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Egg consumption and risk of cardiovascular diseases and diabetes: A meta-analysis

Yuehua Li [a,b,c,1], Chenghui Zhou [a,d,1], Xianliang Zhou [a,b,*], Lihuan Li [a,d,**]

[a] State Key Laboratory of Cardiovascular Medicine, Fuwai Hospital, National Center for Cardiovascular Disease, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100037, China
[b] Department of Hypertension, Fuwai Hospital, National Center for Cardiovascular Disease, Beijing 100037, China
[c] Key Laboratory for Clinical Cardiovascular Genetics and Sino-German Laboratory for Molecular Medicine, Fuwai Hospital, National Center for Cardiovascular Disease, Beijing 100037, China
[d] Department of Anesthesiology, Fuwai Hospital, National Center for Cardiovascular Disease, Beijing 100037, China

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ABSTRACT

Objectives: To assess the dose–response relationship between egg consumption and the risk of cardiovascular diseases (CVD) and diabetes.
Methods: We systematically searched MEDLINE database through December 2012. Fixed- or random-effects model was used to pool the relative risks (RRs) and their 95% confidence intervals (CIs). Subgroup analyses was performed to explore the potential sources of heterogeneity. Weighted linear regression model was used to estimate the dose–response relationship.
Results: Fourteen studies involving 320,778 subjects were included. The pooled RRs of the risk of CVD, CVD for separated diabetes patients, and diabetes for the highest vs lowest egg intake were 1.19 (95% CI 1.02–1.38), 1.83 (95% CI 1.42–2.37), 1.68 (95% CI 1.41–2.00), respectively. For each 4/week increment in egg intake, the RRs of the risk for CVD, CVD for separated diabetes patients, diabetes was 1.06 (95% CI 1.03–1.10), 1.40 (95% CI 1.25–1.57), 1.29 (95% CI 1.21–1.37), respectively. Subgroup analyses showed that population in other western countries have increased CVD than ones in USA (RR 2.00, 95% CI 1.14 to 3.51 vs 1.13, 95% CI 0.98 to 1.30, $P = 0.02$ for subgroup difference).
Conclusions: Our study suggests that there is a dose–response positive association between egg consumption and the risk of CVD and diabetes.

1. Introduction

Egg is one of the most common, available, and inexpensive food in our daily life. Egg serves as the major source of dietary cholesterol, containing 213 mg cholesterol per egg [1,2]. Evidence from animal and human metabolic studies have found that dietary cholesterol from egg could raise serum levels of low density lipoprotein cholesterol (LDL-C), a well-established independent risk factor for cardiometabolic diseases including cardiovascular diseases (CVD) and diabetes [3–6]. The main effect of dietary cholesterol is not on fasting lipids, but on the post-prandial state [7]. Dietary cholesterol increases postprandial inflammation and oxidative stress, and impairs endothelial function [8,9]. Furthermore, lecithin (approximately 250 mg in a large egg yolk) is converted by intestinal bacteria to trimethylamine, in turn oxidized by the liver to trimethylamine oxide, which is pro-atherosclerotic [10,11]. On the other hand, egg also provides other essential nutrients including high-quality proteins, unsaturated fat, folate, and various vitamins, which are regarded as the protective factors for health status [1,2]. Partly owing to the multifacet effect of egg intake, current international dietary guidelines are conflicted in recommending or limiting egg consumption for prevention of cardiometabolic diseases. For example, guidelines from American Heart Association (AHA) and the National Cholesterol Education Program (NCEP) Adult Treatment Panel III advice healthy adults limit dietary cholesterol intake less than 300 mg each day and egg intake [12–14]. However, several other guidelines have yielded different points, ranging from no restriction to recommend regular intakes of egg [15,16].

* Corresponding author. State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishilu, Beijing 100037, China. Tel.: +86 10 88398868; fax: +86 10 8839 8358.
** Corresponding author. State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, 167 Beilishilu, Beijing 100037, China. Tel./fax: +86 10 88372598.
E-mail addresses: xlzhou-fw@hotmail.com (X. Zhou), llhfw59@163.com (L. Li).
[1] Yuehua Li and Chenghui Zhou contributed equally to this article.

