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SYSTEMATIC REVIEWS AND META-ANALYSES

Impact of whole egg intake on blood pressure, lipids and lipoproteins in middle-aged and older population: A systematic review and meta-analysis of randomized controlled trials

M.X. Wang [a,b], C.H. Wong [a], J.E. Kim [a,*]

[a] Food Science and Technology Program, Department of Chemistry, National University of Singapore, 3 Science Drive 3, 117543, Singapore
[b] Centre for Infectious Disease Epidemiology and Research, Saw Swee Hock School of Public Health, National University of Singapore, Tahir Foundation Building, 12 Science Drive 2, 117549, Singapore

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Abstract *Background and aim:* Effects of whole egg consumption on cardiovascular diseases (CVD) risk in the middle-aged and older population remain unclear due to inconsistent findings from observational and randomized controlled trials (RCTs). This meta-analysis aimed to assess the impacts of whole egg and egg category (whole eggs versus egg substitutes) intake quantity on CVD risk factors from systematically searched RCTs. Egg substitutes were hypothesized to have minimal effects of the blood lipid and lipoprotein profile as they are void of dietary cholesterol.

Methods and results: As many as 434 studies identified from PubMed, Cochrane Library, CINAHL and Medline (Ovid) databases were screened and data were extracted from 8 selected RCTs. Quality of the selected studies were assessed and the overall effect sizes of weighted mean differences (WMD) were calculated using a random effects model. Non-differential effects in blood pressures, lipids and lipoproteins were observed when >4 whole eggs/week compared to ≤4 whole eggs/week were consumed. Intake of >4 whole eggs/week compared to equivalent amounts of egg substitutes caused greater elevations in blood total cholesterol (WMD: 0.198 mmol/L; 95% CIs: 0.056, 0.339), HDL cholesterol (WMD: 0.068 mmol/L; 95% CIs: 0.006, 0.130) and LDL cholesterol (WMD: 0.171 mmol/L; 95% CIs: 0.028, 0.315) but did not differentially affect triglycerides concentration.

Conclusion: Overall, the results support the notion that quantity of whole egg intake does not affect CVD risk factors and consuming egg substitutes may also be beneficial compared to whole eggs on lowering CVD risk in the middle-aged and older population.

Abbreviations: CVD, cardiovascular diseases; RCT, randomized controlled trials; TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC:HDL, TC-to-HDL-cholesterol ratio; LDL:HDL, LDL-to-HDL-cholesterol ratio.

* Corresponding author. Department of Chemistry, National University of Singapore, 3 Science Drive 3, 117543, Singapore. Fax: +65 6775 7895.
E-mail addresses: ephwmx@nus.edu.sg (M.X. Wang), wong.chunhong@u.nus.edu (C.H. Wong), chmkje@nus.edu.sg (J.E. Kim).

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Introduction

Cardiovascular diseases (CVD) remain the leading global cause of death attributing to 31% of deaths worldwide [1]. Age remains as a major risk factor [2], corresponding to a higher CVD prevalence in the middle-aged and older population [3,4]. Increased interest on the impact of diet, another prominent CVD risk factor, revealed associations between dietary cholesterol intake and CVD incidence. Positive associations between CVD risk factors, such as blood lipid and lipoprotein concentrations, and dietary cholesterol intake were consistently observed across various studies [4–6].

Nonetheless, the role of chicken egg, a dietary cholesterol-rich food, on CVD progression remains unclear. A high whole egg intake may increase blood lipid and lipoprotein concentrations, thereby increasing CVD risk, due to its high dietary cholesterol content, especially in the egg yolk. However, studies assessing the effects of whole eggs produced mixed results about the impact of whole egg quantity on CVD risk factors [7–13]. Different egg categories, including egg yolk or substitutes, may also provide differential responses on CVD risk factors, although this comparison has not been well observed.

Generally, egg substitutes are nutritionally similar to whole eggs but contain relatively lower lipids and dietary cholesterol concentrations, or may even be free of these compounds, compared to whole eggs [14–18]. However, as egg substitute can be prepared with a wide variety of ingredients, from egg white to non-egg protein such as mung bean protein [19,20], nutrient compositions across different egg substitute products could vary greatly. Thus, egg substitute is considered a product category by itself. Nevertheless, consuming egg substitutes instead of equivalent amounts of whole eggs may not increase blood pressures, lipid and lipoprotein concentrations since the former contains lesser lipids and dietary cholesterol.

A recent study utilizing pooled individual participant data from 6 prospective US cohorts between 1985 and 2016 observed increased probability for CVD incidence, for each additional half an egg consumed daily (Hazard Ratio (HR): 1.06; 95% confidence intervals (CIs): 1.3, 1.10) [21]. However, epidemiological evidences generated from other large cohort studies generally do not support the association between whole egg consumption and CVD risk [11,12]. Thus, conflicting epidemiological results induce debate on the association between egg consumption and CVD risk. Nonetheless, results from observation studies are unable to prove the causal effect of eggs intake on CVD risk, which can be demonstrated by randomized controlled trials (RCTs). Currently, studies summarizing the impact of whole egg or egg category intake on blood cholesterol concentration with data from RCTs observe conflicting evidences [9,13].

