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Egg consumption and risk of type 2 diabetes: a meta-analysis of prospective studies[1]

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ABSTRACT

Background: Observational data on the association between egg consumption and risk of type 2 diabetes mellitus (DM) have been inconsistent. Because eggs are a good source of protein and micronutrients and are inexpensive, it is important to clarify their role in the risk of developing DM.

Objective: We conducted a meta-analysis of published prospective cohort studies to evaluate the relation of egg consumption with the risk of DM.

Design: We searched PubMed, Ovid, Cochrane, and Google Scholar (up to October 2015) to retrieve published studies. We used RRs from extreme categories of egg consumption for the main analysis but also evaluated dose response by using cubic splines and generalized least squares regression.

Results: We identified 12 cohorts for a total of 219,979 subjects and 8911 cases of DM. When comparing the highest with the lowest category of egg intake, pooled multivariate RRs of DM were 1.09 (95% CI: 0.99, 1.20) using the fixed-effect model and 1.06 (95% CI: 0.86, 1.30) using the random-effect model. There was evidence for heterogeneity (I^2 = 73.6%, $P < 0.001$). When stratified by geographic area, there was a 39% higher risk of DM (95% CI: 21%, 60%) comparing highest with lowest egg consumption in US studies (I^2 = 45.4%, P = 0.089) and no elevated risk of DM with egg intake in non-US studies (RR = 0.89; 95% CI: 0.79, 1.02 using the fixed-effect model, $P < 0.001$ comparing US with non-US studies). In a dose-response assessment using cubic splines, elevated risk of DM was observed in US studies among people consuming ≥3 eggs/wk but not in non-US studies.

Conclusions: Our meta-analysis shows no relation between infrequent egg consumption and DM risk but suggests a modest elevated risk of DM with ≥3 eggs/wk that is restricted to US studies. *Am J Clin Nutr* doi: 10.3945/ajcn.115.119933.

Keywords: nutrition, epidemiology, diet, eggs, diabetes mellitus

INTRODUCTION

Diabetes mellitus (DM)[4] remains a worldwide health concern (1–4), estimated to affect 350 million people by 2030 (5). The lifetime risk of DM ranges from 27% to 53% at birth in the United States (6), and projected direct costs for DM will reach $300 billion by 2030 (7). Despite concerted efforts to reduce risk factors among diabetic patients, 65% of people with DM will die of cardiovascular disease (8). Coronary artery disease (CAD) and stroke are the leading causes of death and for which elevated LDL cholesterol is a major determinant (9). This led to the American Heart Association's recommendation of limiting daily cholesterol intake to <300 mg/d for healthy individuals and <200 mg/d for at-risk individuals (10), a message consistent with the 2015 dietary guidelines for Americans (11). Eggs are one of the main sources of dietary cholesterol, with a large egg containing ~200 mg cholesterol (12). It is noteworthy that evidence linking dietary cholesterol to elevated plasma LDL cholesterol is weak at present (13–15). Although data on the association of egg consumption with CAD or stroke have been inconsistent in the general population (16–19), few studies suggested that egg consumption may be associated with a higher risk of mortality, CAD, or stroke among people with DM (17, 20–24). Shin et al. (17) in a prior meta-analysis of prospective cohort studies demonstrated no relation between eggs and CAD or stroke in general but a 69% increased risk of CVD among diabetic subjects; in addition, an increased risk of DM was reported with egg consumption when 5 studies were pooled. However, data on the dose-response relation between egg consumption and DM are lacking, and several subsequent studies have reported conflicting results on the relation of eggs with DM (25–29).

Elucidating the role of egg consumption in the development of DM is important given the affordability of eggs worldwide as a good source of protein. Therefore, we conducted this meta-analysis of currently available prospective cohort studies to assess the relation of egg consumption with DM risk.

METHODS

Search strategy and study selection

We conducted a search in PubMed, Ovid, Cochrane, and Google Scholar up to October 2015 for prospective cohort studies that reported the association between egg consumption

[1] The authors reported no funding received for this study.

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[4] Abbreviations used: CAD, coronary artery disease; DM, diabetes mellitus; TMAO, trimethylamine-N-oxide.

