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FULL ARTICLE

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The responses of different dosages of egg consumption on blood lipid profile: An updated systematic review and meta-analysis of randomized clinical trials

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Abstract

Diverse notions exist regarding egg intake, which is one of the main sources of dietary cholesterol, and its effect on blood lipids. We conducted this study to update the previous meta-analysis for their flaw in calculated effect size. PubMed, Scopus, ISI, and Cochrane were searched up to April 2019, for relevant randomized controlled clinical trials. Mean changes in total cholesterol (TC), LDL-cholesterol (LDL-C), HDL-cholesterol (HDL-C), triglyceride (TG), very low-density lipoprotein cholesterol (VLDL-C), LDL-C/HDL-C, TC/HDL-C, apolipoprotein (apo)A1, and apoB100 were assessed. Meta-analysis of 66 RCTs with 3,185 participants revealed that egg consumption can significantly increase TC, LDL-C, HDL-C, TC/HDL-C, apoA1/and B100, but there was no significant effect on other serum lipids. Dose-response analysis showed a linear effect for TC, HDL-C, ApoA1, ApoB100, and nonlinear for LDL-C, and TC/HDL-C. In conclusion, intake of more than one egg daily in less than 12 weeks may increase some blood lipids without any changes in the ratio of LDL-C/HDL-C.

Practical applications

There are controversies reports for egg intake, which is one of the main sources of dietary cholesterol. This study provides comprehensive information about the effect of the number of eggs consumed per day (dietary cholesterol) on blood lipids for nutritionists, physicians, researchers, and the general population. In this regard, our results indicated that there is a linear correlation between consumption of greater than one egg per day in a short time (no long time) and increasing lipid profiles which may increase the risk of cardiovascular diseases. However, consumption of one egg daily can be safe and this can be a useful recommendation for prevention of cardiovascular disease and promotion of healthy life which indeed are the potential or actual uses of this research.

KEYWORDS

adult, apolipoproteins, egg consumption, lipid profile, meta-analysis

Abbreviations: apoA1, apolipoprotein A1; apoB100, apolipoprotein B100; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disorder; HDL-C, high density lipoprotein cholesterol; HF, heart failure; LDL-C, low density lipoprotein cholesterol; PRISMA, preferred reporting items of systematic reviews and meta-analysis; RCTs, randomized clinical trials; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglyceride; VLDL-C, very low-density lipoprotein cholesterol; WMD, weighted mean difference.

1 | INTRODUCTION

Dyslipidemia is one of the most important risk factor for many diseases such as cardiovascular disease (CVD) (Tietge, 2014), metabolic syndrome (Blesso, Andersen, Barona, Volek, & Fernandez, 2013a), non-insulin-dependent diabetes mellitus (Tirosh et al., 2008), hypertension (Baszczuk et al., 2014), and nonalcoholic fatty liver disease (Cohen & Fisher, 2013). Overall, dyslipidemia is defined as elevated total or low-density lipoprotein cholesterol (LDL-C) levels, or low levels of high-density lipoprotein cholesterol (HDL-C).

However, recent studies suggest that evaluation of plasma apoA1 (primary protein in HDL-C particles) and apoB100 (primary protein in LDL-C particles) may be more sensitive and specific measures as risk factors for dyslipidemia-related disease, as increased ratio of apoB100/apoA1 has been observed, despite normal total and LDL-C (Leiviskä, Sundvall, Jauhiainen, & Laatikainen, 2014; Zhang et al., 2012).

Diet has fundamental correlations with lipid profiles (Daoud, Scheede-Bergdahl, & Bergdahl, 2014). Until recently, recommendations by the American Heart Association (AHA) and American College of Cardiology (ACC) emphasized restriction of dietary cholesterol (Clayton, Fusco, & Kern, 2017). In the current Dietary Guidelines for Americans (2015–2020), the recommendations for healthy individuals to limit dietary cholesterol intake has been removed, due to poor relationships between dietary cholesterol and increased CVD risk (2015–2020 Dietary Guidelines for Americans. 8th Edition). Nevertheless, some studies have reported that dietary cholesterol increases the abundance of atherogenic lipoproteins (i.e., LDL-C and VLDL-C), but results are mixed, as others have reported a decrease or no change (Berger, Raman, Vishwanathan, Jacques, & Johnson, 2015; Harman, Leeds, & Griffin, 2008; Houston et al., 2011).

For years, egg consumption was limited due to dietary cholesterol content (Berger et al., 2015; Griffin & Lichtenstein, 2013). However, eggs contain high quality protein, high amount of choline, many of vitamins and minerals, and as well as have low saturated and trans-fatty acids than other cholesterol-rich food (Watson & De Meester, 2015).

Epidemiological studies demonstrated little relevance between high intake of egg and cardiovascular-related mortality (Fuller, Sainsbury, Caterson, & Markovic, 2015). Some studies have shown different effects in various populations. A meta-analysis of 14 cohort studies in adults showed that consumption of one egg per day versus less than two eggs per week was not associated with CHD and may reduce stroke risk by 12% (Alexander, Miller, Vargas, Weed, & Cohen, 2016). However, a recent meta-analysis of prospective cohort studies indicated that greater than one egg per day was associated with incidence of heart failure (HF) (Khawaja et al., 2017). Notably, several other clinical trials, not included in the most recent meta-analysis (Khawaja et al., 2017), showed egg consumption can increase, or decrease or does not change the lipid profiles in different populations (Table 1).

The aim of the present study was to conduct an updated review of the literature and to expand a previous meta-analysis of egg consumption (Rouhani, Rashidi-Pourfard, Salehi-Abargouei, Karimi, & Haghighatdoost, 2018). The mentioned study reported consumption of egg effects on TC, LDL-C, and HDL-C, but not LDL-C/HDL-C, TC/HDL-C, and TG compared with low egg consumption or control diets. Notably, the present meta-analysis provides findings of seven more eligible trials, which were not included in the most recent meta-analysis (Rouhani et al., 2018). Also, our study is a first meta-analysis that evaluated effect of egg ingestion on apoA1, apoB100 and VLDL. Therefore, in the present systematic review and meta-analysis we determine the effect of egg consumption on serum concentration of TC, LDL-C, HDL-C, LDL-C to HDL-C ratio, TC to HDL-C ratio, VLDL-C, TG, apoA1, and apoB100 in adults.

2 | METHODS

The current systematic review and meta-analysis was performed in accordance with the guidelines of PRISMA at all stages of the study (Moher, Liberati, Tetzlaff, Altman, & PRISMA Group, 2009). The study protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews. (CRD42018089112).

2.1 | Search strategy

We performed systematic literature searches in the PubMed, Scopus, ISI and Cochrane with no time limitation and language restriction on July 2017 for clinical trial studies that examined the association between egg consumption and level of blood lipids. We updated our searches up to April 2019. Search terms were “egg” OR “eggs” OR “dietary cholesterol” AND “Lipoproteins” OR “Lipids” OR “Serum lipids” OR “Cholesterol” OR “triglycerides” OR “High-density lipoproteins” OR “HDL-cholesterol” OR “Low-density lipoprotein” OR “LDL-cholesterol”. The full database search strategy in PubMed is available in the Table S1. Searching other databases had similar that strategy. Moreover, the reference list of relative studies was checked to find any additional relevant articles.

2.2 | Study selection

Abstracts or full-text articles were further reviewed to assess eligibility based on diet intervention, population, and outcomes. Studies were included if they had the following criteria: (a) randomized clinical trials (RCTs) (parallel or cross-over design) that assessed the effect of egg consumption on blood lipids, (b) adult populations (greater than 18 years old). The clinical trials in the analysis were only included if there was a control group, but blindness was not a requirement because in some studies the egg was administered in the form of foods (not substitute). Study exclusion criteria were as follows: (a) review and meta-analysis, letters,

TABLE 1 Characteristic of randomized controlled trials that evaluated the effect of the egg consumption on level of serum lipids and were eligible to be included in systematic review

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Porter et al. (1977)	USA	114 (M:114, W:0)	44	Cross-over	1 egg/d	0 egg	12	0	Healthy	Normal diet	12 hr	↓TG ↔TC
Bronsgeest-Schoute et al. (1979a)	Netherland	44 (M:25, W:19)	45	Cross-over	>7 egg/wk	0 egg	3	0	Healthy	Normal diet	12 hr	↓TC
Bronsgeest-Schoute et al. (1979b)	Netherland	18 (M:10, W:8)	22	Cross- over	2 egg/d	0 egg	3	0	Healthy	High saturated fat diet	12 hr	↑TC ↔TG
Flynn et al. (1979)	USA	116 (M:116, W:0)	46	Cross-over	2 whole egg/d	0 egg	12	0	Healthy	Normal diet	12 hr	↔TC ↔TG
O'Brien and Reiser (1980)	USA	29 (M:29, W:0)	41	Cross-over	1) red meat + 3 egg/d	1) red meat + no egg	6	0	Healthy	Normal diet	12 hr	↑TC
					2) fish or poultry + 3 egg/d	2) fish or poultry + no egg						↑HDL-C
Chenoweth et al. (1981)	USA	32 (M:32, W:0)	25	Cross-over	1) control diet (42%–45% fat + 2 egg/d	1) control diet (42%–45% fat) + cholesterol free egg substitute	4	0	Healthy	High fat diet	12 hr	↓TC ↔TG ↔HDL-C
					2) modified fat diet(35%) + 2 egg/d	2) modified fat diet (35%) + cholesterol free egg substitute				Modified diet		↔TC/HDL-C ↔LDL-C/HDL-C
Roberts et al. (1981)	USA	16 (M:8, W:8)	44	Cross-over	½ cup whole egg (500 mg chol)	Substitute	4	0	Healthy	Normal diet	12 hr	↑TC ↔TG
Katan et al. (1986)	Netherland	Experiment1: *n* = 94	33	Cross-over	Experiment 1:625 mg/d Chol (High cholesterol diet)	Experiment 1:121 mg/d Chol (low cholesterol diet)	2	0	Healthy	Normal diet	12 hr	Experiment 1:
		Experiment2: *n* = 41			Experiment 2:673 mg/d Chol (High cholesterol diet)	Experiment 2:106 mg/d Chol (low cholesterol diet)						↑TC
		Experiment3: *n* = 32 (M:46, W:48)			Experiment 3:989 mg/d Chol (High cholesterol diet)	Experiment 3:129 mg/d Chol (low cholesterol diet)						↑HDL-C

(Continues)

TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Buzzard et al. (1982)	USA	40 (M:40, W:0)	26	Parallel	3 egg/d	0 egg/d	6	_	Healthy	Normal diet	14 hr	↔TC ↔HDL-C ↔TC/HDL-C
Packard et al. (1983)	UK	7 (M:3, W:4)	25	Cross-over	6 egg/d	Regular Diet	<8	_	Healthy	Normal diet	12 hr	↑TC ↑ LDL-C ↑HDL-C ↓TG ↔VLDL-C
Flynn et al. (1984)	USA	26 (M:26, W:0)	25	Cross-over	2 egg/d	0 egg	12	6	Healthy	Normal diet	14 hr	↑TG ↔TC ↔HDL-C
Applebaum-Bowden et al. (1984)	USA	9 (M:6, W:3)	26	Cross-over	5 egg/d High Chol diet (egg yolk) = 1,034 ± 25 mg Chol/d	Substitute Low Chol diet (SUB-egg white) =137 ± 25 mg Chol/d	8	4	Healthy	Normal diet	12 hr	↑LDL-C ↔TC ↔TG ↔HDL-C ↔VLDL-C
Sacks et al. (1984)	USA	17 (M:4, W:13)	21	Cross-over	1 egg/d	Substitute	3	0	Healthy	Lactovegetarian	12 hr	↑LDL-C ↑apoB100 ↔HDL-C ↔apo A1 ↔VLDL-C ↔TG
Flynn et al. (1986)	USA	70 (M:54, W:16)	52	Cross-over	3 egg/d	0 egg	12	0	Healthy	Normal diet	12 hr	↑TC ↔HDL-C
Edington et al. (1987)	USA	168 (M:47, W:121)	45	Cross-over	1 egg/d	2 egg/wk	8	0	Normo & hyperlipidemic	Low fat diet	12 hr	↔TC ↔LDL-C
McNamara et al. (1987)	USA	50 (M:50, W:0)	47	Cross-over	1) 3 whole egg/d + SAFA (high cholesterol ~750mg) 2) 3 whole egg/d + PUFA (high cholesterol ~750 mg)	1) no egg + SAFA (low cholesterol) 2) no egg + PUFA (low cholesterol)	2	0	Healthy	Normal diet	14 hr	↑TC ↑LDL-C ↑HDL-C ↔TG

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TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Zanni et al. (1987)	USA	9 (M:0,W:9)	27	Cross-over	1) corn oil + 875 mg cholesterol (3 egg yolk) 2) lard + 875 mg cholesterol (3 egg yolk)	1) Corn oil + 130 mg cholesterol 2) lard + 130 mg cholesterol	2	3	Healthy	Normal diet	12 hr	Corn diet: ↓TC ↓LDL-C ↓LDL-C/HDL-C ↔HDL-C ↔TG ↔VLDL-C ↔apoA1 ↔apoB100 lard diet: ↔TC ↔LDL-C ↔HDL-C ↔TG ↔LDL-C/HDL-C ↔VLDL-C ↔apoA1 ↔apoB100
Bowman et al. (1988)	USA	24 (M:24, W:0)	22	Parallel	1) Usual Fat (31%) + High Cholesterol (504 mg/d) 2) High Fat(46%) -Usual Cholesterol (504 mg/d)	1) Usual fat (31%) + Low Cholesterol (193mg/d) 2) High fat(46%) -Low Cholesterol (193mg/d)	10	_	Healthy	Normal diet	14 hr	↔TC ↔TG ↔LDL-C ↔HDL-C ↔VLDL-C
Kestin et al., (1989)	Australia	25 (M:25, W:0)	46	Cross-over	2 egg yolk/d	Substitute	4	0	Healthy	High fat diet Modified fat diet	12 hr	↔TC ↔TG ↔LDL-C ↔HDL-C ↔apoA1 ↔apoB100

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TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Clifton et al. (1990)	Australia	56 (M:33, W:23)	50	Cross-over	700 mg egg yolk cholesterol	Substitute	4	0	Hyper & normocholes-terolemic	low fat diet	12 hr	↑TC ↑LDL-C ↑HDL-C ↓TG
Vorster et al. (1992)	South Africa	70 (M:70, W:0)	18	Parallel	1 egg/d 2 egg/d	3 egg/wk	21	–	Healthy	High fat diet	12 hr	↔TC ↔TG ↔LDL-C ↔HDL-C
Martin et al. (1993)	USA	30 (M:30, W:0)	23	Cross-over	5 egg/d 1,044 mg/d (320 mg Chol/ 1,000 kcal)	Substitute 261mg/d (80 mg Chol/ 1,000 kcal)	5	2	Healthy	Normal diet	14 hr	↑TC ↑LDL-C ↑HDL-C ↑apoB100 ↔TG ↔VLDL-C ↔apoA1
Duane (1993)	USA	12 (M:12, W:0)	57	Cross-over	5 egg/d	Substitute	1	1	Healthy	Normal diet	12 hr	↑LDL-C ↔TC ↔TG ↔ HDL-C
Ginsberg et al. (1994)	USA	20 (M:20, W:0)	24	Cross-over	1 egg/d 2 egg/d 4 egg/d	Substitute	8	0.5 4 1.4	Healthy	Normal diet	12 hr	↑TC ↑LDL-C ↔TG ↔HDL-C
Schnohr et al. (1994)	Denmark	24 (M:12, W:12)	39	Cross-over	2 egg/d	0 egg/d	6	0	Healthy	Normal diet	12 hr	↑ TC ↑HDL-C ↔TC/HDL-C ↔TG ↔LDL-C
Ginsberg et al. (1995)	USA	20 (M:0, W:13)	24	Cross-over	1 egg/d 3 egg/d	Substitute	8	0.5 1	Healthy	Normal diet	12 hr	↑TC ↑LDL-C ↑HDL-C ↔ TG

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TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
De Oliveira e Silva et al. (1996)	USA	18 (M:11, W:7)	23.5	Cross-over	2 egg/d	300 gr shrimp	3	0	Healthy	Normal diet	12 hr	↑TC ↑LDL-C ↑HDL-C ↑VLDL-C ↑TC/HDL-C ↑LDL-C/HDL-C ↑TG
Sutherland et al. (1997)	Australia	32 (M:21, W:23)	36	Parallel	1 egg/d	usual diet	1.7	–	Healthy	Normal diet	12 hr	↑TC ↑HDL-C ↑TG
Knopp et al. (1997)	USA	131 (M:86, W:45)	56	Parallel	2 egg yolk/d	Substitute	12	–	Hyperchole-sterolemic or hyperlipidemic	Normal diet	12 hr	↑TC ↑LDL-C ↑HDL-C ↔TG ↔VLDL-C ↔apoB100 ↔apoA1
Blanco-Molina et al. (1998)	Spain	15 (M:15, W:0)	23	Cross-over	1) 2 egg/d + NCEP diet 2) 2 egg/d + MUFA diet	1) NCEP diet 2)MUFA diet	3.4	0	Healthy	Normal diet	12 hr	↓TC ↓LDL-C ↓HDL-C ↓apo B100 ↓apo A1 ↔TG ↔TC/HDL-C
Romano et al. (1998)	Italy	21 (M:21, W:0)	36	Cross-over	4 egg/d	Substitute	3	0	IDDM & Healthy	Normal diet	12 hr	↑LDL-C (in both group) ↑HDL-C (in healthy subjects) ↔VLDL-C (in both group)

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TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Schwab et al. (2000)	USA	13 (M:6, W:7)	63	Cross-over	1) corn oil enriched diet + supplemental Chol (1.5 egg/d)	1) corn oil enriched diet	5	?	Hyperlipidemic	Normal Diet	14 hr	Corn oil diet: ↑TC ↑LDL-C ↑HDL-C ↑TG ↑apoB100 Beef tallow diet: ↑TC ↑LDL-C ↑apoA1 ↑apoB100 ↓VLDL-C ↔HDL-C
					2) beef tallow enriched diet + supplemental Chol (1.5 egg/d)	2) beef tallow enriched diet						
Lewis et al. (2000)	USA	25 (M:13, W:12)	26–73	Cross-over	12 egg/wk	0 egg/d	6	6	Hypercholesterolemic (responder & non-responder)	Low fat, self-selected diet	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG
Boucher et al. (2000)	France	10 (M: ?,W: ?)	22–45	Cross-over	2–4 egg/d	0 egg	1	0	Healthy	Low fat diet	12 hr	↓TC ↑LDL-C ↓HDL-C ↓TC/HDL-C ↓TG ↓ApoA1 ↓ApoB100
Chakrabarty et al. (2002)	India	18 (M:7, W:11)	24	Cross-over	1 egg/d	0 egg/d	8	0	Healthy	Lacto-ovo-vegetarian	12 hr	↑TC ↑LDL-C ↔HDL-C ↔TG ↔TC/HDL-C ↔VLDL-C

(Continues)

TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Knopp et al. (2003)	USA	197 (M:78, W:119)	53	Cross-over	1) 2 egg/d 2) 4 egg/d	Substitute	4	4	1)Insulin sensitive (IS) 2)Insulin resistant (IR) 3) obese Insulin resistant (OIR)	Normal Diet	12 hr	↑TC (in all 3 groups) ↓TG (in IS group) ↑LDL-C (in the IS and IR) ↑HDL-C (in all 3 groups) ↔apoB100
Chakrabarty et al. (2004)	India	34 (M:22, W:12)	26	Cross-over	1 egg/d	0 egg/d	8	0	Healthy (hyper responder& hypo responder)	Lacto-ovo-vegetarian	12 hr	↑TC/HDL-C ↔TC ↔LDL-C ↔HDL-C ↔TG ↔VLDL-C
Greene et al. (2005)	USA	42 (M:13, W:29)	> 60 y	Cross-over	3 egg/d	Substitute	4	3	Healthy	Normal diet	12 hr	↑LDL-C ↑HDL-C ↔LDL-C/HDL-C↔TC/HDL-C ↔TG ↔apoB100
César et al. (2006)	Brazil	25 (M:25, W: 0)	19	Parallel	3 whole egg/d	3 white egg/d	2	–	Healthy	Normal diet	12 hr	↑TC ↑LDL-C ↑HDL-C ↑apoB100 ↔TG ↔apoA1
Wenzel et al. (2006)	USA	24 (M:0, W:24)	33	Parallel	6 egg/wk	Pill (gelatin capsule containing sugar)	12	–	Healthy	Normal diet	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG ↔TC/HDL-C

(Continues)

TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Herron et al. (2006)	USA	91 (M:40, W:51)	30	Cross-over	3 egg/d	Substitute	4	3	Healthy (hyper responder& hypo responder)	Normal Diet	12 hr	↑TC ↑LDL-C ↑HDL-C ↔TG ↔TC/HDL-C
Goodrow et al. (2006)	USA	33 (M:7, W:26)	79	Cross-over	1 egg/d	Substitute	5	4	healthy	Normal Diet	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG
Clark et al. (2006)	USA	40 (M:20, W:20)	33	Cross-over	3 egg/d	Substitute	4	3	Healthy (hyper responder& hypo responder)	Normal Diet	12 hr	↔TC ↔LDL-C ↑HDL-C
Waters et al. (2007)	USA	22 (M:0, W:22)	55	Cross-over	3 egg/d	Substitute	4	3	Healthy (hyper responder& hypo responder)	Normal Diet	12 hr	↑TC ↑LDL-C ↑HDL-C ↔TG
Mutungi et al. (2008)	USA	28 (M:28, W:0)	55	Parallel	3 liquid eggs/d	Substitute	12	–	Overweight/ obese	Carbohydrate restricted	12 hr	↑HDL-C ↔TC ↔LDL-C ↔TG ↔LDL-C/ HDL-C
Harman et al. (2008)	UK	45 (M:14, W:32)	44	Parallel	2 egg/d	0 egg	12	–	Healthy	Energy-restricted diet	12 hr	↓TC ↓LDL-C ↔TG ↔HDL-C ↔apoA1
Vishwanathan et al. (2009)	USA	52 (M:21, W:31)	69	Cross-over	4 egg yolk/d	2 egg yolk/d	5	4	Hypercholes-terolemic	Normal diet	12 hr	↑HDL-C ↔TC ↔LDL-C ↔TG ↔TC/HDL-C

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TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Njike et al. (2010)	USA	40 (M:24, W:16)	60	Cross-over	2 eggs/d	Substitute	6	4	Hyperlipidemic	Carbohydrate restricted	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG ↔TC/HDL-C
Mutungi et al. (2010)	USA	28 (M:28, W:0)	55	Parallel	3 liquid eggs/d	Substitute	12	–	Overweight/ obese	Carbohydrate restricted	12 hr	↓VLDL-C ↓apoB100 ↔apoA1
Tanchoco et al. (2011)	Philippine	115 (M:58, W:57)	43	Cross-over	1 egg/d	0 egg	12	2	Healthy	Normal Diet	12 hr	↑TC ↑LDL-C ↓HDL-C ↓TG
Pearce et al., (2011)	Australia	65 (M:29, W:36)	54	Parallel	(High Protein High Cholesterol) isoenergic + 2 eggs/d	(High Protein Low Cholesterol) isoenergic + 100 gr lean animal protein (meat or chicken or fish and avoid egg)	12	–	T2DM	Energy restricted	12 hr	↓TC ↓TG ↓apoB100 ↑HDL-C ↔LDL-C ↔TC/HDL-C
Techakriengkrai et al. (2012)	Thailand	40 (M:0, W:40)	39	Cross-over	1) 1 egg/d 2) 3 eggs/d	0 egg	4	4	Hypercholes-terolemia	Cholesterol lowering diet (CLD)	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG
Rueda and Khosla (2013)	USA	73 (M:27, W:46)	18	Parallel	10 eggs/wk	0 egg	14	–	Healthy	Normal diet	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG ↔TC/HDL-C

(Continues)

TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Putadechakum et al. (2013)	Thailand	71 (M:8, W:63)	51	Cross-over	1) 1 egg/d 2) 3 eggs/d	0 egg/d	4	4	Hyperlipidemic	Thai food	12 hr	↑TC ↑LDL-C ↔TG ↔HDL-C ↔TC/HDL-C ↔LDL-C/HDL-C
Blesso et al. (2013a)	USA	37 (M:12, W:25)	52	Parallel	3 eggs/d	Yolk free egg substitute	12	–	Metabolic Syndrome	Carbohydrate restricted diet	12 hr	↓TG ↑HDL-C ↓LDL-C/HDL-C ↔TC ↔LDL-C ↔apoA1 ↔apoB
Baumgartner et al. (2013)	Netherland	77 (M:42, W:55)	41	Parallel	1 egg/d	1–2 egg/wk	12	–	Healthy	Normal diet	12 hr	↑TC ↑LDL-C ↔TG ↔HDL-C ↔TC/HDL-C ↔apoA1 ↔apoB100
van der Made et al. (2014)	Netherland	88 (M:29, W:59)	62	Parallel	1.5eggs yolk + 80 mg butter milk/d	butter milk	52	–	Healthy	Normal diet	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG ↔TC/HDL-C↔apoB100 ↔apoA1
Katz et al. (2015)	USA	32 (M:26, W:6)	67	Cross-over	2 eggs/d	Egg substitute	6	4	Coronary artery disease	Normal diet	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG ↔TC/HDL-C

(Continues)

TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Burns-Whitmore et al. (2014)	USA	20 (M:16, W:4)	38	Cross-over	6 eggs/wk (egg W3)	28.4 g walnuts, (6×/wk)	8	4	Healthy	Lacto-ovo-vegetarian	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TG ↔LDL-C/HDL-C ↔apoA1 ↔apoB
Severins et al. (2015)	Netherlands	95 (M:49, W:46)	58	Parallel	1) skimmed milk + 1.5 eggs/d 2) buttermilk + 1.5 eggs/d	1) skimmed milk 2)buttermilk	12	–	Healthy	Normal diet	12 hr	↑TC ↑LDL-C ↔HDL-C ↔TG ↔apoA1 ↔apoB100 ↔TC/HDL-C
Fuller et al. (2015)	Australia	140 (M: ?, W: ?)	60	Parallel	2 eggs/d	<2 eggs/wk	12	–	T2DM	Normal diet	12 hr	↔TC ↔HDL-C ↔LDL-C ↔TG
DiMarco, Norris, et al. (2017)	USA	38 (M:19, W:19)	24	Cross-over	1 egg/d 2 eggs/d 3 eggs/d	0 egg	4	2	Healthy	Normal diet	12 hr	↑apoA1
DiMarco, Missimer, et al. (2017)	USA	38 (M:19, W:19)	24	Cross-over	1 egg/d 2 eggs/d 3 eggs/d	0 egg	4	2	Healthy	Normal diet	12 hr	↑HDL-C ↓LDL-C ↓LDL-C/HDL-C ↔TC ↔TG
Alphonse et al. (2017)	Canada	49 (M: 21, W:28)	33	Cross-over	3 egg/d + milkshake	1) 0 egg/d + milkshake 2) 2 gr/d plant sterol + milkshake	4	4	Healthy	Normal diet	12 hr	↑TC ↑HDL-C ↑LDL-C ↔TG

(Continues)

TABLE 1 (Continued)

Author year	country	Number of subjects (men/women)	Mean age (year)	RCT design	Intervention in egg group (number)	Intervention in control group (egg or substitute)	Duration (weak)	Washout duration (in cross-over studies)	Population characteristics	Specific diet adherence	Fasting duration for blood sampling	Results
Wright et al. (2018)	USA	22 (M:12, W: 10)	70	Parallel	3 egg/d	0 egg	12	–	Obese and overweight	Normal diet	12 hr	↓TC ↓LDL-C ↓HDL-C ↓TC/HDL-C ↓TG
Pourafshar et al. (2018)	USA	42 (M:13, W: 29)	61	Parallel	1 egg/d	Egg substitute	12	–	T2DM overweight-obese	Normal diet	12 hr	↓TC ↓LDL-C ↑HDL-C ↑ApoA1 ↔TG
Aljohi et al. (2019)	USA	45 (M:14, W:31)	75	Parallel	2 egg/d	0 egg	52	–	Healthy	Normal diet	12 hr	↔TC ↔LDL-C ↔HDL-C ↔TC/HDL-C ↔LDL-C/HDL-C ↔TG

Abbreviations: apoA1, apolipoprotein A1; apoB100, apolipoprotein B100; HDL-C, high density lipoproteins; LDL-C, low density lipoproteins; TC, total cholesterol; TG, triglyceride; VLDL-C, very low-density lipoproteins.

editorials, cross-sectional, cohort, case-control, case report, single-arm studies (intervention without control group), unpublished articles, and conference papers; (b) non-human studies, (c) specific groups such as athletics or pregnant women, children or subjects had major chronic diseases such as cancer, chronic kidney disease and etc. (d) studies used egg white or egg enriched by omega 3 or other nutrients in intervention group. (e) intervention with the eggs of poultry (other than chicken). (f) no suitable control group (egg compared with other food that did not have cholesterol, such as oat-meal). (g) repeated publications and reports with insufficient information. (h) studies which egg co-intervention with another component that was not applied in both groups.

2.3 | Data extraction

Full texts of all eligible studies were assessed by two reviewers and data from each study were extracted and confirmed by two investigators (MKS and RKM). The interested outcomes included: TC, LDL-C, HDL-C, TG, VLDL-C, TC/HDL-C, LDL-C/HDL-C, apoA1, and apoB100. The following information were extracted: first author, year of publication, study location, sample size, sex, age, number of population, and amount of egg consumption in intervention group, number of population and kind of intervention in control group, population characteristics, study design and their duration. If published data were inadequate for systematic and meta-analysis required information were requested from authors of the original articles. If we observed repeated publication from the same population, data were extracted from the most complete paper, such as Herron studies (Herron et al., 2002, 2003; Herron, Lofgren, Adiconis, Ordovas, & Fernandez, 2006; Herron, Lofgren, Sharman, Volek, & Fernandez, 2004). In our study all biochemical units of lipid profiles are reported as mg/dl and for apolipoproteins g/L. To convert the units from mmol/L to mg/dl, for lipoproteins including TC, LDL-C, HDL-C, and VLDL-C, we multiplied mmol/L by 38.67 and for TG multiplied by 88.57 (Rugge et al., 2011). Some studies using eggs replacement have reported the amount milligrams of cholesterol from the egg diet or the total number of consumed egg yolks. Based on USDA Food Composition Databases, we considered approximately each 200 mg of cholesterol or an egg yolk equal to one egg. Studies in which the interventions were with different amount of eggs, we considered intervention group who received the maximum amount of egg and control group who had the lowest amount of egg. All study duration converted to week from day or month or year. If results were reported separately for men and women, we combined results to retrieve an overall effect before including them to the main analysis.

2.4 | Quality assessment

Quality of each study was assessed by Cochrane Handbook for Systematic Reviews of Interventions (www.cochrane-handbook.org) (Higgins, Green, & The Cochrane Collaboration, 2009) for the following domains: random-sequence generation, allocation concealment, blinding (performance and detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Trials were reflected on "high risk" when they contained methodologic imperfection that has affected the results, "low risk" if the imperfection was supposed to be negligible, and "unclear risk" if insufficient data were provided to determine bias. The overall quality was considered as: good quality: all criteria met (i.e., low for each domain); fair quality: one criterion not met (i.e., high risk of bias for one domain) or two criteria unclear, and the assessment that this was unlikely to have biased the outcome, and there was no known important limitation that could invalidate the results; poor quality: two or more criteria listed as high or unclear risk of bias.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool was used to assess the overall quality and strength of available evidence (Schünemann, Brożek, Guyatt, & Oxman, 2013). According to this approach, evidence is classified as "very low," "low," "moderate," or "high" quality. Clinical trials study at first receives a grade of "high" quality and may be downgraded by following prespecified criteria: risk of bias based on Cochrane Collaboration's tool, inconsistency (high heterogeneity between studies; $I^2 \geq 75\%$), indirectness (indirect population, intervention, control, outcomes that can limited the generalizability of the results), imprecision of results (wide confidence intervals), and publication bias (high probability of publication bias for evidence that has small-study effects).