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The controversy among the dietary guidelines maybe directly derived from inconsistent results of epidemiologic studies about the relationship of egg consumption and cardiometabolic diseases. Some observational studies have reported that frequent egg consumption was associated with high risk of CVD or diabetes [17–27], while others have found null disease-specific association [1,28–34]. Given the mixed results among the studies, a systematic review and meta-analysis will help to clarify this issue. The purpose of this meta-analysis was to provide quantitative assessment of relationship between egg consumption and the risk of CVD and diabetes. Furthermore, we tried to quantify the dose–response relationship as well as to explore the potential modifiable factors.

2. Materials and methods

We performed this meta-analysis according to the MOOSE (Meta-Analysis of Observational Studies in Epidemiology) guidelines [35].

2.1. Search strategy

We searched MEDLINE (from 1930 to Dec 2012), reviews and relevant articles. The keywords used in the search were “egg or egg consumption or diet cholesterol” paired with “CVD or diabetes or mortality or coronary heart disease or heart failure”. No language restriction was applied.

2.2. Outcomes and study selection

One outcome was risk of CVD which included coronary heart disease, ischaemic heart disease, or heart failure. The other outcome was the risk of diabetes. Both of the outcomes were defined by each individual study.

Inclusion criteria for retrieved studies were: (1) cohort, case–control or cross-sectional design; (2) provided at least one of the pre-mentioned outcomes; (3) provided the multi-variable adjusted relative risk (RR) and their 95% confidence intervals (CIs); (4) considered the lowest category of egg consumption as the referent group and other categories as exposed group; (5) studies were not performed in special population such as pregnant women.

2.3. Data extraction

Data were extracted by two independent author (Y.L. and C.Z.). Discrepancies were resolved by group discussion. The extracted data included source of study (author, publication year, country), population characteristics (including mean age, male proportion, number of subjects and cases), study design, follow-up term, category of egg intake, methods for measuring egg consumption, adjusted covariates, the outcomes, RRs and their 95% CIs. For each category, we extracted the most fully adjusted RR.

2.4. Data synthesis and analysis

We pooled the RRs and their 95% CIs from the highest versus lowest category of egg consumption in each study. We primarily used the fixed-effects model weighted by inverse variance. If there was significant heterogeneity, we would report it and use the random-effects model [36]. The heterogeneity was assessed by Q statistic, I-squared and P value ($P < 0.1$ was considered to be statistically significant) [37]. Subgroup analysis was conducted to explore the potential sources of heterogeneity by specified study characteristics including follow-up term, gender, study design and area. The weighted liner regression model was used to explore the dose–response relationship between egg consumption and the outcomes of interest [38]. The average intake of egg in each category which estimated by mean of the lower and upper bound. If the highest category of egg intake had an open upper boundary, mean egg intake was estimated to be 1.2 times the lower boundary [38].

Publication bias was assessed by Begg’s funnel plot and Egg’s regression asymmetry [39]. Two sided P value < 0.05 was considered to be significant, except where otherwise specified. All data analysis were performed by STATA software (10.0 version, StataCorporation, TX, USA).

3. Results

3.1. Search results

We identified 4198 articles by database and manual searching. We further excluded nonrelevant 4168 ones. Thirty potential articles were selected for detailed evaluations. Sixteen articles were excluded for the following reasons: reviews ($n = 3$), not relevant to the outcomes of interest ($n = 8$), performed in pregnant women ($n = 1$), without providing the multi-variable adjusted RR ($n = 2$), without providing the lowest category of egg intake as the referent ($n = 2$) (Fig. 1). Therefore, fourteen studies involved 320 778 subjects were included in our meta-analysis [1,17–25,31–34]. Because five studies separately reported the results about male and female [1,22,24,32,33], nineteen independent studies were included. Among them, twelve reported the risk of CVD [1,17–21,23,31,33,34], six reported the risk of CVD in separated diabetes patients [1,20,23,31,33], and seven reported the risk of diabetes [22,24,25,32].