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and incident DM. We used the keywords eggs, egg, eggs or egg, diabetes, diabetic, and diabetes or diabetic for our search. We restricted the search to studies written in English and human subjects. In case of multiple reports from the same study, we used the most complete and/or recently reported data. References of the retrieved articles were manually screened for additional eligible studies.

Exposure and outcome

We used the midpoint as the average intake of eggs per week or per day in each category. If the highest category of egg consumption had an open upper boundary, we multiplied the lower boundary by 1.5 to obtain an estimate of average egg consumption in that category as previously described for open-ended categories (30). When egg consumption was provided as grams per day, we assumed that one average egg was equivalent to 50 g for conversion (31, 32). The primary outcome was DM as defined within each individual study. Most studies defined DM by using the American Diabetic Association criteria [fasting glucose ≥126 mg/dL (7.0 mmol/L), hemoglobin A1c ≥6.5% (48 mmol/mol), or 2-h value in an oral glucose tolerance test or nonfasting glucose ≥200 mg/dL (11.1 mmol/L)] (33).

Data extraction

Data were extracted by 2 independent authors (LD and OAK). Discrepancies were resolved by group discussion. Each author used the same template to extract from the study the first author's name, year of publication, country where the study was conducted, population characteristics (mean age and range, sex proportion, sample size), incidence of DM, mean follow-up, categories of egg consumption, person-time of follow-up within each category of egg consumption, statistical method used to obtain effect size (logistic regression or Cox proportional hazard model), covariates adjusted for, and RR with 95% CI. For each category, we extracted the fully adjusted RR. Where appropriate, we

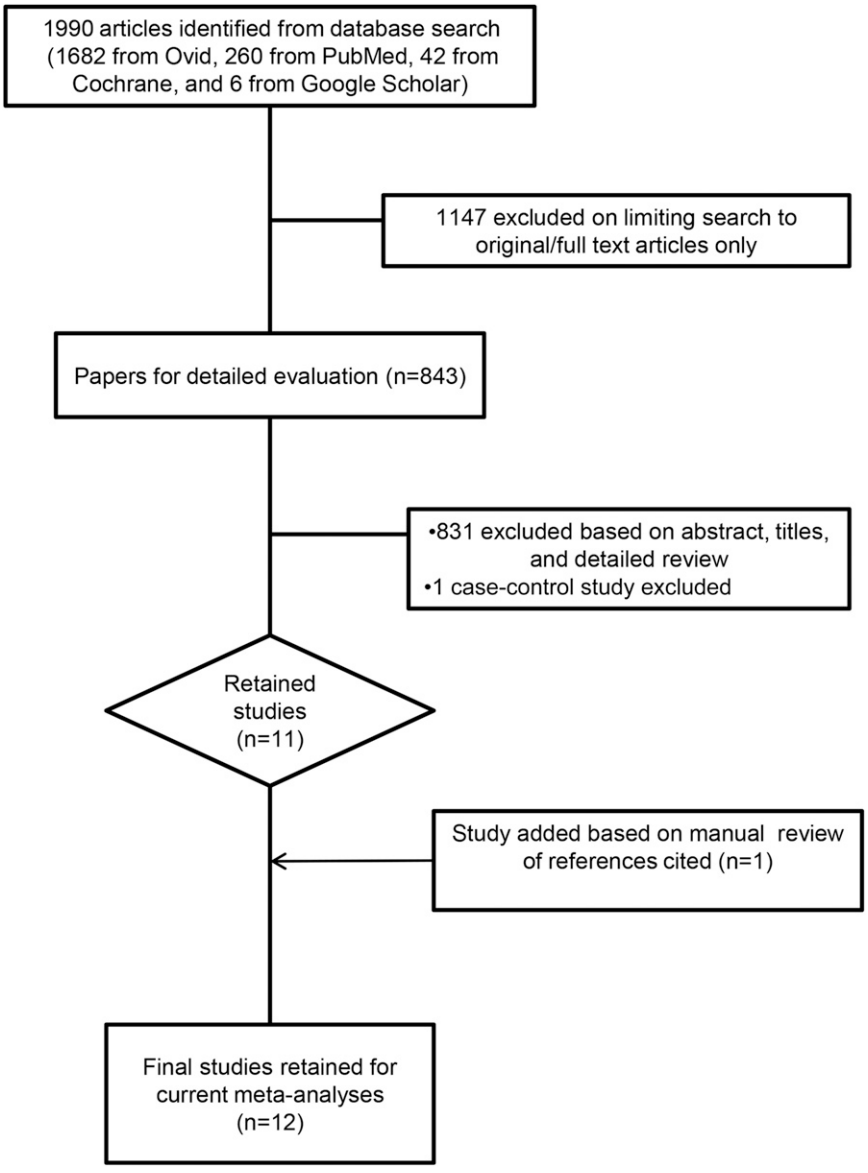

FIGURE 1 Flow diagram of study selection process.