2.5 | Statistical analysis

We used mean changes and their corresponding standard deviations (*SD*), that were extracted from each study, to calculated mean differences for TC, LDL-C, HDL-C, TG, VLDL, LDL-C/HDL-C ratio, TC/HDL-C ratio, apoA1, and apoB100 between intervention (egg group) and control groups to be used as effect size for meta-analysis. All data are based on mean ± *SD*. If data were reported as median and SE or CI, we changed to mean and *SD* by formulas ($SD = \sqrt{n} \times SE$ or $SD = \sqrt{N} \times$ (Upper limit of CI − Lower limit of CI)/3.92). For studies that just reported mean ± *SD* at baseline and endpoint, we calculated the mean changes and also estimated *SD* for mean change using correlation *r* using studies that reported baseline, after and change values [$r = 0.822$ for TC (Baumgartner et al., 2013; Flynn et al., 1984; Katz et al., 2015; Njike, Faridi, Dutta, Gonzalez-Simon, & Katz, 2010; Pearce, Clifton, & Noakes, 2011; Roberts, McMurry, & Connor, 1981; Severins, Mensink, & Plat, 2015; Tanchoco, Infante, Rodriguez, Aquino, & Orense, 2011), $r = 0.722$ for TG (Baumgartner et al., 2013; Flynn et al., 1984; Katz et al., 2015; Njike et al., 2010; Pearce et al., 2011; Severins et al., 2015; Tanchoco et al., 2011), $r = 0.785$ for LDL-C (Baumgartner et al., 2013; Katz et al., 2015; Njike et al., 2010; Pearce et al., 2011; Severins et al., 2015; Tanchoco et al., 2011), $r = 0.861$ for HDL-C (Baumgartner et al., 2013; Blesso et al., 2013a; Flynn et al., 1984; Goodrow et al., 2006; Katz et al., 2015; Mutungi et al., 2008; Njike et al., 2010; Pearce et al., 2011; Severins et al.,

2015; Tanchoco et al., 2011), r = 0.858 for TC/HDL-C (Baumgartner et al., 2013; Katz et al., 2015; Njike et al., 2010; Pearce et al., 2011; Severins et al., 2015), r = 0.854 for apoA1 (Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Greene, Waters, Clark, Contois, & Fernandez, 2005; Knopp et al., 2003; Mutungi et al., 2010; Severins et al., 2015; Zanni, Zannis, Blum, Herbert, & Breslow, 1987), r = 0.864 for apoB100 (Baumgartner et al., 2013; Pearce et al., 2011; Severins et al., 2015), and r = 0.5 were considered for other factors]. Summary weighted means and their corresponding SDs were estimated following DerSimonian and Laird (DerSimonian & Laird, 1986) and using the random-effects model. Statistical heterogeneity among studies was checked with Cochran's Q test and the I^2 statistic (I^2). There was low heterogeneity among studies when I^2 estimated ≤50%, moderate heterogenety when I^2 between 50% and 70%, and high heterogenety when I^2 ≥ 70% (Higgins et al., 2003). We conducted a subgroup analysis to identify the probable source of heterogeneity among trials; separating studies in which sex (men, women, and both), study design (parallel or cross-over), study duration (less or greater than 8 weeks), type of interventions ((a) intervention with egg compared to no egg, (b) diet with high egg intake compared to diet with low egg intake, (c) comparing egg and egg substitute that were similar in terms of appearance, consistency, color, and volume, (d) specific diet adherence in both group with or without egg, (e) specific diet adherence in both groups with high or low egg intake, (f) specific diet adherence in both group with egg or substitute, (g) camparison of egg intake with other source of cholesterol), population charactaristics (healthy, hyperlipidemia, diabetes, metabolic syndrome, obese or over weight, coronary artery disease). The sensitivity analysis was performed by excluding the studies one by one, to determine which inferences might depend on one study or one group of studies. Publication bias was assessed by visual inspection of funnel plots, and the funnel plot asymmetry was statistically checked using Egger's and Begg's regression asymmetry test and adjusted rank correlation test (Egger et al., 1997). The nonlinear potential effects of egg dosage (number/day) on lipid profiles concentration were examined using fractional polynominal modeling (polynomials). All statistical analyses were perfomed using STATA, version 12 (STATA Corp, College Station, TX). p values ≤ .05 were considered to be significant.

3 | RESULTS

3.1 | Studies characteristics

Our primary databases searches have retrieved 1,480 articles, of which, 177 published articles were eligible for second screening. After assessing the full text of articles, 62 studies (Aljohi, Dopler-Nelson, Cifuentes, & Wilson, 2019; Alphonse, Ramprasath, & Jones, 2017; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Boucher et al., 2000; Bronsgeest-Schoute, Hermus, Dallinga-Thie, & Hautvast, 1979a, 1979b; Burns-Whitmore, Haddad, Sabaté, & Rajaram, 2014; Buzzard, McRoberts, Driscoll, & Bowering, 1982; César, Oliveira, Mesquita, & Maranhão, 2006; Chakrabarty et al., 2002, 2004; Chenoweth, Ullmann, Simpson, & Leveille, 1981; Clark, Herron, Waters, & Fernandez, 2006; Clifton, Kestin, Abbey, Drysdale, & Nestel, 1990; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; DiMarco, Norris, Millar, Blesso, & Fernandez, 2017; Duane, 1993; Edington et al., 1987; Flynn et al., 1984, 1986; Fuller et al., 2015; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Harman et al., 2008; Herron et al., 2006; Katan, Beynen, de Vries, & Nobels, 1986; Katz et al., 2015; Kestin, Clifton, Rouse, & Nestel, 1989; Knopp et al., 1997, 2003; Lewis, Schalch, & Scheideler, 2000; Martin et al., 1993; Mutungi et al., 2008, 2010; Njike et al., 2010; O'Brien & Reiser, 1980; Packard, McKinney, Carr, & Shepherd, 1983; Pearce et al., 2011; Porter, Yamanaka, Carlson, & Flynn, 1977; Pourafshar et al., 2018; Putadechakum, Phanachet, Pakpeankitwattana, Klangjareonchai, & Roongpisuthipong, 2013; Roberts et al., 1981; Romano et al., 1998; Rueda & Khosla, 2013; Sacks et al., 1984; Schnohr et al., 1994; Schwab et al., 2000; Severins et al., 2015; Sutherland, Ball, & Walker, 1997; Tanchoco et al., 2011; Techakriengkrai, Klangjareonchai, Pakpeankitwattana, Sritara, & Roongpisuthipong, 2012; van der Made et al., 2014; Vishwanathan, Goodrow-Kotyla, Wooten, Wilson, & Nicolosi, 2009; Vorster et al., 1992; Waters, Clark, Greene, Contois, & Fernandez, 2007; Wenzel et al., 2006; Wright, Zhou, Sayer, Kim, & Campbell, 2018) were included in the meta-analysis; however, Duane (1993) for all factors and Chenoweth et al. (1981) just for TC, because of lack of enough data, were removed from our analysis. Furthermore, we hand searched in previous related reviews and articles, and found five studies (Applebaum-Bowden et al., 1984; Bowman et al., 1988; Flynn, Nolph, Flynn, Kahrs, & Krause, 1979; McNamara et al., 1987; Zanni et al., 1987) to add to the analysis (Figure 1).

Finally, 66 clinical trials were analyzed that contained 3,185 adult participants. Sixty-one articles conducted the effect of egg consumption on serum TC (Aljohi et al., 2019; Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Boucher et al., 2000; Bowman et al., 1988; Bronsgeest-Schoute et al., 1979a, 1979b; Burns-Whitmore et al., 2014; Buzzard et al., 1982; César et al., 2006; Chakrabarty et al., 2002, 2004; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; Edington et al., 1987; Flynn et al., 1979, 1984, 1986; Fuller et al., 2015; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Harman et al., 2008; Herron et al., 2006; Katan et al., 1986; Katz et al., 2015; Kestin et al., 1989; Knopp et al., 1997, 2003; Lewis et al., 2000; Martin et al., 1993; McNamara et al., 1987; Mutungi et al., 2008; Njike et al., 2010; O'Brien & Reiser, 1980; Packard et al., 1983; Pearce et al., 2011; Porter et al., 1977; Pourafshar et al., 2018; Putadechakum et al., 2013; Roberts et al., 1981; Rueda & Khosla, 2013; Sacks et al., 1984; Schnohr et al., 1994; Schwab et al., 2000; Severins et al., 2015; Sutherland et al., 1997; Tanchoco et al., 2011; Techakriengkrai et al., 2012; van der Made et al., 2014; Vishwanathan et al., 2009; Vorster et al., 1992; Waters et al.,

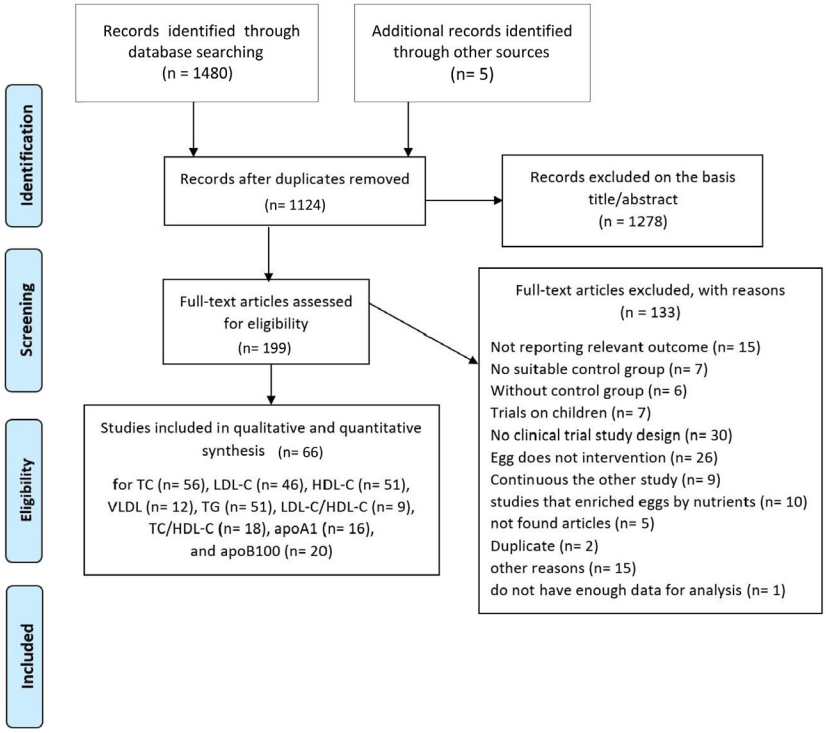

FIGURE 1 Summary of the screening and selection process of trials included in the meta-analysis