3.2. Study characteristics

The main characteristics of all included trials were listed in Table 1. The sample size ranged from 488 to 117,943. Study design types were as follows: prospective cohort studies ($n = 11$) [1,17,19–23,31–34] case–control study ($n = 1$) [25], cross-sectional studies ($n = 2$) [18,24]. Studies were conducted in USA ($n = 10$) [1,19–23,31–33], other western countries ($n = 4$) [17,18,25,34], and China ($n = 1$) [24]. The mean age ranged from 33.4y to 74.5y. The follow-up term varied from 6.1y to 20y in prospective studies. Egg intake in each individual study was classified into 2 to 6 categories.

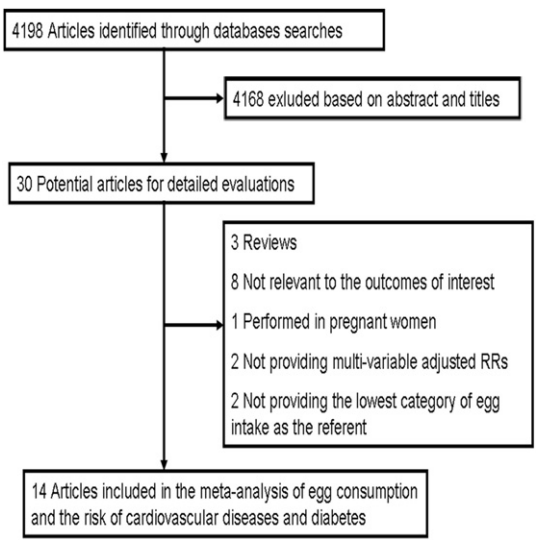

Fig. 1. Flow chart of the trial selection process. RR: relative risk.

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Table 1
Characteristics of included studies.

Study	Year	Country	Study design	Men %	Mean age	Follow-up term y	No. of subjects	No. of cases	Outcome assessments
Mann et al. [17]	1997	New Zealand	Cohort	38	33.4	13.3	10,802	525	ICD codes 410-414
Hu et al. (M) [1]	1999	USA	Cohort	100	53.3	8	37,851	866	Medical record
Hu et al. (F) [1]	1999	USA	Cohort	0	45.9	14	80,082	939	Medical record
Qureshi et al. [31]	2007	USA	Cohort	38.7	49.2	20	9734	1239	ICD codes 9
Burke et al. [18]	2007	Australia	Cross-sectional	50.8	NA		488	130	Medical records, ICD codes 9, 10, 410-414, 427, 428
Djousse et al. [19]	2008	USA	Cohort	100	53.7	20.4	21,275	1084	Medical record
Djousse et al. [20]	2008	USA	Cohort	100	53.7	20.4	21,327	8071	The Endpoint Committee of the PHS
Nerrleton et al. [21]	2008	USA	Cohort	45.5	54.2	13.3	14,153	1140	ICD-9 (codes 428 and I50, ICD-10
Scrafford et al. (M) [33]	2011	USA	Cohort	100	42.1	8.8	6833	261	ICD codes I20-I25; I60-69
Scrafford et al. (F) [33]	2011	USA	Cohort	0	42	8.9	8113	142	ICD codes I20-I25; I60-69
Zazpe et al. [34]	2011	Spain	Cohort	40.9	38.4	6.1	14,185	91	Medical record
Houston et al. [23]	2011	USA	Cohort	45.5	74.5	9	1941	203	Medical record
Djousse et al. (M) [22]	2009	USA	Cohort	100	53.5	20	20,703	1921	Self-report or medical record
Djousse et al. (F) [22]	2009	USA	Cohort	0	54.5	11.7	36,295	2112	Self-report or medical record
Djousse et al. (M) [32]	2010	USA	Cohort	42.8	73.2	11.3	1668	142	Medical record
Djousse et al. (F) [32]	2010	USA	Cohort	57.2	72.1	11.3	2230	161	Medical record
Shi et al. (M) [24]	2011	China	Cross-sectional	100	47		1308	39	Fasting plasma glucose >7.0 mmol/L
Shi et al. (F) [24]	2011	China	Cross-sectional	0	47		1541	40	Fasting plasma glucose >7.0 mmol/L
Radzeviciene et al. [25]	2012	Lithuania	Case-control	28.2	64.7		702	234	WHO criteria