TABLE 1
Baseline characteristics of studies included in the meta-analysis[1]

Reference	Study name	Age, mean (range), y	Sample size, *n*	Sex	Follow-up time, y	Dietary assessment	Categories of egg intake	Diabetes events, *n*	Adjusted variables
Vang (36), 2008, United States	Adventist Mortality Study and Adventist Health Study	65 (45–88)	8401	61% M	17.0	Semiquantitative questionnaire	Three groups: 0, <1, and ≥1/wk	543	Age and sex
Djoussé (37), 2009, United States	Physician's Health Study	53.5 (39.7–85.9)	20,703	100% M	20.0	Self-administered semiquantitative FFQ	Six groups: 0, <1, 1, 2–4, 5–6, and ≥7/wk	1,921	Age, BMI, smoking, alcohol, exercise, HTN, and dyslipidemia
Djoussé (37), 2009, United States	Women's Health Study	54.5 (38.7–89.9)	36,295	100% F	11.7	131 FFQ	Six groups: 0, <1, 1, 2–4, 5–6, and ≥7/wk	2,112	Age, BMI, smoking, alcohol, exercise, energy intake, fruits and vegetables, saturated FA, *trans* FA, PUFA, red meat, HTN, dyslipidemia, and family history of DM
Djoussé (38), 2010, United States	Cardiovascular Health Study	73.2 (65–95)	1669	100% M	11.3	Picture-sorted food questionnaire	Five groups: 0, <1/mo, 1–3/mo, 1–4/wk, and almost every day	142	Age, race, BMI, smoking, alcohol, exercise, cereal-fiber intake, and field center
Djoussé (38), 2010, United States	Cardiovascular Health Study	72.1 (65–98)	2229	100% F	11.3	Picture-sorted food questionnaire	Five groups: 0, <1/mo, 1–3/mo, 1–4/wk, and almost every day	171	Age, race, BMI, smoking, alcohol, exercise, cereal-fiber intake, and field center
Zazpe (25), 2013, Spain	Sun Project	38.5 (20–90)	15,956	40% M	6.6	136 FFQ	Four groups: <1, 1, 2–4, and >4/wk	91	Age, sex, BMI, smoking, alcohol, exercise, adherence to Mediterranean food pattern, energy intake, CVD, HTN, dyslipidemia, and family history of DM
Kurotani (26), 2014, Japan	Japan Public Health Center	51 (45–75)	27,248	100% M	5.0	147 FFQ	Four groups: 11, 21, 33, and 64 g/d	672	Age, BMI, smoking, alcohol, physical activity, energy, dietary variables, public health center area, HTN, and family history of DM
Kurotani (26), 2014, Japan	Japan Public Health Center	51 (45–75)	36,218	100% F	5.0	147 FFQ	Four groups: 10, 19, 29, and 56 g/d	493	Age, BMI, smoking, alcohol, physical activity, energy, dietary variables, public health center area, HTN, and family history of DM
Virtanen (27), 2015, Finland	Kuopio Ischemic Heart Disease Risk Factor Study	53 (42–60)	2332	100% M	19.3	4-d food records	Four groups: <14, 14–26, 27–45, and >45 g/d	432	Age, BMI, HTN, smoking, alcohol, physical activity, exam year, energy, family history of DM, education, fiber, fruits/berries/vegetables, **ω**-3 PUFA, and dietary cholesterol
Djoussé (28), 2015, United States	Jackson Heart Study	53.5 (21–95)	1297	100% M	7.2	FFQ	Six groups: <1/mo, 1–3/mo, 1/wk, 2/wk, 3–4/wk, and ≥5/wk	191	Age adjusted only
Djoussé (28), 2015, United States	Jackson Heart Study	54.2 (21–92)	2267	100% F	7.3	FFQ	Six groups: <1/mo, 1–3/mo, 1/wk, 2/wk, 3–4/wk, and ≥5/wk	340	Age adjusted only
Lajous (29), 2015, France	E3N Study	52.7	65,364	100% F	14	FFQ	Five groups: 0, <1, 1–1.9, 2–4.9, and ≥5/wk	1803	Age, education, smoking, physical activity, hormone replacement therapy, hypertension, dyslipidemia, energy, dietary variables, and BMI