2007; Wenzel et al., 2006; Wright et al., 2018; Zanni et al., 1987), 57 on TG (Aljohi et al., 2019; Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Boucher et al., 2000; Bowman et al., 1988; Bronsgeest-Schoute et al., 1979b; Burns-Whitmore et al., 2014; César et al., 2006; Chakrabarty et al., 2002, 2004; Chenoweth et al., 1981; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; Flynn et al., 1979, 1984; Fuller et al., 2015; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Harman et al., 2008; Herron et al., 2006; Katan et al., 1986; Katz et al., 2015; Knopp et al., 1997, 2003; Lewis et al., 2000; Martin et al., 1993; McNamara et al., 1987; Mutungi et al., 2008; Njike et al., 2010; Packard et al., 1983; Pearce et al., 2011; Porter et al., 1977; Pourafshar et al., 2018; Putadechakum et al., 2013; Roberts et al., 1981; Rueda & Khosla, 2013; Sacks et al., 1984; Schnohr et al., 1994; Severins et al., 2015; Sutherland et al., 1997; Tanchoco et al., 2011; Techakriengkrai et al., 2012; van der Made et al., 2014; Vishwanathan et al., 2009; Vorster et al., 1992; Waters et al., 2007; Wenzel et al., 2006; Wright et al., 2018; Zanni et al., 1987), 52 on LDL-C (Aljohi et al., 2019; Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Boucher et al., 2000; Bowman et al., 1988; Burns-Whitmore et al., 2014; César et al., 2006; Chakrabarty et al., 2002, 2004; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; Edington et al., 1987; Fuller et al., 2015; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Harman et al., 2008; Herron et al., 2006; Katz et al., 2015; Kestin et al., 1989; Knopp et al., 1997, 2003; Lewis et al., 2000; Martin et al., 1993; McNamara et al., 1987; Mutungi et al., 2008; Njike et al., 2010; Packard et al., 1983; Pearce et al., 2011; Pourafshar et al., 2018; Putadechakum et al., 2013; Romano et al., 1998; Rueda & Khosla, 2013; Sacks et al., 1984; Schnohr et al., 1994; Schwab et al., 2000; Severins et al., 2015; Tanchoco et al., 2011; Techakriengkrai et al., 2012; van der Made et al., 2014; Vishwanathan et al., 2009; Vorster et al., 1992; Waters et al., 2007; Wenzel et al., 2006; Wright et al., 2018; Zanni et al., 1987), 57 on HDL-C (Aljohi et al., 2019; Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Boucher et al., 2000; Bowman et al., 1988; Burns-Whitmore et al., 2014; Buzzard et al., 1982; César et al., 2006; Chakrabarty et al., 2002, 2004; Chenoweth et al., 1981; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; Flynn et al., 1984, 1986; Fuller et al., 2015; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Harman et al., 2008; Herron et al., 2006; Katan et al., 1986; Katz et al., 2015; Kestin et al., 1989; Knopp et al., 1997, 2003; Lewis et al., 2000; Martin et al., 1993; McNamara et al., 1987; Mutungi et al., 2008; Njike et al., 2010; O'Brien & Reiser, 1980; Packard et al., 1983; Pearce et al., 2011; Pourafshar et al., 2018; Putadechakum et al., 2013; Romano et al., 1998; Rueda & Khosla, 2013; Sacks et al., 1984; Schnohr et al., 1994; Schwab et al., 2000; Severins et al., 2015; Sutherland et al., 1997; Tanchoco et al., 2011; Techakriengkrai et al., 2012; van der Made et al., 2014; Vishwanathan et al., 2009; Vorster et al., 1992; Wenzel et al., 2006; Wright et al., 2018; Zanni et al., 1987), 13 on VLDL-C (Applebaum-Bowden et al., 1984;

Bowman et al., 1988; Chakrabarty et al., 2002, 2004; Clifton et al., 1990; De Oliveira e Silva et al., 1996; Knopp et al., 1997; Martin et al., 1993; Packard et al., 1983; Romano et al., 1998; Sacks et al., 1984; Schwab et al., 2000; Zanni et al., 1987), 12 on LDL-C/HDL-C (Aljohi et al., 2019; Alphonse et al., 2017; Blesso et al., 2013a; Burns-Whitmore et al., 2014; César et al., 2006; Chenoweth et al., 1981; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; Greene et al., 2005; Mutungi et al., 2008; Putadechakum et al., 2013; Zanni et al., 1987), 21 on TC/HDL-C (Aljohi et al., 2019; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Burns-Whitmore et al., 2014; Buzzard et al., 1982; Chakrabarty et al., 2002, 2004; Chenoweth et al., 1981; De Oliveira e Silva et al., 1996; Herron et al., 2006; Katz et al., 2015; Njike et al., 2010; Pearce et al., 2011; Putadechakum et al., 2013; Rueda & Khosla, 2013; Schwab et al., 2000; Severins et al., 2015; van der Made et al., 2014; Vishwanathan et al., 2009; Wenzel et al., 2006; Wright et al., 2018), 19 on apoA1 (Aljohi et al., 2019; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Boucher et al., 2000; Burns-Whitmore et al., 2014; César et al., 2006; De Oliveira e Silva et al., 1996; DiMarco, Norris, et al., 2017; Harman et al., 2008; Kestin et al., 1989; Knopp et al., 1997; Martin et al., 1993; Mutungi et al., 2010; Sacks et al., 1984; Schwab et al., 2000; Severins et al., 2015; van der Made et al., 2014; Zanni et al., 1987), 22 on apoB100 (Aljohi et al., 2019; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Blesso et al., 2013a; Boucher et al., 2000; Burns-Whitmore et al., 2014; César et al., 2006; Fuller et al., 2015; Ginsberg et al., 1994; Greene et al., 2005; Harman et al., 2008; Kestin et al., 1989; Knopp et al., 1997, 2003; Martin et al., 1993; Mutungi et al., 2010; Pearce et al., 2011; Sacks et al., 1984; Schwab et al., 2000; Severins et al., 2015; van der Made et al., 2014; Zanni et al., 1987). The design of 20 studies was parallel (Aljohi et al., 2019; Baumgartner et al., 2013; Blesso et al., 2013a; Bowman et al., 1988; Buzzard et al., 1982; César et al., 2006; Fuller et al., 2015; Harman et al., 2008; Knopp et al., 1997; Mutungi et al., 2008, 2010; Pearce et al., 2011; Pourafshar et al., 2018; Rueda & Khosla, 2013; Severins et al., 2015; Sutherland et al., 1997; van der Made et al., 2014; Vorster et al., 1992; Wenzel et al., 2006; Wright et al., 2018) and 46 crossover (Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Blanco-Molina et al., 1998; Boucher et al., 2000; Burns-Whitmore et al., 2014; Chakrabarty et al., 2002, 2004; Chenoweth et al., 1981; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Norris, et al., 2017; Edington et al., 1987; Flynn et al., 1986; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Herron et al., 2006; Katz et al., 2015; Kestin et al., 1989; Knopp et al., 2003; Lewis et al., 2000; Martin et al., 1993; Njike et al., 2010; Porter et al., 1977; Putadechakum et al., 2013; Roberts et al., 1981; Romano et al., 1998; Sacks et al., 1984; Schnohr et al., 1994; Schwab et al., 2000; Tanchoco et al., 2011; Techakriengkrai et al., 2012; Vishwanathan et al., 2009; Waters et al., 2007; Zanni et al., 1987) and duration of 45 trials was less than 12 weeks (Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Blanco-Molina et al., 1998; Boucher et al., 2000; Bowman et al., 1988; Bronsgeest-Schoute et al., 1979a, 1979b; Burns-Whitmore et al., 2014; Buzzard et al., 1982; César et al., 2006; Chakrabarty et al., 2002, 2004; Chenoweth et al., 1981; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Norris, et al., 2017; Edington et al., 1987; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Greene et al., 2005; Herron et al., 2006; Katan et al., 1986; Katz et al., 2015; Kestin et al., 1989; Knopp et al., 2003; Lewis et al., 2000; Martin et al., 1993; McNamara et al., 1987; Njike et al., 2010; O'Brien & Reiser, 1980; Packard et al., 1983; Putadechakum et al., 2013; Roberts et al., 1981; Romano et al., 1998; Sacks et al., 1984; Schnohr et al., 1994; Schwab et al., 2000; Sutherland et al., 1997; Techakriengkrai et al., 2012; Vishwanathan et al., 2009; Waters et al., 2007; Zanni et al., 1987) and 21 was more than 12 weeks (Aljohi et al., 2019; Baumgartner et al., 2013; Blesso et al., 2013a; Flynn et al., 1979, 1984, 1986; Fuller et al., 2015; Harman et al., 2008; Knopp et al., 1997; Mutungi et al., 2008, 2010; Pearce et al., 2011; Porter et al., 1977; Pourafshar et al., 2018; Rueda & Khosla, 2013; Severins et al., 2015; Tanchoco et al., 2011; van der Made et al., 2014; Vorster et al., 1992; Wenzel et al., 2006; Wright et al., 2018). In 23 articles, egg consumption was compared to egg substitute (Applebaum-Bowden et al., 1984; Blesso et al., 2013a; Chenoweth et al., 1981; Clark et al., 2006; Clifton et al., 1990; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Herron et al., 2006; Katz et al., 2015; Kestin et al., 1989; Knopp et al., 1997, 2003; Martin et al., 1993; Mutungi et al., 2008, 2010; Njike et al., 2010; Pourafshar et al., 2018; Roberts et al., 1981; Romano et al., 1998; Sacks et al., 1984; Waters et al., 2007) and in 33 studies high amount of egg consumption in a day was compared to low amount or no egg in control groups (Aljohi et al., 2019; Alphonse et al., 2017; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Boucher et al., 2000; Bowman et al., 1988; Burns-Whitmore et al., 2014; Buzzard et al., 1982; César et al., 2006; Chakrabarty et al., 2002, 2004; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; DiMarco, Norris, et al., 2017; Edington et al., 1987; Flynn et al., 1986; Fuller et al., 2015; Harman et al., 2008; Lewis et al., 2000; Pearce et al., 2011; Putadechakum et al., 2013; Rueda & Khosla, 2013; Schnohr et al., 1994; Schwab et al., 2000; Severins et al., 2015; Sutherland et al., 1997; Tanchoco et al., 2011; Techakriengkrai et al., 2012; van der Made et al., 2014; Vishwanathan et al., 2009; Vorster et al., 1992; Wenzel et al., 2006; Wright et al., 2018). Forty-eight trials were conducted on healthy adults (Aljohi et al., 2019; Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Baumgartner et al., 2013; Blanco-Molina et al., 1998; Boucher et al., 2000; Bowman et al., 1988; Bronsgeest-Schoute et al., 1979a, 1979b; Burns-Whitmore et al., 2014; Buzzard et al., 1982; César et al., 2006; Chakrabarty et al., 2002, 2004; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; DiMarco, Norris, et al., 2017; Edington et al., 1987; Flynn et al., 1979, 1984, 1986; Ginsberg et al., 1994, 1995; Goodrow et al., 2006; Greene et al., 2005; Harman et al., 2008; Herron et al., 2006; Katan et al., 1986; Kestin et al., 1989; Martin