Study	Outcome	Exposure assessments	No. of categories	Adjusted variables
Mann et al. [17]	All-cause mortality; IHD	Semiquantitative FFQ	<1/w; 1–5/w; ≥6/w	Age, sex, smoking, social class
Hu et al. (M) [1]	CHD, stroke,	Diet questionnaire	<1/w; 1/w; 2–4/w; 5–6/w; ≥1/d	Age, sex, smoking, BMI, parental history of MI, multivitamin supplement, hypertension, physical activity, menopausal statas
Hu et al. (F) [1]	CHD, stroke,	Diet questionnaire	<1/w; 1/w; 2–4/w; 5–6/w; ≥1/d	Age, sex, smoking, BMI, parental history of MI, multivitamin supplement, hypertension, physical activity, menopausal statas
Qureshi et al. [31]	IHD; stroke; all-cause mortality;	Diet questionnaire	<1/w; 1–6/w; >6/w	Age, sex, serum cholesterol, hypertension, waist girth
Burke et al. [18]	CHD,	Interviewer administered questionnaire	<8/m; >8/m	Age, sex, race, DM, serum cholesterol, smoking, hypertension, BMI, educational status
Djousse et al. [19]	HF	Semiquantitative FFQ	Rarely; 1–3/m; 1/w; 2–4/w; 5–6/w; 1/d; 2+/d	Age, BMI, smoking, alcohol consumption; DM, AF, hypertension, physical activity; history of valvular disease and treatment of cholesterol
Djousse et al. [20]	All-cause mortality; MI; stroke;	Semiquantitative FFQ	Rarely; 1–3/m; 1/w; 2–4/w; 5–6/w; 1/d; 2+/d	Age, BMI, smoking, alcohol consumption; DM, AF, hypertension, physical activity, history of valvular disease and treatment of cholesterol
Nerrleton et al. [21]	HF	Interviewer administered questionnaire	<1/d, 1/d	Age, race, education, BMI, physical activity, energy, smoking, alcohol, fiber, sodium, meat, fruit consumption, baseline history of disease
Scrafford et al. (M) [33]	CHD mortality; stroke mortality;	Semiquantitative FFQ	<1/w; 1–6/w; >6/w	Age, energy, marital status, race/ethnicity, smoking, BMI, WHR, DM, hypertension, dietary variables
Scrafford et al. (F) [33]	CHD mortality, stroke mortality;	Semiquantitative FFQ	<1/w; 1–6/w; > 6/w	Age, energy, marital status, race/ethnicity, smoking, BMI, WHR, DM, hypertension, dietary variables
Zazpe et al. [34]	CVD	Semiquantitative FFQ	<1/w; 1/w 2–4/w; 5+/w	Age, sex, energy, alcohol, smoking, BMI, DM, hypertension, physical activity, adherence to Mediterranean food pattern; hyperlipidemia, family history of CVD
Houston et al. [23]	CVD	Interviewer administered questionnaire	<1/w; 1–2/w; > 3/w	Age, sex, race, energy, education, field center, smoking, alcohol, physical activity, BMI, multivitamin, aspirin, or statin, oral estrogen use, DM, hypertension, fiber, protein, or saturated fat intake
Djousse et al. (M) [22]	DM	Semiquantitative FFQ	Rarely; <1w; 1/w; 2–4/w; 5–6/w; ≥1/d	Age, smoking, alcohol, physical activity, BMI, DM, hypertension, hyperlipidemia
Djousse et al. (F) [22]	DM	Semiquantitative FFQ	Rarely; <1w; 1/w; 2–4/w; 5–6/w; ≥1/d	Age, smoking, alcohol, physical activity, BMI, family history of DM, hypertension, hyperlipidemia, red meat intake, energy, fruits and vegetables, saturated fatty acids, trans fatty acids, polyunsaturated fatty acids
Djousse et al. (F) [32]	DM	Picture-sort FFQ	Never; <1/mon; 1–3/mo; 1–4/w; 1/d	Age, race, field center, BMI, physical activity, energy, smoking, alcohol, fiber intake
Djousse et al. (F) [32]	DM	Picture-sort FFQ	Never; <1/mon; 1–3/mon; 1–4/w; 1/d	Age, race, field center, BMI, physical activity, energy, smoking, alcohol, fiber intake
Shi et al. (M) [24]	DM	FFQ	<2/w; 2–6/w; ≥1/d	Age, energy, education, BMI, sedentary activity, smoking, family history of DM
Shi et al. (F) [24]	DM	FFQ	<2/w; 2–6/w; ≥1/d	Age, energy, education, BMI, sedentary activity, smoking, family history of DM
Radzeviciene et al. [25]	DM	FFQ	<1/w; 1–1.9/w; 2–2.9/w; 3–4.9/w; ≥5/w	Education, BMI, morning exercise, smoking, family history of DM, plasma TAG level