[1]Dietary variables: magnesium intake, calcium intake, coffee consumption, rice intake, fish and shellfish intake, meat intake, vegetable intake, soft drink intake. CVD, cardiovascular disease; DM, type 2 diabetes mellitus; E3N, Etude Epidemiologique aupres des femmes de la Mutuelle Generale de l'Education Nationale; FA, fatty acids; FFQ, food-frequency questionnaire; HTN, hypertension.

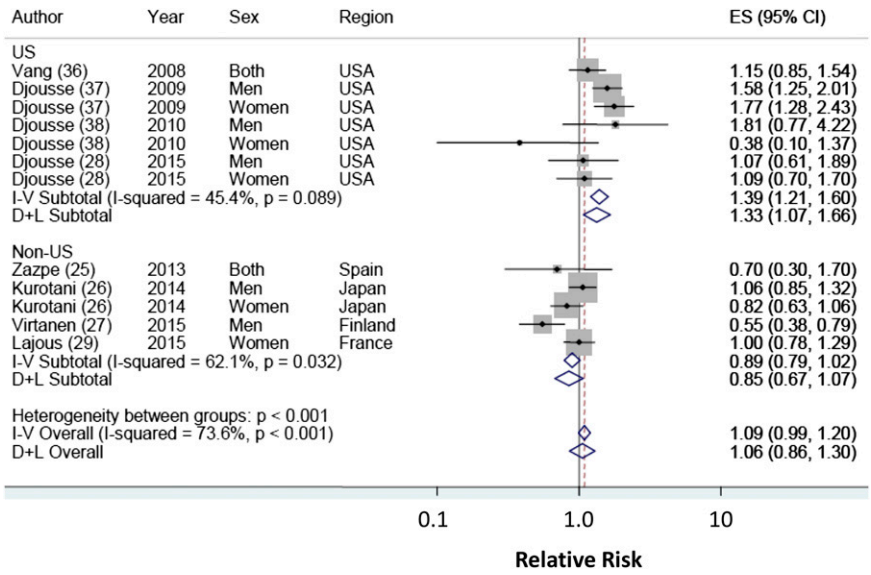

FIGURE 2 Meta-analysis of the association of egg consumption with diabetes mellitus risk (overall and stratified by geographic location: US compared with non-US studies). D+L: DerSimonian-Laird method; ES, effect size; I-V, inverse-weighted variance method.

contacted lead authors to obtain missing person-time and/or events by category of egg consumption.

Statistical method

We initially pooled RRs and their 95% CIs from the highest compared with the lowest category of egg consumption in each study. For studies that stratified analyses by sex, we considered each sex as an independent study. We presented both fixed (using inverse weighted variance) and random [using the DerSimonian-Laird method (34)] estimates of effects. We assessed heterogeneity by using the Q statistic, I^2, and P value <0.05. However, we did not want to rely on the I^2 value to pick between the random- and fixed-effect model because I^2 can be influenced by small studies and sampling error when estimating a fixed effect. We conducted subgroup analyses by geographic location. Furthermore, we assessed the presence of influential studies by using the method of removing one study at a time. We assessed publication bias by using Begg's and Egger's tests and visual inspection of the funnel plot. To assess the dose-response relation and evaluate the shape of the egg-DM relation, we used generalized least squares regression described by Greenland and Longnecker (35) and fitted cubic splines with knots at the 5th, 35th, 65th, and 95th percentile of egg distribution (corresponding to 0, 1, 2.7, and 8.6 eggs/wk). Two-sided P value was used with an α level of 0.05. All data analyses were performed by using STATA software (version 13.1; StataCorp LP).