et al., 1993; McNamara et al., 1987; O'Brien & Reiser, 1980; Packard et al., 1983; Porter et al., 1977; Roberts et al., 1981; Romano et al., 1998; Rueda & Khosla, 2013; Sacks et al., 1984; Schnohr et al., 1994; Severins et al., 2015; Sutherland et al., 1997; Tanchoco et al., 2011; Vishwanathan et al., 2009; Vorster et al., 1992; Wenzel et al., 2006; Zanni et al., 1987), nine on adults with hyperlipidemia (Clifton et al., 1990; Edington et al., 1987; Knopp et al., 1997; Lewis et al., 2000; Njike et al., 2010; Roberts et al., 1981; Schwab et al., 2000; Techakriengkrai et al., 2012; Vishwanathan et al., 2009), five on adults with insulin resistance (Fuller et al., 2015; Knopp et al., 2003; Pearce et al., 2011; Pourafshar et al., 2018; Romano et al., 1998), five on obese adults or adults with metabolic syndrome (Blesso et al., 2013a; Knopp et al., 2003; Mutungi et al., 2008, 2010; Wright et al., 2018), and one on CVD patients (Katz et al., 2015). Intervention in 12 studies was one egg/d (Baumgartner et al., 2013; Burns-Whitmore et al., 2014; Chakrabarty et al., 2002, 2004; Edington et al., 1987; Goodrow et al., 2006; Porter et al., 1977; Pourafshar et al., 2018; Sacks et al., 1984; Sutherland et al., 1997; Tanchoco et al., 2011; Wenzel et al., 2006) and in 54 studies was more than one egg per day (Aljohi et al., 2019; Alphonse et al., 2017; Applebaum-Bowden et al., 1984; Blanco-Molina et al., 1998; Blesso, Andersen, Barona, Volek, & Fernandez, 2013b; Boucher et al., 2000; Bowman et al., 1988; Bronsgeest-Schoute et al., 1979a, 1979b; Buzzard et al., 1982; César et al., 2006; Chenoweth et al., 1981; Clark et al., 2006; Clark et al., 2006; Clifton et al., 1990; De Oliveira e Silva et al., 1996; DiMarco, Missimer, et al., 2017; DiMarco, Norris, et al., 2017; Flynn et al., 1979, 1984, 1986; Fuller et al., 2015; Ginsberg et al., 1994, 1995; Greene et al., 2005; Harman et al., 2008; Katan et al., 1986; Katz et al., 2015; Kestin et al., 1989; Knopp et al., 1997, 2003; Lewis et al., 2000; Martin et al., 1993; McNamara et al., 1987; Mutungi et al., 2008, 2010; Njike et al., 2010; O'Brien & Reiser, 1980; Packard et al., 1983; Pearce et al., 2011; Putadechakum et al., 2013; Roberts et al., 1981; Romano et al., 1998; Rueda & Khosla, 2013; Schnohr et al., 1994; Schwab et al., 2000; Severins et al., 2015; Techakriengkrai et al., 2012; van der Made et al., 2014; Vishwanathan et al., 2009; Vorster et al., 1992; Waters et al., 2007; Wright et al., 2018; Zanni et al., 1987). All studies evaluated lipid profiles following a 12 hr fast. Descriptive characteristics of studies are summarized in Table 1.

3.2 | Results of meta-analysis

3.2.1 | Serum TC

A meta-analysis of 61 studies has shown that the overall effect of egg consumption on serum total cholesterol was +9.121 mg/dl (95% CI: 7.350, 10.893; $p < .001$). There was a high heterogeneity between studies (Q statistics = 535.49, $p < .001$, $I^2 = 88.8\%$). The intervention of one egg/day can be the source of heterogeneity for TC ($I^2 = 47.2\%$, p between group <.001) (Figure 2). In a subgroup analysis, egg intake had a: (a) more incremental effect in women and healthy populations, (b) studies with a cross-over design and durations less than 12 weeks, demonstrated a greater increase in serum TC than studies with the duration greater than 12 weeks and parallel study design, (c) total cholesterol increased more in participants who consumed greater than one egg/d than who consumed one egg/d, (d) interventions with egg as compared to egg substitute had the most increasing effect on serum TC. Subgroup meta-analysis for serum TC is reported in Table S2.

3.2.2 | Serum TG

Based on the results obtained from the analysis of 57 clinical trials, egg consumption had no significant effect on serum triglyceride (WMD: −1. 217 mg/dl; 95% CI: −3.377, 0.942; $p = .269$). There was a moderate heterogeneity between studies (Q statistics = 130.82, $p < .001$, $I^2 = 57.2\%$) (Figure S1). We did not observe any significant effect of egg consumption on serum TG in each of the subgroup analysis except comparison egg intervention with other food (WMD: +4.745 mg/dl; CI: 0.009, 9.481; $p = .050$) (Table S3).

3.2.3 | Serum LDL-C

Fifty-three included studies evaluated serum LDL-C and overall analysis demonstrated that egg consumption significantly increased LDL-C (WMD: +7.389 mg/dl; 95% CI: 5.824, 8.955; $p < .001$). There was a high heterogeneity between studies (Q statistics = 219.39, $p < .001$, $I^2 = 76.6\%$) which potential sources of heterogeneity was in sex subgroup in women ($I^2 = 40.4\%$, p between group <.001) (Figure 3). According to Table S4: (a) egg consumption significantly increased serum LDL-C in men, and healthy people, (b) study durations of less than 12 weeks and studies with cross-over design had more incremental effects on serum LDL-C in comparison to studies with parallel design and durations of greater than 12 weeks, (c) consuming greater than one egg/d resulted in an even greater increase in serum LDL-C, (d) increased in serum LDL-C was more pronounced in studies that used increasing amounts of eggs, relative to a control group.

3.2.4 | Serum HDL-C

Overall, the 57 studies showed that egg consumption can increase HDL-C (WMD: +1.411 mg/dl; 95% CI: 0.768, 2.054; $p < .001$). There was a high heterogeneity between studies (Q statistics = 497.35, $p < .001$, $I^2 = 88.7\%$). The potential sources of heterogeneity was in type of egg intervention in comparison egg with other food ($I^2 = 32.4\%$, p between group <.001) (Figure 4). Subgroup analyses revealed that: (a) the effects which was more pronounced in men and with obesity, (b) there was no significant effect of egg consumption on serum HDL-C in women, (c) studies with a parallel design or duration of less than 12 weeks resulted in a greater increase in HDL-C., (d) interventions

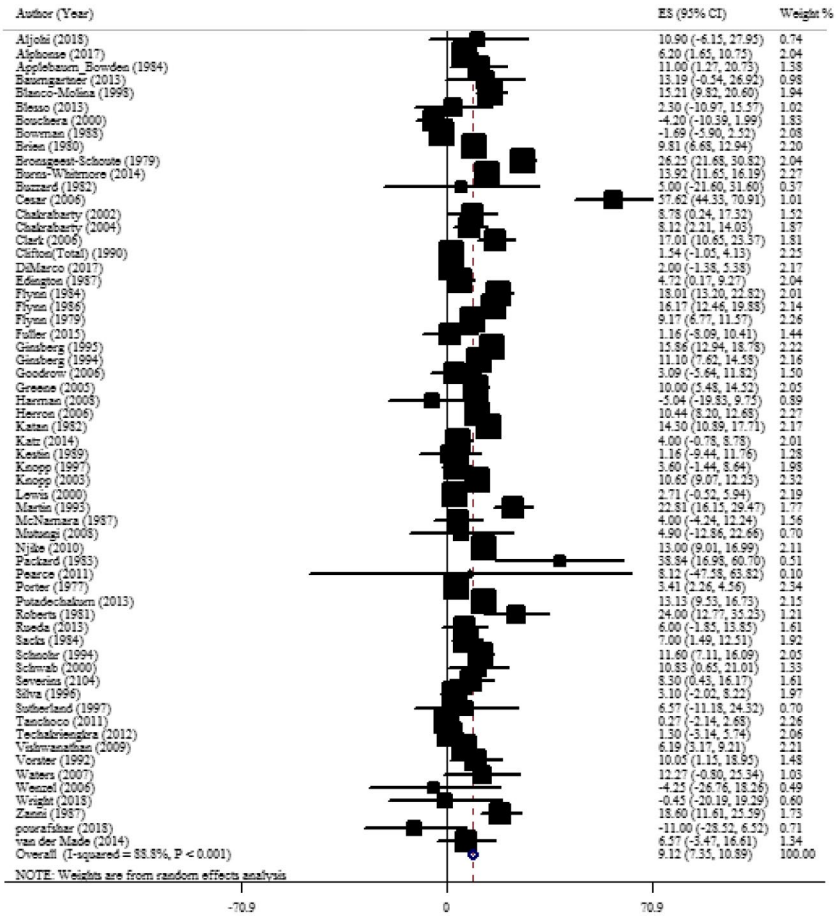

FIGURE 2 Forest plot of randomized controlled clinical trials illustrating weighted mean difference in total cholesterol (mg/dl) between the egg and control groups for all eligible studies in overall analysis. Analysis was conducted using random effects model

in which participants consumed greater than one egg/d significantly increased serum HDL-C; however, consumption of one egg/d had no significant effect, (e) the most increasing effect on serum HDL-C was seen in studies that evaluated different amounts of eggs relative to a control group. The several subgroup-analysis is introduced in Table S5.

3.2.5 | Serum VLDL-C

Meta-analysis of 13 studies demonstrated that egg consumption does not influence serum VLDL-C (WMD: −0.368 mg/dl; 95% CI: −1.446, 0.710; p = .504). There was not heterogeneity among studies (Q statistics = 18.25, p = .108, I^2 = 34.3%) (Figure S2). Likewise, we found the same result in a subgroup analysis when egg consumption was compared to egg substitute with same specific diet in both groups. In addition, egg consumption was shown to reduce VLDL-C in patients with dyslipidemia (Table S6).