AF: atrial fibrillation; BMI: body mass index; CHD: coronary heart disease; CVD: cardiovascular disease; DM: diabetes mellitus; F: female; FFQ: food frequency questionnaire; ICD: international classification of diseases; IHD: ischaemic heart disease; M: male; WHO: world health organization; WHR: waist-hip ratio.

3.3. Egg consumption and risk of CVD

First, compared with the lowest category, high egg consumption was associated with increased risk of CVD (12 studies, 226,784 participants, 6592 cases, RR 1.19, 95% CI 1.02 to 1.38, $P = 0.001$; chi-squared = 24.13, I-squared 54.4%, P for heterogeneity = 0.012; Fig. 2A). The trend seemed more obvious in separated diabetes patients (6 studies, RR 1.83, 95% CI 1.42 to 2.37, $P = 0.000$, chi-squared = 5.86, I-squared 14.7%, P for heterogeneity = 0.32; Fig. 2B). Second, subgroup analyses indicated that the association between egg consumption and risk of CVD was not modified by gender, duration of follow-up and study design. We found that the positive association was more evident in populations of other western countries than in the ones of USA (RR 2.00, 95% CI 1.14 to 3.51 VS 1.13, 95% CI 0.98 to 1.30; $P = 0.02$ for subgroup difference). In separated diabetes patients, the relationship between egg intake and the risk of CVD was not modified by gender and duration of follow-up (Table 2). Third, the dose–response analyses showed that, for each 4/week increment in egg intake, the pooled RRs was 1.06 (95% CI 1.03 to 1.10; $P = 0.001$) for risk of CVD in all subjects (Fig. 3A) and 1.40 (95% CI 1.25 to 1.57; $P = 0.000$) for risk of CVD in separated diabetes patients (Fig. 3B). Finally, no evidence of significant publication bias was observed in generally symmetrical funnel plot for the studies which reported the risk of CVD. The result was also confirmed by Begg's adjusted rank correlation test ($P = 0.27$) and Egger's regression asymmetry test ($P = 0.64$).