RESULTS

Overall, the search yielded 1990 reports, and we excluded 1979 studies because of nonhuman subjects, non-English language, nonrelevant topic, and one case-control study design. With 1 study identified through manual review, we included 12 prospective cohorts from 8 unique cohorts after full-text review. The results of the literature search along with the excluded studies are summarized in **Figure 1**. Characteristics of individual studies are shown in **Table 1**.

Population-based unique prospective cohort studies included in this meta-analysis were those by Vang et al. (36), Djoussé et al. (28, 37, 38), Zazpe et al. (25), Kurotani et al. (26), Virtanen et al. (27), and Lajous et al. (29). Of the 12 studies, 7 were conducted in the United States, whereas 5 were conducted outside the United States. Study participants were followed over a range of 5–20 y. Of the 8 unique cohorts, Lajous et al. (29) had the largest sample size (n = 65,364), whereas Virtanen et al. (27) had the least number of study participants (n = 2332).

Overall, we analyzed data from 219,979 subjects, including 8911 cases of DM. When comparing the highest with the lowest category of egg intake, pooled multivariate RRs of incident DM were 1.09 (95% CI: 0.99, 1.20) using a fixed-effect model and 1.06 (95% CI: 0.86, 1.30) using a random-effect model (**Figure 2**). When stratified by geographic location, we observed a 39% higher risk of DM (RR = 1.39; 95% CI: 1.21, 1.60) comparing the highest and lowest egg consumption categories when restricted to US studies and using the fixed-effect model. In

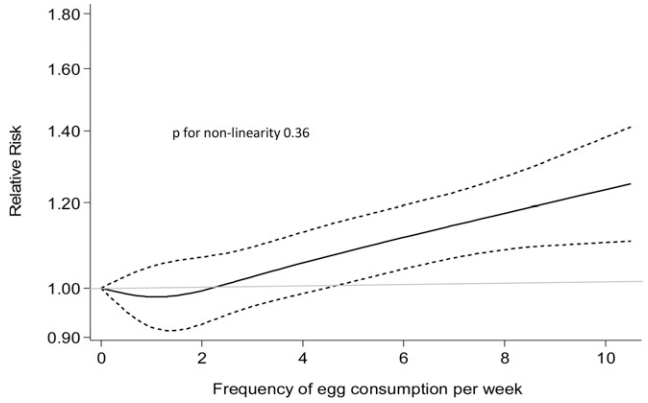

FIGURE 3 Dose-response relation between egg consumption and incident diabetes mellitus. Data were modeled with fixed-effects restricted cubic spline models with 4 kn (5th, 35th, 65th, and 95th percentiles) and using generalized least squares regression to estimate the covariances of multivariable-adjusted RRs.