Collectively, mixed results of egg quantity on blood cholesterol concentrations and limited observation with egg categories demonstrate the need of a further systematic approach to examine the effects of whole egg intake on blood pressures, lipid and lipoproteins concentrations, which are known as classical modifiable risk factors of CVD [22]. Furthermore, there is currently no meta-analysis focused on these effects especially in the middle-aged and older adults, who are at risk of CVD development. Thus, this meta-analysis aimed to systematically search the literature, specifically RCTs, to summarize and assess the impacts of (i) the quantity of readily available commercial whole egg consumed and (ii) egg categories consumption on CVD risk factors, namely blood lipid and lipoprotein concentrations and/or blood pressures, in the middle-aged and older population. Although the relationship between egg intake and CVD risk remains uncertain, previous Dietary Guidelines for Americans and the Dietary Approaches to Stop Hypertension diet, and existing dietary guidelines for middle-aged and older adults in Singapore recommend a daily dietary cholesterol intake limit ($\leq$300 mg/d), or to consume $\leq$4 eggs yolks/week [23–25]. Hence the cut-off point for high whole egg intake was defined as $>$4 whole eggs/week in this meta-analysis.

Methods

Search strategy and study selection

The systematic search protocol in the PRISMA guidelines was followed in this meta-analysis [26]. A literature search identifying relevant studies in PubMed, Cochrane Library, CINAHL and Medline (Ovid) databases was conducted originally in August 2017 and updated in May 2018. Specific search terms used, defined by the PICOS criteria (Table 1), search fields and filters applied for each database are identified in Supplementary Table 1. Reference lists of relevant reviews were also hand-searched to identify additional studies.

Studies were included based on the following inclusion criteria: 1) an RCT study design, 2) subjects' mean age $\geq$50 years old, 3) an intervention group or phase consuming $>$4 whole eggs/week compared with a control group of (i) $\leq$4 whole eggs/week, (ii) $>$4 egg yolks/week or (iii) egg substitutes equivalent to $>$4 whole eggs/week, 4) reporting of the numerical values of $\geq$1 CVD risk factor as an outcome of interest [i.e., total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), TC-to-HDL-cholesterol ratio (TC:HDL), LDL-to-HDL-cholesterol ratio (LDL:HDL), triglycerides (TG), systolic blood pressure (SBP), and diastolic blood pressure (DBP)]. Studies utilizing eggs with any altered nutrient component(s) in their interventions were excluded since these "designer eggs" may have differential effects from readily available commercial whole eggs. The cut-off point for high whole egg intake was defined as $>$4 whole eggs/week in this meta-analysis, based on dietary recommendations for middle-aged and older adults [24,25].

Based on the inclusion criteria, 356 out of 434 identified studies were excluded in the primary screening and 49 studies were further excluded after screening the

Table 1 PICOS criteria used to define the research question for this meta-analysis[a].

Variable	Description		
Population	Adults mean aged ≥50 years old		
Intervention	Groups consuming >4 whole eggs/week		
Comparator	Groups consuming ≤4 whole eggs/week	Groups consuming only >4 egg yolks/week	Groups consuming egg substitute equivalent to >4 whole eggs/week
Outcome	Changes in TC, TG, HDL and LDL concentrations, SBP and DBP[b] levels, and ratios of TC:HDL and LDL:HDL		
Study Design	Randomized Controlled Trials		
Research Question	Does consuming >4 whole eggs/week compared to *i*) ≤4 whole eggs/week, or *ii*) >4 egg yolks/week, or *iii*) egg substitutes equivalent to >4 whole eggs/week impact the blood pressure levels and blood lipid and lipoprotein concentrations in middle-aged and older adults?		

[a] PICOS, Population, Intervention, Comparator, Outcome, Study design.
[b] TC, total cholesterol; TG, triglycerides; HDL, high density lipoprotein cholesterol; LDL, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure.

full texts. Thus, 9 and 8 studies were included in the systematic review and meta-analysis respectively; 1 study was excluded from the meta-analysis as SDs were not reported and could not be calculated with available information [27] (Fig. 1).