3.2.6 | Ratio of LDL-C to HDL-C

Based on our analysis of 12 studies that evaluated LDL-C/HDL-C, egg consumption did not significantly increase this risk indicator for heart disease (WMD: 0.083 mg/dl; 95% CI: −0.011, 0.178; p = .084). There was no heterogeneity among studies (Q statistics = 12.19, p = .349, I^2 = 9.8%) (Figure S3). In the subgroup analyses, similar to the overall result, we did not observe any significant effect; however, a significant increase was observed in studies with duration of greater than 12 weeks (Table S7).

3.2.7 | Ratio of TC to HDL-C

Overall, results from analysis of 21 studies showed egg consumption increased TC/HDL-C (WMD: 0.110 mg/dl; 95% CI: 0.039, 0.180; p = .002). Heterogeneity of these studies was high (Q statistics = 79.30, p < .001, I^2 = 74.8%). The source of heterogeneity was parallel study design (Figure S4). Our subgroup analyses demonstrated: (a) there was no sex-specific effect, (b) patients with dyslipidemia were most affected, (c) studies utilizing a cross-over design or intervention period of less than 12 weeks were more affected than studies utilizing a parallel design on intervention duration greater than 12 weeks, (d) Participants who consumed greater than one egg/d showed increased TC/LDL-C ratio. Interventions using different amounts of egg in both groups, had the greatest effect on increasing this ratio. Subgroup analysis was reported in Table S8.

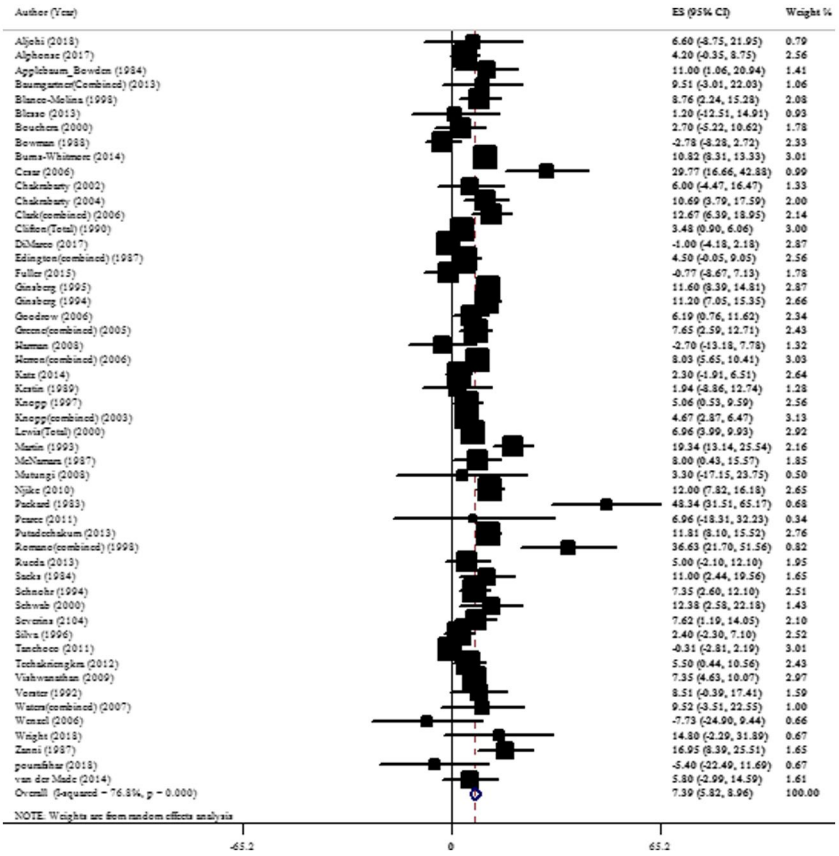

FIGURE 3 Forest plot of randomized controlled clinical trials illustrating weighted mean difference in LDL-cholesterol (mg/dl) between the egg and control groups for all eligible studies in overall analysis. Analysis was conducted using random effects model

3.2.8 | Serum apoA1

Analysis of 19 studies illustrated egg consumption increased 0.025 g/L (95% CI: 0.006, 0.045; p = .012) serum apoA1 in all subjects. High heterogeneity was evident between these studies (Q statistics = 75.35, p < .001, I^2 = 75.8%) which source of heterogeneity can be in type of intervention in egg and placebo group (Figure S5). In subgroup analysis, we observed: (a) apoA1 increased in women, (b) patients with dyslipidemia, (c) studies utilizing a cross-over design, (d) studies less than 12 weeks in duration. Furthermore, ingestion of greater than one egg/d increased apoA1 and this effect was more pronounced in studies that evaluated egg consumption compared to egg substitute (Table S9).

3.2.9 | Serum apoB100

Twenty-two included studies in the present meta-analysis showed that egg consumption significantly increased serum apoB100 (WMD: 0.058 g/L; 95% CI: 0.034, 0.082; p < .001). There was a high heterogeneity between studies (Q statistics = 165.58, p < .001, I^2 = 87.3%) which potential sources of heterogeneity was in insulin resistance population (Figure S6). Based on subgroup analyses, this effect was: (a) more pronounced in men and obese populations, (b) studies utilizing a cross-over design and with a duration less than 12 weeks have more incremental effect on serum level of apoB100, (c) there were no significant differences between participants who consumed one egg/d or greater than one egg/d, (d) studies that compared participants who received egg versus other foods, demonstrated a greater effect on serum apoB100 (Table S10).

3.2.10 | Nonlinear dose-responses between dose and duration of egg intake and outcomes

Following dose-response evaluation, we observed there was a linear correlation between the number of eggs consumed per a day and increase in serum level of TC (p nonlinearity = .077), HDL-C (p nonlinearity = .182), apoA1 (p nonlinearity = .494), and ApoB100 (p nonlinearity = .311) and there is a non-linear correlation for LDL-C (p nonlinearity = .014), and TC/HDL-C (p nonlinearity = .012) (Figure 5).

3.3 | Sensitivity analysis and publication bias

In the sensitivity analysis, we observed that just results of TC total cholesterol was sensitive to the study by Porter et al. (1977) study

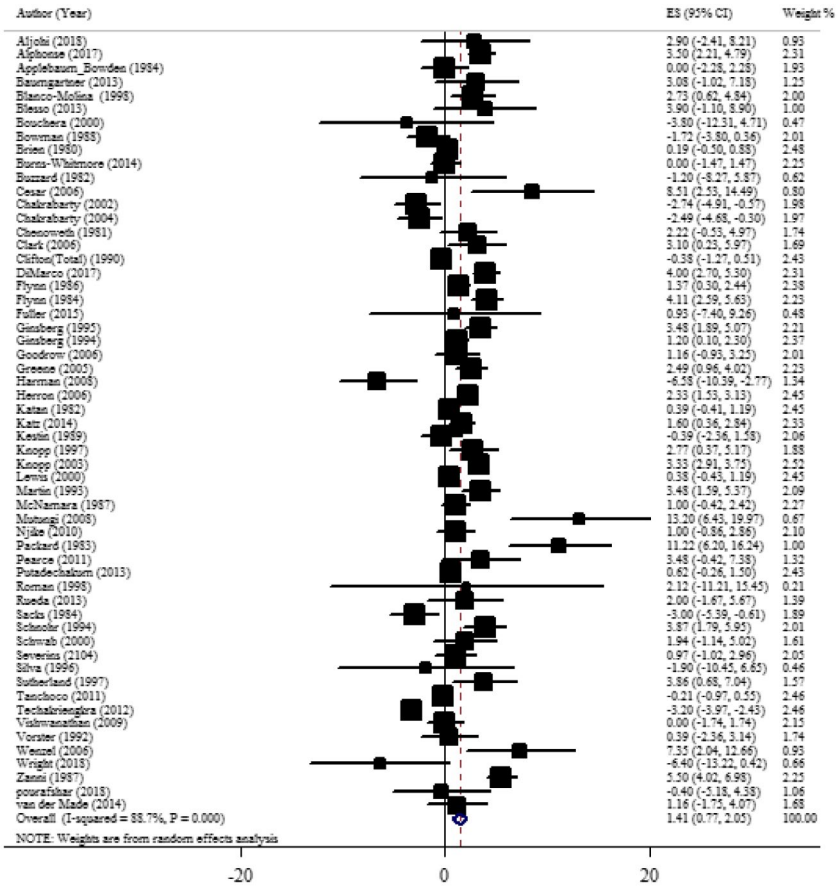

FIGURE 4 Forest plot of randomized controlled clinical trials illustrating weighted mean difference in HDL-cholesterol (mg/dl) between the egg and control groups for all eligible studies in overall analysis. Analysis was conducted using random effects model

and HDL-C was sensitive to the study by Knopp et al. (2003) study. The results without consideration of these studies are (WMD: +9.065; 95% CI: 8.495, 9.634; $p < .001$) and (WMD: +1.352; 95% CI: 0.724, 1.980; $p < .001$), respectively. Furthermore, the Egger and Begg's tests did not indicate the attendance of publication bias in analyzed studies. Funnel plots no revealed asymmetry.

3.4 | Assessment of risk bias

Based on bias assessment of Cochrane Collaboration's tool 13 trials included in the meta-analysis had a good quality, 26 trials were classified as fair, and 27 trials were classified as poor (Table S11).

3.5 | GRADE assessment

The GRADE assessment for the overall strength of evidence for the effect of egg consumption on various blood lipids is described in Table S12. The evidence was graded as moderate quality for TC, LDL-C, HDL-C, TG, TC/HDL-C, apoA1, and apoB100, owing to risk of bias for blinding, and as a low quality for VLDL-C and LDL-C/HDL-C, due to risk of bias for blinding and low heterogeneity between studies.

4 | DISCUSSION

The findings of this systematic review and meta-analysis of 66 clinical trials revealed that, overall, egg consumption can significantly increase the serum levels of TC, LDL-C, HDL-C, TC/HDL-C ratio, apoA1, and apoB100 but does not significantly influence TG, VLDL, and LDL-C/HDL-C ratio. Studies utilizing a cross-over design and an intervention duration of less than 12 weeks, demonstrated the greatest effect on blood lipids. Furthermore, the increase in blood lipids was more pronounced in healthy populations (both male and female), and subjects who consumed greater than one egg per day. There was a positive linear effect of egg consumption on TC, HDL-C, TG, ApoA1, ApoB100, VLDL-C, and LDL-C/HDL-C but not for LDL-C, and TC/HDL-C.

A previous meta-analysis of 27 RCTs (Rouhani et al., 2018) illustrated that egg consumption significantly increased serum levels of TC, LDL-C, and HDL-C but did not significantly influence serum TG, LDL-C/HDL-C, and TC/HDL-C ratio. However, this study did not include seven critical articles that were published between 2000 and 2016 (Burns-Whitmore et al., 2014; Katz et al., 2015; Lewis et al., 2000; Putadechakum et al., 2013; Tanchoco et al., 2011; Techakriengkrai et al., 2012; Vishwanathan et al., 2009), and used repeated publications in which blood lipids analyses were performed on the same population (Herron et al., 2002, 2003, 2004, 2006).