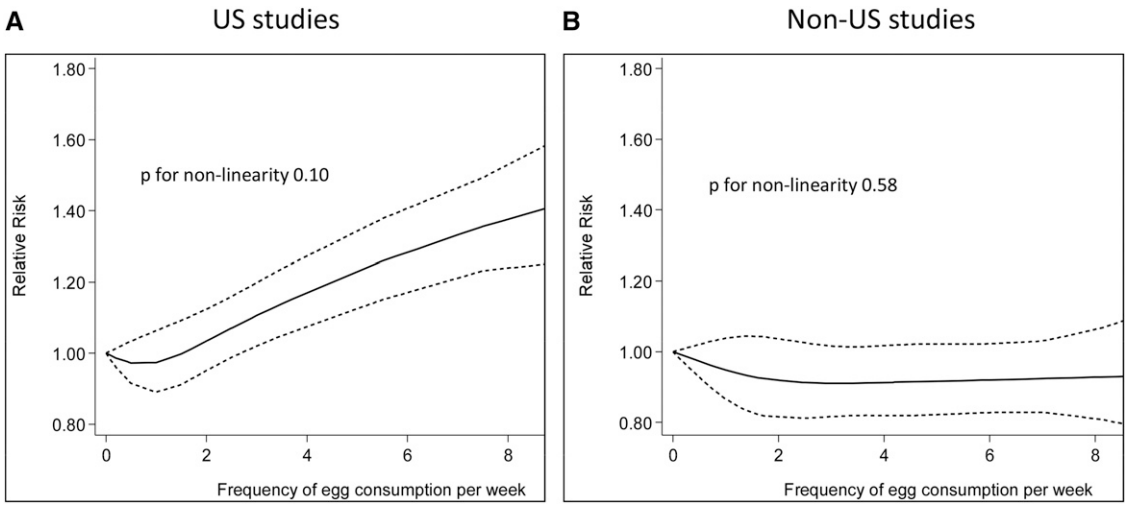

FIGURE 4 Dose-response relation between egg consumption and incident diabetes mellitus stratified by geographic location [US (A) compared with non-US (B) studies] using fixed-effect restricted cubic spline models with 4 kn (5th, 35th, 65th, and 95th percentiles) and generalized least squares regression.

contrast, there was no statistically significant association of egg consumption with DM in non-US studies (RR = 0.89; 95% CI: 0.79, 1.02 using the fixed-effect model, $P < 0.001$ when comparing US with non-US studies) (Figure 2). In a dose-response analysis using cubic splines, we observed a modestly elevated risk of DM only with more frequent consumption of eggs [i.e., HR of 1.07 (95% CI: 1.00, 1.15) for egg consumption of 4.6/wk; *P*-nonlinearity = 0.36 from generalized least squares regression] (**Figure 3**). In a secondary analysis stratified by geographic location, the suggestive threshold relation was seen in US studies (*P*-nonlinearity = 0.10) but not in non-US studies (**Figure 4**).

There was evidence of statistically significant heterogeneity ($I^2 = 73.6\%$; $P < 0.001$) across studies (Figure 2). However, when stratified by geographic location, there was modest heterogeneity among US studies ($I^2 = 45.4\%$; $P = 0.089$) and substantial heterogeneity noted among Non-US studies ($I^2 = 62.1\%$; $P = 0.032$) (Figure 2). There was no evidence for publication bias on visual inspection of the funnel plot (**Figure 5**) as supported by the Begg's ($P = 0.45$) and Egger's test ($P = 0.53$). Last, exclusion of one study at a time did not influence the main results (data not shown).

DISCUSSION

In this meta-analysis of 12 prospective cohort studies, we found that consumption of <4 eggs/wk was not associated with the risk of DM. However, a stratified analysis showed an elevated risk of DM with consumption of ≥3 eggs/wk among US studies but no elevated risk among non-US studies (*P*-difference < 0.001). There was no evidence of publication bias or influential study.

Despite the limited number of published studies on egg consumption with DM risk, this meta-analysis provides novel and important information on the dose-response relation. First, our results are consistent with no elevated risk of DM with infrequent

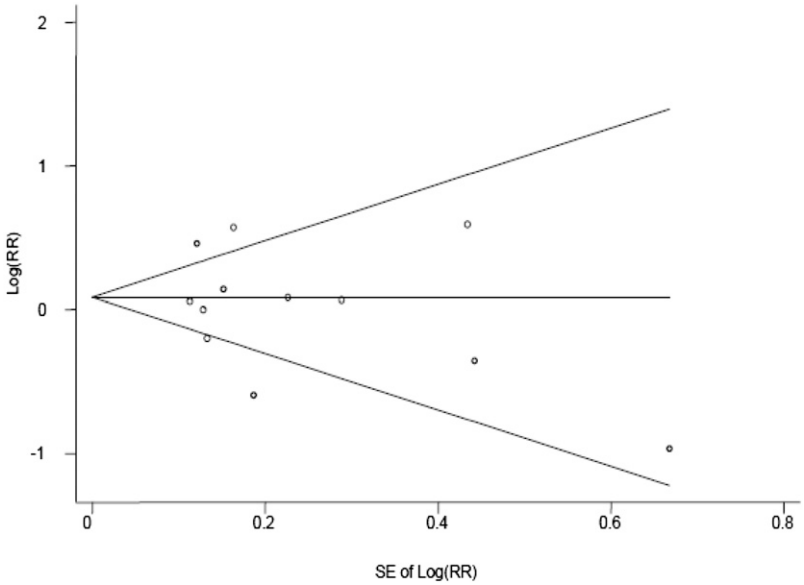

FIGURE 5 Begg's funnel plot with 95% pseudo–CIs.