Data extraction, calculations and quality assessment

The following data were extracted from selected studies: first author name, publication year, population size and description, study design, intervention duration, egg

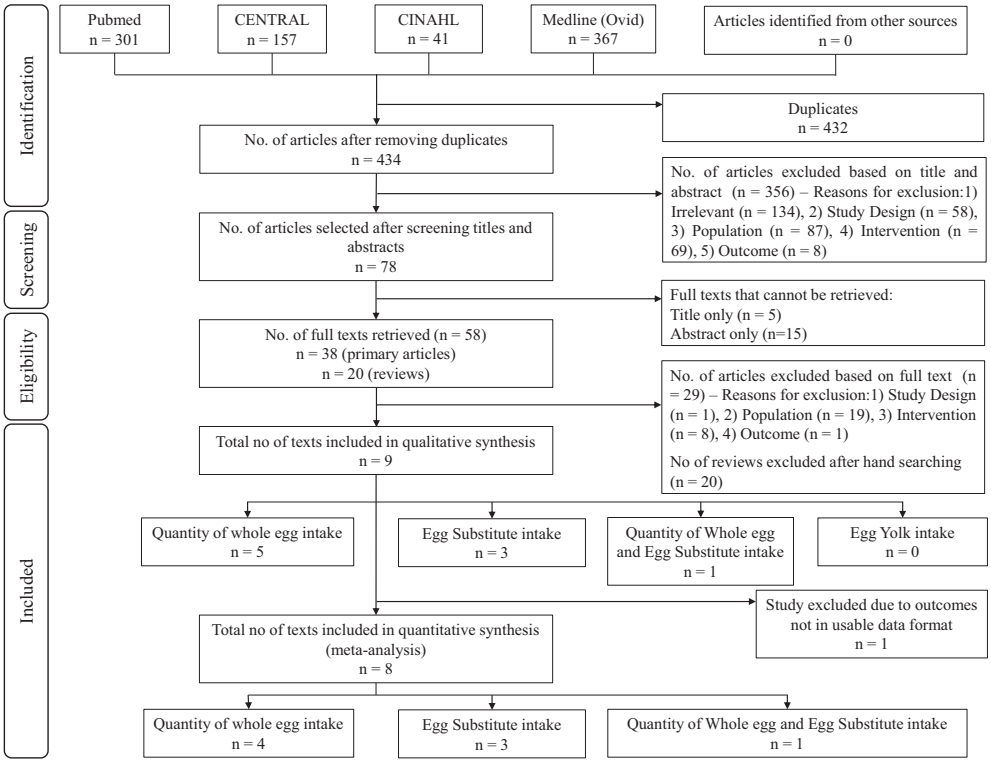

Figure 1 PRISMA flowchart of study selection process.

category and quantity consumed weekly in control and intervention phases or groups, assessment of dietary compliance, and net changes in concentrations or levels and/or pre- and post-intervention values of outcomes of interest reported for both control and intervention phases or groups. If the control group or phase was instructed to consume alternative control foods during the intervention duration, the identity and quantity of the foods consumed per week were also extracted. Corresponding authors were contacted when clarification was required or data were presented as a graph. In this project, we did contact a corresponding author for extra information when required data was presented in a graph. However, we did not receive any response from the corresponding author despite a few attempts. Hence, as no unpublished data were used in the analysis, it was not provided in the manuscript or supplementary material.

All blood lipid and lipoprotein data were converted to mmol/L if reported in mg/dL. The conversion factors are as follows: TC, LDL, and HDL conversion: mg/dL÷38.67; TG conversion: mg/dL÷88.57 [28,29]. The pre- and post-intervention means, standard deviations (SDs), change values, and SDs of the change values were extracted from studies when available. If unavailable, the values were calculated from information that was provided in the study and change-value SDs were calculated using a correlation factor representative of the change-value SDs that were available from the other studies [30,31]. The change value SDs for an outcome were calculated separately for control and intervention groups for each study not reporting it. Subsequently, the change value SDs were respectively pooled for all control and intervention groups reporting that outcome. In addition, the reported and/or calculated change values for each outcome were summarized and the median change value and range of change values were presented.

The risk of biases in selected studies were evaluated with the Quality Assessment of Controlled Intervention Studies Tool by the National Heart, Lung, and Blood Institute, National Institutes of Health (NHLBI) [32]. The tool utilizes 14 questions with a scoring system to assess the risk of selection, performance, detection, attrition and reporting biases in each study. The maximum score attainable by a study is 14 and the score range for study quality are: 0–7: poor; 8–11: fair, 12–14: good.

All procedures were performed independently by the two reviewers (WMX and WCH) and discrepancies were discussed and resolved by consensus at the end of each procedure.

Statistical analyses

An intra-class correlation test was conducted using a two-way mixed-effects model to validate the quality assessment tool, through assessing the inter-rater reliability of the two reviewers in performing the quality assessment [33,34]. The score range was: 0–0.39: poor; 0.4–0.59: fair; 0.6–0.74: good; 0.75–1.00: excellent [34].