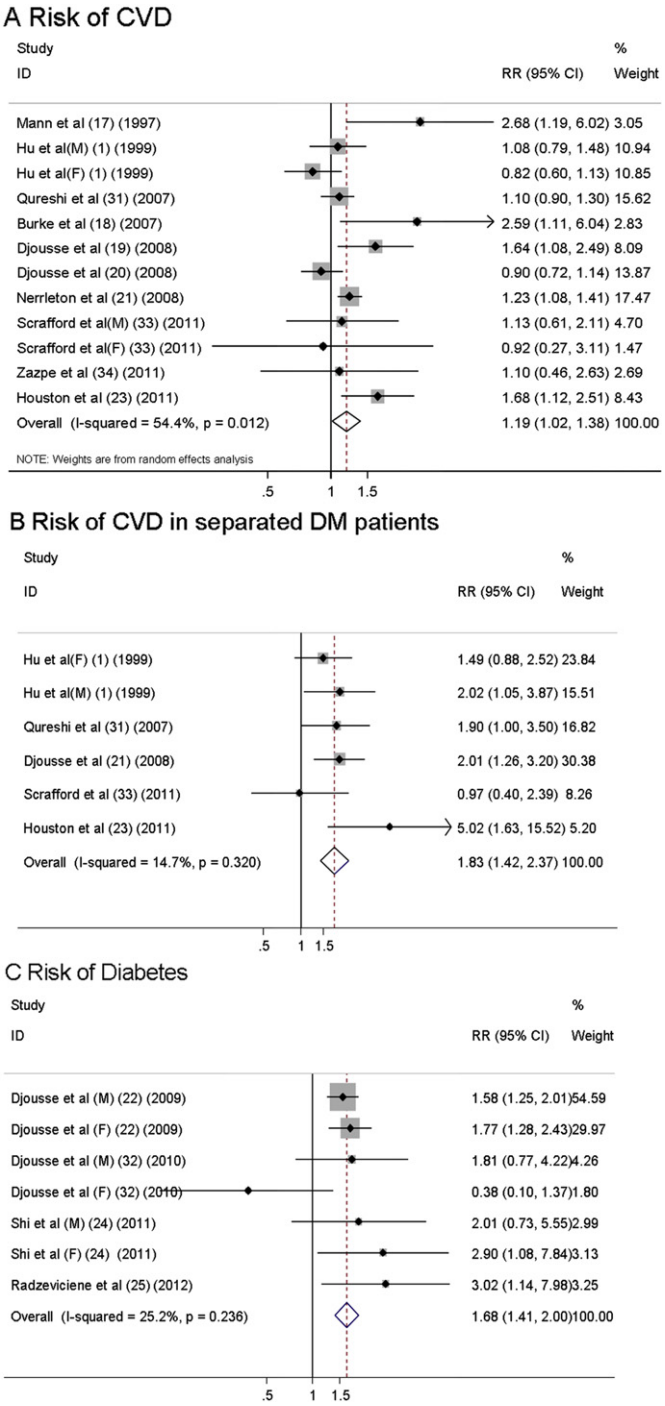

Fig. 2. High egg consumption and risk of CVD and diabetes. Meta-analysis of the highest vs lowest category egg consumption for (A) Risk of CVD; (B) Risk of CVD in separated diabetes patients; (C) Risk of diabetes; CI: confidence interval; CVD: cardiovascular diseases; RR: relative risk.

3.4. Egg consumption and risk of diabetes

First, compared with the lowest category, high egg consumption was associated with increased risk of diabetes (7 studies, 64 447 participants, 4649 cases, RR 1.68, 95% CI 1.41 to 2.00, $P = 0.000$, chi-squared = 8.02, I-squared 25.2%, P for heterogeneity = 0.236; Fig. 2C). Second, subgroup analyses indicated that the association between egg intake and risk of diabetes was not modified by gender, follow-up term, area and study design (Table 2). Third, the dose–response analysis showed that, for each 4/week increment in egg intake, the pooled RRs was 1.29 (95% CI 1.21 to 1.37; $P = 0.000$) (Fig. 3C). Finally, there was no evidence of significant publication bias which confirmed by Begg's adjusted rank correlation test ($P = 0.88$) and Egger's regression asymmetry test ($P = 0.054$).

4. Discussion

To the best of our knowledge, this is the first meta-analysis which systematically reviewed the association between egg consumption and the risk of CVD and diabetes. In this meta-analysis of 14 studies involving 320 778 subjects, we found a positive association between egg consumption and the risk of CVD (the trend seemed to be more obvious in separated diabetes patients) and diabetes. Furthermore, the dose–response analyses was evident. An increment of 4/week of egg intake could possibly increase risk of CVD by 6% (40% in separated diabetes patients) and diabetes by 29%. In addition, the positive association between egg consumption and the risk of CVD was more apparent in the populations of other western countries than the ones in USA.

Previous data from literature about the relationship between egg consumption and the cardiometabolic diseases inconsistent. We combined all available studies and found the positive association between egg consumption and risk of CVD and diabetes. Our findings supported the AHA dietary guidelines which advice restricted egg consumption in adults for preventing cardiometabolic diseases [12–14]. Especially, the dose–response analyses revealed a linear association between egg intake and the risk of CVD and diabetes, strengthening the statistic power. CVD is the leading cause of mortality and morbidity globally and diabetes has been highlighted for its rising incidence and prevalence [40,41]. Therefore, it was helpful to identify the modifiable factors for disease prevention. All of the included studies in the present meta-analysis had controlled for numerous factors that related to the risk of cardiometabolic diseases, including age, gender, race, physical activity, smoking, alcohol use, hypertension, hyperlipidemia, body mass index or family history. We used the most fully

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Table 2
Subgroup analysis by specific study characteristics.