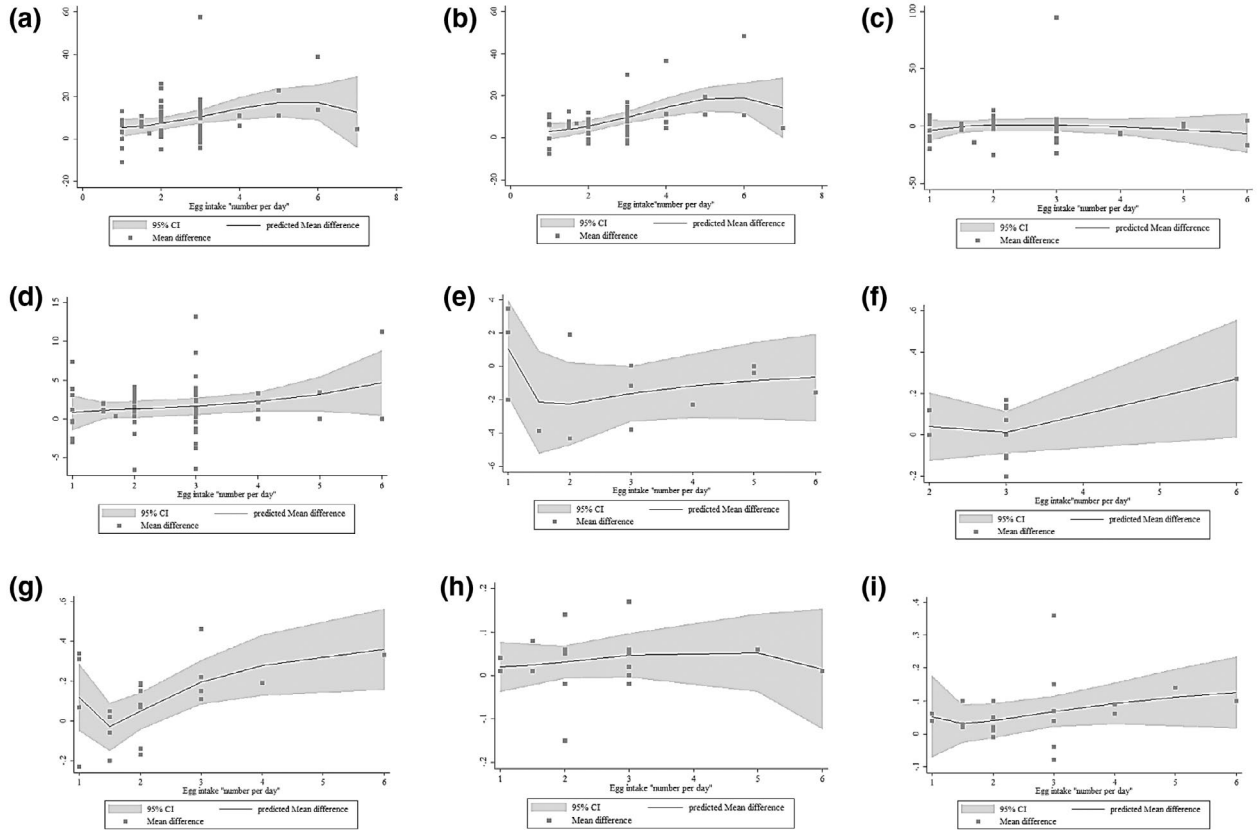

FIGURE 5 Linear dose-responses between egg intake and unstandardized mean difference for (a) TC, (c) HDL-C, (d) TG, (h) ApoA1, (i) ApoB100, (e) VLDL-C, and (f) LDL-C/HDL-C and nonlinear dose-responses in (b) LDL-C, and (g) TC/HDL-C. The 95% CI is depicted in the shaded regions

Also, they could not calculate the effect size for a study by Knopp et al. (2003), however, we extracted data from the percent change that reported in the article. In addition, in the current meta-analysis we examined all trials that assessed the effects of dietary cholesterol on lipid profiles (with the addition of apoA1 and apoB100, which were not assessed in the previous meta-analysis) independent of study duration, which allowed for a greater number of data points in the final analyses. Furthermore, our data support findings of previous meta-analysis 17 trials (Weggemans, Zock, & Katan, 2001), which investigated the effects of egg consumption on blood lipids and concluded that adding 100 mg of cholesterol per day to the diet can increase serum TC, HDL-C and TC/HDL-C ratio levels.

The concentration of serum TC, LDL-C, HDL-C, LDL-C/HDL-C ratio, apoA1, and apoB100 are all primary risk factors for the development of atherosclerosis (Kannel, Castelli, Gordon, & McNamara, 1971; Prospective Studies Collaboration et al., 2007). Saturated and trans unsaturated fatty acids are known to strongly increase plasma LDL-C by increasing the formation of LDL in the plasma compartment and by decreasing LDL turn-over (de Souza et al., 2015; Fernandez & West, 2005; Sacks et al., 2017). A recent systematic review and meta-analysis (including 17 cohorts and 19 trials) demonstrated that various sources of dietary cholesterol did not have a significant effect on CVD risk despite a mild increase in blood lipoproteins (Berger et al., 2015). Dietary guidelines recommend that saturated fats should be limited to lesser than 10%, trans fats to lesser than 1% of total energy intake per day (Eckel et al., 2014), and as previously mentioned, the recommendation to limit dietary cholesterol to less than 300 mg per day has been removed (Graham et al., 2007; 2015–2020 Dietary Guidelines for Americans. 8th Edition). In support of this, a study by Mutungi, Torres-Gonzalez, McGrane, Volek, and Fernandez (2007) showed egg consumption with carbohydrate restriction diet (CRD) significantly reduced HMG-CoA reductase (rate-limiting enzyme in cholesterol synthesis) mRNA while an increase was observed for the control group with CRD. Therefore, these data demonstrate that restriction of saturated and trans fats may be preferable to cholesterol intake restriction for influencing HMG-CoA. Moreover, in the current meta-analysis we did not observe a significant increase in LDL-C/HDL-C ratio. Notably, in all studies that assessed this ratio, the subjects consumed greater than one egg/day. In addition, previous studies indicated that the diameter of the LDL-C and HDL-C increases with egg consumption and these lipoproteins become less susceptible to oxidation, ultimately reducing the likelihood for atherosclerotic plaque formation (Ballesteros et al., 2015; Blesso et al., 2013a; Greene et al., 2006; Herron et al., 2004; Mutungi et al., 2010).

The study design may influence the final outcome of the study. Indeed, our findings showed that egg consumption was more likely to increase lipoproteins when studies implemented a cross-over

design relative to a parallel design. In a cross-over design, each participant receives all interventions at different times, which are generally separated by a washout period. The major disadvantage of cross-over designs is that treatments effect on consequences of outcomes (Crossover study––an overview | ScienceDirect Topics, n.d.). Lipid status may remain changed 6 weeks after interventions (Jellinger et al., 2017). Accordingly, the 2–4 weeks washout period in the studies considered in the present meta-analysis may not be enough to control the effect of dietary cholesterol on lipid profiles. Moreover, we found that short-term consumption of eggs (interventions that were less than 12 weeks) had a greater effect on blood lipids. This condition may be due to the fact that most studies with duration less than 12 weeks utilized a cross-over design.

In the current meta-analysis, there are studies which assessed the effect of egg consumption on risk of certain diseases associated with elevated blood lipids. The prospective study by Hu et al. (1999) found that consumption lesser than one egg/d is unlikely to have an impact on overall CHD or stroke risk in healthy middle-age and older adults. A study by Djoussé et al. (2010) assessed effect of varying portions of egg intake in men and women from the Cardiovascular Health Study (1989–2007) on incidence of Type 2 Diabetes Mellitus (T2DM) and founds there was no association between egg consumption and elevated risk of T2DM. However, the systematic review and meta-analysis by Shin et al. (2013) and Li et al. (2013) on egg consumption and risk of CVD and T2DM illustrated that egg ingestion was not associated with elevated CVD risk and CV-related mortality in the general population but it is associated with an increased incidence of T2DM in the general population and CV-related morbidity among diabetic patients. Furthermore, the study by Li et al. suggested there is a dose (egg quantity)-dependent increase in CVD risk and diabetes. Notably, eggs are a rich source of phosphatidylcholine and sphingomyelin that are known to decrease intestinal cholesterol absorption (Cohn, Kamili, Wat, Chung, & Tandy, 2010), which may explain the discrepancy in the findings of the aforementioned studies. Therefore, more studies are needed to examine the effect of other components of eggs on diseases related to lipoproteins.

This is the first systematic review and meta-analysis of RCTs investigating dose response of different quantities of daily egg consumption on blood lipids, without limitation of study duration. Also, we utilized subgroup analyses to evaluate the effect of sex, population characteristic, type of diet and intervention, design and duration of the study on the influence of egg consumption on serum lipids. Cochrane Collaboration's tool and GRADE assessment were used for quality evaluation of each trials and bias of analyses. Nevertheless, this study has some limitation: (a) We were not able to use the data from the Duane study and the analysis of serum TC from the Chenoweth et al. study, (b) there was high heterogeneity between studies that was not completely resolved by subgroup analysis, (c) the quality of a majority of the studies was low due to the fact that these studies were unblinded, (d) the low number of studies in some sub-groups prevented us from making particular conclusions.

Other notable considerations are that the individual response to dietary cholesterol is heterogeneous, such that there is individual variability in the rise in blood cholesterol following consumption of dietary cholesterol, and these individuals are referred to as hypo-, normal- or hyper-responders (Beynen, Katan, & Zutphen, 1987; McNamara 2000). In the current meta-analysis we did not perform a sub-analysis on hypo-, norma,l and hyper-responders; however, the influence of egg consumption on blood lipids within these groups should be considered in future studies. Furthermore, estrogen plays a critical role in LDL-C metabolism (Palmisano, Zhu, Eckel, & Stafford, 2018), which may explain the rise in LDL-C in women over the age of 40 years and the sex differences observed in the present study.

5 | CONCLUSION

Overall, the finding of the present study indicate there is a positive linear correlation between consumption of greater than one egg/d and the alteration of blood lipids in studies conducted in healthy populations and lesser than 12 weeks in duration; however, this effect was less predominant in subjects who consumed lesser than one egg/d. Furthermore, intake of greater than one egg/d does not influence LDL-C/HDL-C, which is an important indicator of atherosclerotic disease risk; however, consumption of greater than one egg/d for greater than 12 weeks may lead to an increase in this ratio.

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CONFLICT OF INTEREST

The authors declared that there were no conflicts of interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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