Results from control and intervention phases in crossover trials were incorporated into the data set as if they were the respective groups in parallel designs [30]. Interventions from studies containing >1 intervention or control groups were also treated as independent trials and presented separately to account for within-study differences [35,36]. For each reported outcome, the mean difference and standard error (of the mean difference) of the post-intervention values between the control and intervention groups were calculated [37]. The overall effect size of the change values was analyzed using the metan function and random-effects model to account for between-study variances [38]. The results were reported as weighted mean differences (WMD) and 95% CIs. Cochran Q test and I^2 statistic generated by metan and heterogi functions were used to evaluate and quantify heterogeneity across individual studies. Significant heterogeneity was defined as I^2 statistic ≥50% and a p-value <0.05. Leave-one-out sensitivity analyzes were also conducted to assess whether results could have been driven by any single study. In addition, subgroup analyses based on the diabetic status of populations was also performed when ≥2 included studies utilized diabetic populations. All analyses were performed by using STATA statistical software (version 13.0; STATA Corp). All statistical tests were 2-sided, and statistical significance was set at p-value <0.05.

Results

Study features and subject characteristics

We identified 9 RCTs including 412 subjects of Caucasian descent, 85% of them with various disease conditions (Table 2).

Results of systematic review and meta-analysis

Overall, summary of the published results in selected studies showed that consuming >4 whole eggs/week or ≤4 whole eggs/week presented decreases in the median values of SBP, DBP, TG, TC:HDL, and LDL:HDL, increases in the median values of HDL and LDL, and relatively neutral change in the median value of TC (Table 3). Meta-analysis revealed that there were no significant differences in the changes observed in SBP and DBP levels, and in TG, TC, HDL and LDL concentrations, when >4 whole eggs/week compared to ≤4 whole eggs/week were consumed in the sample population or the diabetic subpopulation (Supplementary Fig. 1, Supplementary Table 2). In all outcomes, heterogeneity was non-significant ($p > 0.05$; range of 95% CIs for I^2 statistic, of all analyzed outcomes: 0.0, 89.3). Omitting a study decreased heterogeneity in LDL, TC and HDL to a minimum (I^2 = 3.59% (LDL), 0.00% (TC, HDL), $p_{heterogeneity}$ = 0.354 (LDL), 0.746 (TC), 0.672 (HDL)) [39]. Removal of another study showed that consuming >4 whole eggs/week compared to ≤4 whole eggs/week resulted in greater increase in TC concentration (WMD: 0.170 mmol/L, 95% CIs: 0.009, 0.332 mmol/L) with minimal heterogeneity (I^2 = 2.63, $p_{heterogeneity}$ = 0.358)

Table 2 Study design and subject characteristics in selected RCTs.

Effects reported by study	First author year [ref]	Country of study; Intervention duration (weeks); study design	Population size and description; mean age (years)	Weekly whole egg intake in intervention group	Weekly egg intake; egg category consumed in control group; brief description of egg substitute consumed	Alternative food provided for control group; weekly quantity consumed	Dietary pattern	Dietary compliance assessment	Quality assessment score
Quantity of whole egg intake	Katz; 2005 [39]	USA[a]; 6; 2-phase crossover	49 generally healthy men and women; 55.7	14	0; whole eggs; N/A[b]	Uncooked Oats prepared in any way as desired; 420 g	HALD[c]	One 3-day food diary per phase, return of food containers used to provide food	12
	Pearce; 2011 [27]	Australia; 12; 2-arm parallel	65 men and women with type 2 diabetes; 54.4	14	0; whole eggs; N/A	Lean meat; 700 g	30% Energy restricted diet, approximately 1400 kcal (40% carbohydrate, 30% protein, 30% fat)	Fortnightly 3-day food record	10
	Ballesteros; 2015 [43]	Mexico; 5; 2-phase crossover;	29 men and women with type 2 diabetes; 53.5	7	0; whole eggs, N/A	Oatmeal with lactose-free milk; 280 g	HALD but to avoid additional egg or oats consumption outside of what was provided in the study	Return of uneaten food to researchers	10
	Fuller; 2015 [41]	Australia; 12; 2-arm parallel	121 men and women with type 2 diabetes or prediabetes; 60.1 (control group), 59.5 (intervention group)	12	<≤2, whole eggs; N/A	Lean animal protein or protein-rich alternatives; 60 g	Heart healthy diet	Intervention group given prescribed quota of eggs while control group is given grocery voucher of equivalent value	12
	Njike; 2016 [40]	USA; 12; 2-phase crossover	32 men and women with type 2 diabetes; 64.5	10 to 14	0; whole eggs; N/A	N/A	HALD	Egg consumption log, three 24-h dietary recalls at 2 different time points over the course of study	10

(*continued on next page*)

Table 2 (*continued*)