Characteristic	Risk of CVD				Risk of CVD in separated diabetes patients				Risk of diabetes			
	Data points, no	Pooled RR (95%CI)	Pa	Pb	Data points, no	Pooled RR (95%CI)	Pa	Pb	Data points, no	Pooled RR (95%CI)	Pa	Pb
All studies	12	1.15 (1.06–1.25)	0.012		6	1.83 (1.42–2.37)	0.32		7	1.68 (1.41–2.00)	0.24	
Follow-up term												
<10y	6	1.23 (0.99–1.53)	0.51	0.47	3	2.02 (0.91–4.51)	0.08	0.81	3	2.62(1.48–4.64)	0.83	0.11
≥10y	6	1.14 (0.93–1.38)	0.005		3	1.79 (1.32–2.43)	0.69		4	1.56 (1.16–2.11)	0.16	
Study design												
Cohort	11	1.16 (1.00–1.34)	0.02	0.06	6				4	2.62 (1.48–4.64)	0.83	0.11
Non-cohort	1	2.59 (1.11–6.04)	0		0				3	1.56 (1.16–2.11)	0.16	
Gender												
Male	4	1.11 (0.86–1.44)	0.10	0.17	3	1.79 (1.23–2.58)	0.34	0.55	2	1.60 (1.27–2.02)	0.07	0.45
Female	2	0.83 (0.61–1.12)	0.86		1	1.49 (0.88–2.52)	0		2	1.86 (1.37–2.52)	0.86	
Area												
USA	9	1.13 (0.98–1.30)	0.04	0.02	6				5	1.66 (1.21–2.30)	0.11	0.30
Others	3	2.00 (1.14–3.51)	0.26		0				2	2.43(1.19–4.93)	0.61	

CI: confidence interval; CVD: cardiovascular disease; RR: relative risk; a: *P* value for heterogeneity; b: *P* value for subgroup difference.