egg consumption, regardless of geographic region. This is reassuring for individuals who rely on eggs as a source of affordable protein. Second, our meta-regression revealed a statistically significant difference between US and non-US studies in that elevated risk of DM was observed with ≥3 eggs/wk only in US but not European or Japanese studies. This raises the question as to whether frequent consumption of eggs in the United States is generally associated with other dietary factors that might heighten the risk of DM or whether eggs can independently raise the risk of DM. For example, frequent consumption of eggs with processed meats and/or bacon that has been shown to be associated with a higher risk of DM could provide an alternative explanation for observed elevated risk of DM with ≥3 eggs/wk in the United States. However, not all US studies showed elevated risk of DM with eggs, including the Jackson Heart Study (28) or the Adventist (36) and Cardiovascular Health (38) Studies. A lack of data on the overall quality of the diet within individual studies that were pooled prevented us from further examining this issue in the current meta-analysis. The observed elevated risk of DM with consumption of ≥3 eggs/wk in US studies merits some comments. Although an average egg contains about 200 mg cholesterol, there is little evidence from the literature suggesting that dietary cholesterol has a major impact on the pathogenesis of DM. Although Qiu et al. (39) reported a positive association between dietary cholesterol intake and risk of gestational DM, our group did not show any association between dietary cholesterol and incident DM in older adults (38). Furthermore, a Japanese study (26) reported no relation between dietary cholesterol and DM risk in men and a 23% lower odds of DM in women when comparing the highest and lowest quartiles of dietary cholesterol. In addition, cross-sectional analyses revealed no relation between egg consumption and hemoglobin A1c, HOMA-IR, and homeostasis model assessment of beta-cell function from the fasting glucose and fasting insulin equation in the Jackson Heart Study (28). Last, a human study found that 12 wk of a high-protein diet with eggs improved fasting blood glucose (−0.5 mmol/L) (14). Taken together, current data do not lend support to the hypothesis that dietary cholesterol is a major culprit for the development of DM. If not dietary cholesterol from eggs, what else might explain the slight elevated risk of DM observed with a higher frequency of egg intake in the current meta-analysis?

Some authors have proposed that trimethylamine-N-oxide (TMAO) (40)—a metabolite of choline found in eggs as well as seafood—could help explain the positive relation of eggs with DM. Tang et al. (41) showed a positive association between egg consumption and TMAO concentration. In a randomized controlled trial of 6 volunteers, higher consumption of egg yolk increased plasma and urine concentrations of TMAO (42). It is possible that TMAO increases LDL oxidation and promotes inflammation (43), thereby leading to a heightened risk of DM (44). However, given the limited amount of TMAO generated from eggs when contrasted with other sources (45), it is less likely to be the responsible mediator. The lack of prospective studies of TMAO and DM risk prevents us from confirming prior conjecture on the relation of TMAO with DM. In addition, few of the studies meta-analyzed adjusted for relevant dietary factors or dietary patterns to further elucidate this issue. This suggests that confounding by dietary patterns remains a viable and likely explanation of the observed positive relation of ≥3 eggs/wk with DM risk in US studies. It is important for future studies to account for overall dietary patterns and/or foods consumed with eggs that may heighten the risk of DM to further elucidate this topic.

Additional limitations of this meta-analysis include the observational nature of studies pooled that cannot exclude unmeasured or residual confounding as a partial or complete source of explanation for observed results. Furthermore, it was not possible to capture all forms of egg consumption (omelets, pasta, cake, or mixed dishes) or method of preparation (boiled, fried, or raw) in most studies. Self-reported egg consumption could have led to misclassification of egg consumption.

On the other hand, this study has numerous strengths, including a large sample size with almost 9000 DM events, availability of data in men and women from various geographic regions in the world, robustness of the data to various sensitivity analyses, and the prospective design of 12 studies included. It is important for future studies to consider the overall dietary pattern while assessing the role of eggs on the pathogenesis of DM, especially among the US population.

In conclusion, the current meta-analysis showed no relation between infrequent egg consumption and DM risk but suggests a modest elevated risk of DM with consumption of ≥3 eggs/wk that is restricted to US studies.

The authors' responsibilities were as follows—LD: designed research, analyzed data, and had primary responsibility for final content; LD and OAK: wrote the article; and all authors: conducted research and read and approved the final manuscript. The authors declared no conflict of interest.

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