Effects reported by study	First author year [ref]	Country of study; Intervention duration (weeks); study design	Population size and description; mean age (years)	Weekly whole egg intake in intervention group	Weekly egg intake; egg category consumed in control group; brief description of egg substitute consumed	Alternative food provided for control group; weekly quantity consumed	Dietary pattern	Dietary compliance assessment	Quality assessment score
Egg substitute intake	Greene; 2005 [44]	USA; 4; 2-phase crossover	13 generally healthy men; >60	21	21; egg substitute; cholesterol-free, fat-free egg substitute equivalent to 3 eggs daily	N/A	HALD but to avoid additional egg consumption outside of what was provided in the study	Two 7-day dietary records	9
	Njike; 2010 [42]	USA; 6; 2-phase crossover	36 hyperlipidemic men and women; 59.9	14	14; egg substitute; 1/2 cup of egg substitutes equivalent to 2 medium eggs for breakfast daily	N/A	HALD	N/A	12
	Blesso; 2013 [45]	USA; 12; 2-arm parallel	37 men and women with metabolic syndrome; 51.9	21	21; egg substitute; 1/2 cup of yolk-free egg substitutes equivalent to 3 eggs daily	N/A	Ad libitum moderate carbohydrate restricted diet (25−30% carbohydrates, 25−30% protein. 45−50% fat), but to avoid additional egg consumption outside of what was provided in the study	Three 5-day food records at baseline, week 6 and week 12	8

Quantity of whole egg and egg substitute intake	Katz; 2015 [36]	USA; 6; 3-phase crossover	30 men and women with coronary artery disease, 67.1	14	0; whole eggs	High-carbohydrate breakfast; N/A	HALD	Daily food log	11
					14; egg substitute; 1/2 cup of Egg Beaters (ConAgra Foods) equivalent to 2 eggs for breakfast daily, prepared any way as preferred by subject	N/A	HALD		

[a] USA, United States of America.
[b] N/A, not applicable.
[c] HALD, Habitual ad libitum diet.

[40]. No significant differences in changes of other outcomes were observed when sensitivity analyses were conducted (Supplementary Table 3).

Collectively, published results in selected studies demonstrated that consuming >4 whole eggs/week or egg substitutes equivalent to >4 whole eggs/week both presented decreases in the median values of TG and TC:HDL while the range of the changes in the median values of TC, HDL, LDL and LDL:HDL were varied (Table 3). An intake of >4 whole eggs/week presented greater increases in concentrations of TC (WMD: 0.198 mmol/L; 95% CIs: 0.056, 0.339), HDL (WMD: 0.068 mmol/L; 95% CIs: 0.006, 0.130), and LDL (WMD: 0.171 mmol/L; 95% CIs: 0.028, 0.315) compared to consuming equivalent amounts of egg substitutes in middle-aged and older adults in the sample population (Fig. 2). However, consumption of >4 whole eggs/week showed no significant difference in the change in TG concentration, compared to equivalent amounts of egg substitutes (Supplementary Fig. 2). This suggests that TG concentration was not significantly affected by the egg category consumed. In our sample population, heterogeneity was not significant ($p > 0.05$) for all outcomes when the meta-analysis and sensitivity analyzes were conducted (95% CIs for I^2 statistic of all analyzed outcomes: 0.0, 84.7). However, omission of various studies in sensitivity analyses for TC, HDL and LDL showed greater increases in concentration of each of these outcomes when >4 whole eggs/week were consumed, compared to equivalent amounts of egg substitutes (Supplementary Table 4).

Quality of selected studies and intra-class correlation

The mean quality score of selected studies was 10.4 (Table 1). Three out of the 9 selected studies were of good quality [39,41,42] while the rest were of fair quality. There was minimized risk of selection, detection, attrition and reporting biases in these 3 good quality studies. Performance bias was unclear in 2 of these 3 studies as baseline characteristics of the control and intervention group were not matched [41] and dietary compliance was unreported [42]. All selected studies were described as randomized but only 3 clearly reported randomization and allocation concealment methods, and thus were deemed to have a low risk of selection bias [27,41,42]. Remaining studies either reported only randomization methods [39], or reported neither clearly [36,40,43–45]. Most studies were at low risk of performance, reporting and attrition biases but these were undetermined for studies with unclear reporting ([24,28] for performance [44], for reporting and [27,43,45] for attrition). Detection bias was unclear in all but 5 studies which blinded the outcome assessor [36,39,41–43]. The nature of the intervention prevented the blinding of subjects and/or providers to the treatment allocation in all studies (Supplementary Table 5).

The intra-class correlation for the two reviewers is 0.836 (95% CI: 0.273, 0.963), indicating excellent correlation and validity of the quality assessment tool.

Table 3 Summary of changes in blood pressures, lipids and lipoproteins from baseline levels/concentrations after consuming >4 whole eggs/week compared to *i)* ≤4 whole eggs/week or *ii)* egg substitutes equivalent to >4 whole eggs/week.[a]