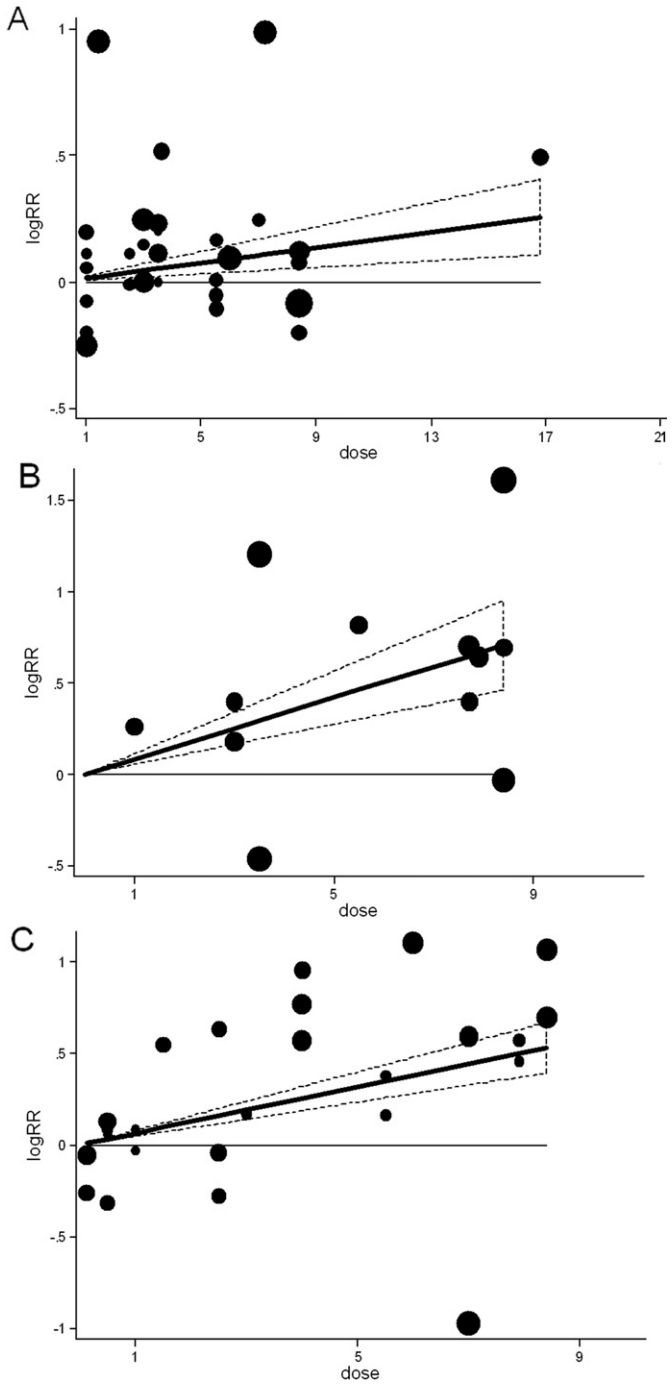

Fig. 3. Dose–response Relationship for egg consumption and risk of CVD, and diabetes. Dose–response relationship of egg intake for (A) Risk of CVD; (B) Risk of CVD in separated diabetes patients; (C) Risk of diabetes. Each black small circle indicates logRR for each category of egg intake which is proportional to its statistical weight; solid line represents weighted logRR, and its two accompanying dashed lines represent its lower and upper CIs. Horizontal solid line indicates the null hypothesis (logRR = 0). CI: confidence interval; CVD: cardiovascular diseases; RR: relative risk.

adjusted results and indicated that high egg consumption was an independent risk factor for CVD and diabetes.

Heterogeneity is often a concern of a meta-analysis. The stratified analyses showed that population from other western countries seemed to have a higher risk of CVD compared with the ones from USA. The results of our study indicated that area might be a modifiable factors. Nevertheless, large-scale randomized controlled

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trials are needed to verify the potential influenced factors of the association between egg intake and risk of CVD in future.

It was not fully understood about the relationship between egg consumption and the risk of CVD. A meta-analysis of randomized trials have demonstrated that egg consumption could raise the levels of serum LDL-C, a well-established and powerful factor in the progressive development of atherosclerosis [5]. Furthermore, evidence from prospective cohort studies have indicated that frequent egg consumption have reflected unhealthy lifestyle including smoking, less physical activity, many unhealthy eating patterns [1,19,20,22,33]. These evidence suggested that high egg consumption maybe harmful to health status. The results from our meta-analysis was consistent with these evidence and revealed a positive association between egg consumption and the risk of CVD. In addition, the harmful effect of egg intake to the risk of CVD might be affected by other metabolic factors. Our finding showed that diabetes patients seemed to have a higher risk of CVD. The results of our meta-analysis appeared to support the idea that egg consumption should be restricted to the target population who have a high risk of CVD. Nevertheless, the effect of egg consumption on the CVD needs further exploration in large-scale randomized trials.

Currently, limited data are available on the impact of egg consumption and risk of diabetes. Animal studies have found that diet rich in cholesterol could raise blood glucose level [42]. However, human metabolic studies have reported that regular egg consumption was not harmful to glucose tolerance in obesity men, even improve the levels of high density cholesterol, a well-established protective factors for cardiometabolic diseases [43–45]. In our analysis, three studies reported the positive association [22,24,25]. Only one which performed in old adults showed no association [32]. We combined them and reported a dose–response positive relationship between egg consumption and the risk of diabetes. Nevertheless, this finding needs further confirmation in subsequent large cohort studies, randomized trials and experimental researches.

Our meta-analysis have several limitations. First, given the nature based on observational studies, the residual confounders became the major limitation. Although we extracted the most fully adjusted RRs for estimation, we could not exclude other residual confounders which might affect the results. Second, several case–control and cross-sectional studies were included in our meta-analysis, so the recall and selection bias could not be excluded. However, our stratified analyses indicated that study design was not a modifiable factor for all the outcomes. Third, the data from the excluded studies cannot be ruled out. Fourth, we did not differentiate the type of diabetes because of limitation of unavailable data from the literature. Fifth, we could not evaluate the effect of egg yolk or egg consumption without yolk because all of the included studies did not provide the required data. Finally, publication bias might affect the results, however, we found no evidence of publication bias.

In conclusion, our meta-analysis indicates that there is positive dose–response association between egg consumption and the risk of CVD and diabetes. The multifacet impact of egg intake for the cardiometabolic diseases are warranted to investigate in both large-scale trials and experimental studies in future.

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Conflicts of interest

None.

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