia	3	0.94 (0.83 to 1.07)	0.28	20.6	0.34
No of participants					
>10 000	4	0.90 (0.80 to 1.02)	0.25	26.9	0.10
≤10 000	4	0.97 (0.75 to 1.27)	0.50	0.0	0.85

Table 3 (continued)

	No of reports*	Relative risk (95% CI)	P for heterogeneity	I ²	P for test
No of cases					
>500	5	0.91 (0.81 to 1.02)	0.38	5.0	0.09
≤500	3	1.00 (0.63 to 1.59)	0.35	4.2	0.99
Duration of follow-up					
>15 years	5	0.91 (0.81 to 1.02)	0.38	5.0	0.09
≤15 years	3	1.00 (0.63 to 1.59)	0.35	4.2	0.99
Repeated egg consumption measurements					
Yes	3	0.90 (0.78 to 1.04)	0.13	51.5	0.14
No	5	0.94 (0.83 to 1.08)	0.64	0.0	0.38
Study quality					
Score ≥7.5	5	1.03 (0.88 to 1.20)	0.51	0.0	0.71
Score <7.5	3	0.88 (0.77 to 1.01)	0.82	0.0	0.07
Controlling for other diet variables in models‡					
Yes	4	0.90 (0.79 to 1.04)	0.25	26.6	0.14
No	5	0.95 (0.83 to 1.08)	0.62	0.0	0.43
Controlling for serum cholesterol levels or use of cholesterol lowering drugs in models					
Yes	4	1.04 (0.91 to 1.18)	0.34	10.0	0.60
No	4	0.89 (0.77 to 1.01)	0.94	0.0	0.07

*Five articles reported their results by sex group; therefore, there were nine reports from six articles for coronary heart disease and eight reports from six articles for stroke.

†Owing to a lack of data for person years, results are relative risks (95% confidence intervals) comparing highest with lowest egg consumption.

‡Study by Scrafford and colleagues reported results both controlling for diet variables and not.

Figures

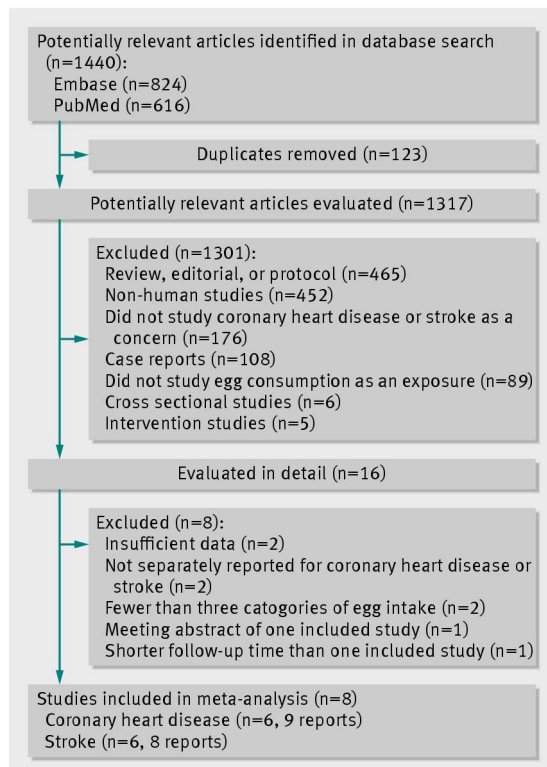


Fig 1 Flow diagram of literature search and study selection

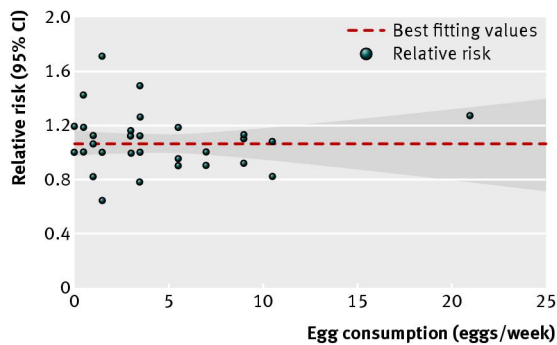


Fig 2 Dose-response analyses of egg consumption and risk of coronary heart disease

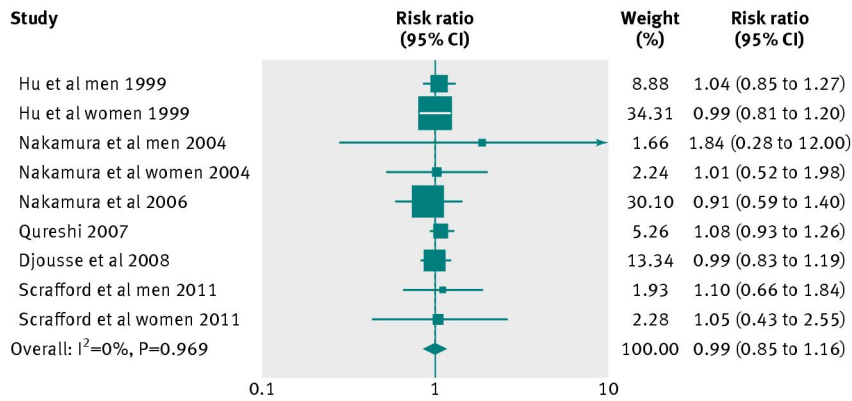


Fig 3 Forest plot of egg consumption and risk of coronary heart disease

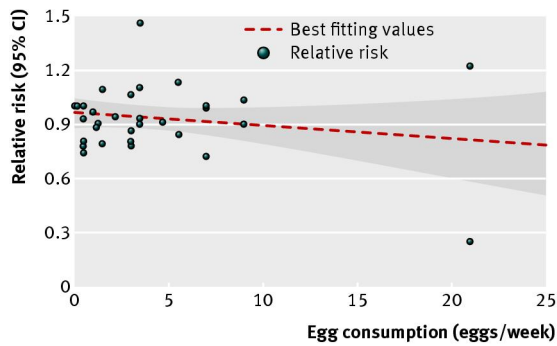


Fig 4 Dose-response analyses of egg consumption and risk of stroke

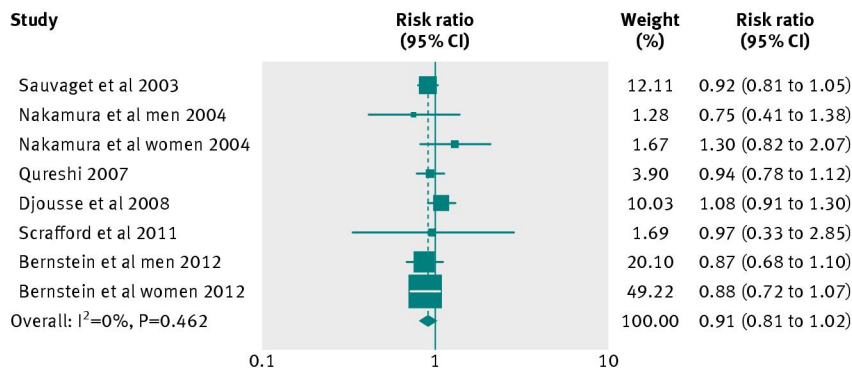


Fig 5 Forest plot of egg consumption and risk of stroke