Outcome (unit)	Quantity of whole egg intake[b]				Egg category consumed[c]			
	>4 whole eggs/week		≤4 whole eggs/week		>4 whole eggs/week		Egg substitutes equivalent to >4 whole eggs/week	
	Median	Range	Median	Range	Median	Range	Median	Range
SBP (mmHg)	−2.00	[−6.10, 0.30]	−1.90	[−3.82, 0.90]	0.30	[0.30, 0.30]	0.10	[0.10, 0.10]
DBP (mmHg)	−3.40	[−10.60, −1.54]	−4.50	[−5.70, −0.80]	−3.40	[−3.40, −3.40]	−0.70	[−0.70, −0.70]
TG (mmol/L)	−0.10	[−0.72, −0.07]	−0.15	[−0.67, −0.11]	−0.01	[−0.46, −0.03]	−0.11	[−0.30, 0.06]
TC (mmol/L)	0.00	[−0.07, 0.16]	−0.10	[−0.28, 0.08]	−0.13	[−0.53, 0.16]	−0.47	[−0.68, 0.06]
HDL (mmol/L)	0.03	[−0.04, 0.17]	0.02	[−0.07, 0.14]	0.01	[−0.06, 0.22]	−0.05	[−0.12, 0.12]
LDL (mmol/L)	0.14	[−0.06, 0.20]	0.05	[−0.21, 0.15]	−0.03	[−0.18, 0.16]	−0.24	[−0.36, 0.10]
TC:HDL	−0.14	[−0.23, −0.04]	−0.01	[−0.06, 0.05]	−0.05	[−0.06, −0.04]	−0.06	−0.21,0.10]
LDL:HDL	−0.41	[−0.41, −0.41]	−0.45	[−0.45, −0.45]	0.12	[−0.20, 0.19]	−0.01	[−0.40, 0.21]

[a] Summary of reported and/or calculated change values for each outcome, presented as the median and range of change values; all values were reported to 2 decimal places.
[b] Five studies reported changes in blood pressures [27,36,39–41], 5 studies reported changes in TC, TG, HDL and LDL concentrations [27,36,39,41,43], 2 studies reported changes in TC:HDL [27,36] and 1 study reported the change in LDL: HDL [43].
[c] Four studies reported changes in TC, TG, HDL and LDL concentrations [36,42,44,45], 1 study reported the change in blood pressures [36], 2 studies reported changes in TC:HDL [36,42] and 2 studies reported changes in LDL:HDL [44,45].

Discussion

This meta-analysis found that consuming >4 whole eggs/week does not influence blood pressure levels, and lipid and lipoprotein concentrations, while consuming >4 whole eggs/week instead of equivalent amounts of whole eggs may influence them.

Quantity of egg intake on CVD risk factors

Our quantitative analysis results indicated that an intake of >4 whole eggs/week had no adverse effects on DBP and SBP levels, and TG, TC, HDL and LDL concentrations, compared to consumption of ≤4 whole eggs/week. Although we were unable to statistically analyze the effects of consuming >4 whole eggs/week compared to ≤4 whole eggs/week on TC:HDL and LDL:HDL ratios, the original studies reported no differences in TC:HDL and LDL:HDL ratios between consuming >4 whole eggs/week and ≤4 whole eggs/week [27,36,43]. Our results are similar to findings for blood lipid and lipoprotein concentrations, and LDL:HDL ratio observed in earlier RCTs on healthy younger adults after a consuming ≤21 whole eggs/week [46–48]. Another review consistently reported non-significant effects on TC and TG concentrations following a higher whole egg intake in diseased adults [13]. Our results also corroborate with some epidemiologic evidence that demonstrated a high egg intake does not adversely affect CVD risk or its risk factors in a middle-aged and older population [49–53]. When up to ≥15 whole eggs/week was consumed in normal middle-aged adults, these observation studies indicated no significant increases in the relative risk or hazard ratio for CVD compared to <1 whole egg/week [52,53]. However, another observation study indicated a 3–10% increased probability for CVD incidence in middle-aged adults, when 3–4 whole eggs/week were consumed, compared to <3 whole eggs/week (HR: 1.06; 95% CI: 1.3, 1.10) [21]. Increased CVD risk was also presented in diabetics when >6 whole eggs/week were consumed [51]. In adults with diabetes, consumption of >1 whole egg/week either decreased [50] or did not change [49] the odds ratio for high BP level, high TG or low HDL concentrations compared to when < 1 whole egg/week was consumed.

The effects, or lack thereof, of consuming >4 whole eggs/week compared to ≤4 whole eggs/week on the analyzed CVD risk factors could be attributed to the presence of compounds with cardio-protective and anti-hypertensive effects in whole eggs. Certain egg white peptides are shown to cause vasodilation [54,55], while in the egg yolk, phospholipids potentially inhibit dietary cholesterol absorption [56,57] and lutein and zeaxanthin are observed to exert cardio-protective effects [58,59]. Hence, these compounds may partially explain our observed blood pressure and lipid-lipoprotein results despite a higher whole egg intake. In summary, our results suggest that the effects of consuming >4 whole eggs/week compared to ≤4 whole eggs/week do not vary visibly across age and may have no effect on CVD risk factors.

Egg categories intake on CVD risk factors

We assessed the effects of whole egg intake compared to equivalent amounts of egg substitutes, which are an increasingly popular alternative to consuming whole eggs. Our results indicated that consuming >4 whole eggs/week instead of equivalent amounts of egg substitutes resulted in greater increases in TC, HDL and LDL concentrations, but had no significantly different effect on the change in TG concentration. Although we were unable to statistically analyze the effects of egg category intake on blood

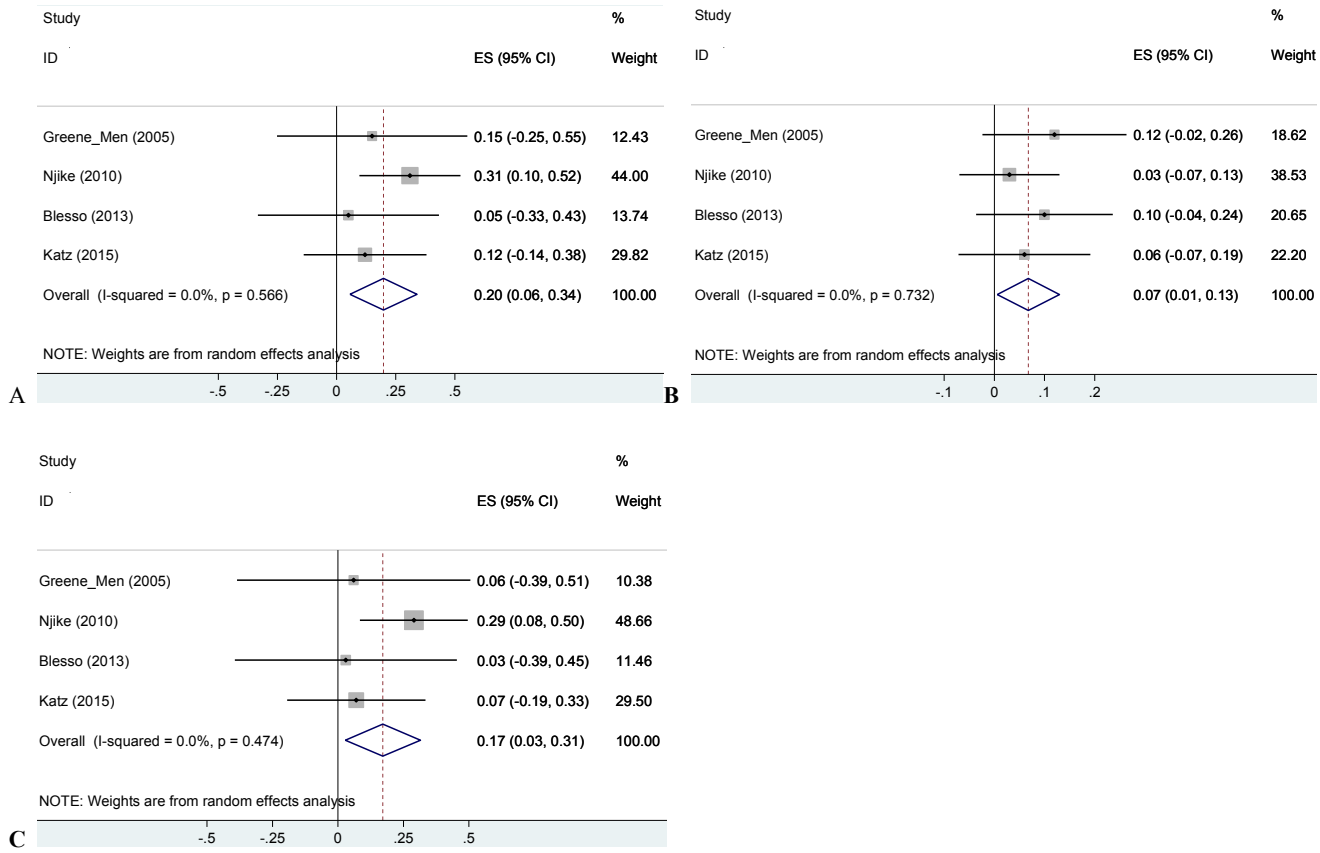

Figure 2 Random-effects model meta-analysis for comparing the changes in (A) TC, (B) HDL and (C) LDL concentrations (mmol/L) from RCTs consuming >4 whole eggs/week compared to equivalent amounts of egg substitutes. Heterogeneity: (A) Cochrane Q = 2.03, df = 3 (P = 0.566), I^2 = 0.0% (95% CI: 0.0, 84.7); (B) Cochrane Q = 1.29, df = 3 (P = 0.732), I^2 = 0.0% (95% CI: 0.0, 84.7); (C) Cochrane Q = 2.51, df = 3 (P = 0.474), I^2 = 0.0% (95% CI: 0.0, 84.7).

pressure and the ratios of TC:HDL and LDL:HDL, original studies reported no differences in the respective outcomes between consuming >4 whole eggs/week and equivalent amounts of egg substitutes [36,42,44,45]. Dietary fats is a known precursor for TC, HDL and LDL synthesis [60,61] and dietary cholesterol intake is associated to these blood lipid and lipoprotein concentrations in our bodies [5,6]. As most of the dietary fat and cholesterol in eggs are localized in the egg yolk, consuming whole eggs instead of egg substitutes may increase blood lipid and lipoprotein concentrations, as observed in our results. Indeed, a recent study observed an association between egg consumption and CVD incidence (HR: 1.06; 95% CI: 1.03, 1.10). However, this association no longer existed after adjusting for dietary cholesterol content in eggs (HR: 0.99; 95% CI: 0.93, 1.05) [21].

Nonetheless, our results do not reflect the qualitative effects of whole egg intake on blood lipid and lipoprotein profiles. Although we observed higher LDL and HDL concentrations with whole eggs intake, previous RCTs demonstrated that an intake of 7–21 whole eggs/week significantly increased concentrations of large-LDL and large-HDL particles, resulting in improved LDL and HDL profiles despite increased overall LDL and HDL concentrations, compared to no egg [62] or equivalent amounts of egg substitute intake [63]. The increase in HDL concentration also suggests clinical significance since every increase in 0.0259 mmol/L HDL is associated to an approximate 2–3% decrease in CVD risk [56]. This suggests that consuming >4 whole eggs/week, which increases HDL concentration by 0.068 mmol/L may reduce about 4–6% CVD risk in middle-aged and older adults, compared to consuming equivalent amounts of egg substitutes. Collectively, an intake of >4 whole eggs/week may not necessarily lead to increased CVD risk compared to an equivalent intake of egg substitutes although the egg category intake has differential effects on CVD risk factors.

Strengths and limitations

To our knowledge, this is the first meta-analysis examining the effects of quantity and egg category intake on blood pressure, lipid and lipoproteins in middle-aged and older adults, using data from RCTs. A strength of this meta-analysis is that the causal relationship between quantitative whole eggs intake or egg category intake and the identified outcomes was assessed. Furthermore, the possibility of biasedness in data selection and interpretation was reduced with the use of an established protocol [64].

It is worth noting some limitations in this meta-analysis. Firstly, publication bias might still exist as we only searched within published RCTs [65] and were unable to examine the presence of publication bias due to the small number of RCTs included. Secondly, due to insufficient RCTs, the analyzed population size is relatively small and, consists of only Caucasians, most of whom are diseased. Hence, our results have limited external validity since it may not represent the effects of consuming >4 whole eggs compared to (i) ≤4 whole eggs/week or (ii) equivalent amounts of egg substitutes on a healthy Caucasian population or an Asian population (of any health status) aged ≥50 years old. Thirdly, alternative control foods were varied across individual studies. This may have caused significant changes in some outcomes when sensitivity analyses were conducted, especially if the control food is known to impact blood lipid profile, such as oats which significantly alters the blood lipid and lipoprotein concentrations when certain amounts are consumed [66,67]. Fourthly, while visible changes in lipoprotein profiles due to dietary egg intake can be observed after 30 days [68], the etiologically relevant time window for a dietary intervention to influence blood lipids have been declared as 6 weeks by the American Association of Clinical Endocrinology guideline [69]. Thus, 2 of the included studies, with intervention durations <6 weeks, may not reflect the complete effect of changes in egg consumption on CVD risk [43,44]. Lastly, selected studies seldom report TC:HDL and LDL:HDL ratios although these outcomes are more representative measures of overall CVD risk [70].

Conclusions

In conclusion, statistical analysis from this review supports the notion that quantitative whole egg intake (>4 whole eggs/week versus ≤4 whole eggs/week) does not affect the mentioned CVD risk factors but the egg category consumed (>4 whole eggs/week versus equivalent amounts of egg substitutes) may influence them in the middle-aged and older population. Our results also suggest that consuming egg substitutes compared to whole eggs may be beneficial on CVD risk by lowering blood cholesterol concentration in the middle-aged and older population. Our results support findings in recent scientific reports, which questioned the supposed association between dietary cholesterol and CVD risk factors [71,72], and the latest 2015–2020 Dietary Guidelines for Americans which removed the restriction for daily dietary cholesterol intake (≤300 mg/day) compared to the previous versions [23]. However, conflicting epidemiological and clinical evidences clearly remain, thus caution on interpretation is still required. Nevertheless, seeing that consuming >4 whole eggs/week compared to equivalent amounts of egg substitutes possibly influence blood pressures, lipid and lipoprotein concentrations in middle-aged and older adults, the egg category consumed could possibly be considered to manage CVD risk in this population.

Author contributions

M.X.W. and J.E.K. designed the research; M.X.W and C.H.W conducted the research; M.X.W. analyzed the data; and M.X.W. and J.E.K wrote the manuscript and have primary responsibility for the final content. All authors have read and approved the final manuscript.

Conflict of interest

The authors declare that there is no duality of interest associated with this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.04.004.

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