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REVIEW

Egg consumption, cardiovascular diseases and type 2 diabetes

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Eggs are rich in nutrients and a source of essential fatty- and amino acids, and the food item with highest cholesterol content. Since the 1970s dietary recommendations have advised limiting egg intake to 2–4 a week for the healthy population, and in those diagnosed with cardiovascular disease (CVD) and type 2 diabetes (T2D) an even more restricted consumption. The aim of the present paper was to assess the recommendation to lower the dietary intake of cholesterol and especially the intake of egg to reduce the risk of CVD and T2D. We performed three web-based literature searches on human studies (observational and interventional) published within the past 10 years during spring 2015. High-quality intervention studies have found nonsignificant effects of increasing the consumption of eggs on risk markers for CVD and T2D in healthy subjects and subjects with T2D. The risk associations found in the observational studies are more likely to be attributed to a dietary pattern often accompanying high egg intake and/or the cluster of other risk factors in people with high egg consumption. Dietary patterns, physical activity and genetics affect the predisposition of CVD and T2D more than a single food item as eggs. In conclusion, up to seven eggs per week can safely be consumed, but in patients with established CVD or T2D only with special emphasis on a healthy lifestyle.

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INTRODUCTION

The incidence of coronary heart disease (CHD), which globally still is the most frequent cause of death, has since the 1980s declined dramatically in most countries in the western Hemisphere. It is still unknown to what extent the various preventive actions including dietary guidelines have contributed to the successful prevention. It seems relevant to assess the effect of some of the recommendations in the dietary guidelines in light of information from newer studies and the use of modern statistical methods applied on the results of the studies. In the present paper we assess the recommendation to lower the dietary intake of cholesterol and especially the intake of egg.

Previous and present dietary advices regarding egg and cholesterol consumption

The most common size of chicken egg is 'Large' (greater than 2 oz. or 54.4 g) and is the size commonly referred to in food recipes. More than half of the calories found in eggs come from fat in the yolk; 56 g of chicken egg (the contents of an egg just large enough to be classified as 'large' in the United States, but 'medium' in Europe) contains approximately 5 g of fat. The energy content per 100 g is 131 kcal (547 kJ), saturated fatty acids 2.52 g, *cis*-monounsaturated fatty acids 3.43 g, *cis*-n3 fatty acids 0.13 g, *cis*-n6 fatty acids 1.31 g, *cis*-polyunsaturated fatty acids 1.44 g, *trans*-fatty acids 0.01 g and cholesterol 350 mg.[1]

Healthy people

The high cholesterol in chicken eggs has in the past been the reason for recommendations advising healthy people to eat at the most 2-4 eggs per week in prevention of cardiovascular disease (CVD). Setting an international benchmark, the Dietary Guidelines for Americans have in many years recommended people to limit cholesterol and egg consumption.[2,3] For this reason the past two generations of Americans have reduced the consumption of eggs and other animal products as they were told that fat and cholesterol were bad for their health. Globally, egg consumption has been, and still, is highest in Europe; Europeans consumes an average of approximately 3.5 eggs per person per week (Figure 1).[4] The country consuming most eggs globally is Denmark, where egg consumption has increased since 1960 and is presently 4.6 eggs per person per week (Figure 2).[4] This may reflect that the Nordic Nutrition Recommendations have not restricted egg consumption.

Internationally there is still no consensus on the recommendations of egg consumption for healthy people (Table 1). The preliminary report on the new Dietary Guidelines for Americans (released February 2015) stated, quite opposite to the existing Dietary Guidelines for Americans, that 'cholesterol is not a nutrient of concern for overconsumption'.[5] Thus, it was surprising that the Dietary Guidelines for Americans 2015 once again included the statement 'individuals should eat as little cholesterol as possible' together with the statement 'Adequate evidence is not available for a quantitative limit for dietary cholesterol specific to the dietary guideline'.[6] These opposite statements about the same dietary substance in the same guidelines have led to some concern.[7,8] The Nordic Nutrition Recommendations in 2004 and again in 2012 did not set an upper intake level for dietary cholesterol.[9,10]

Patients with CVD

For patients diagnosed with CVD the Mayo Clinic[11] and, as the only out of seven national Heart Associations, the German Heart

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Association,[12] recommend limiting the consumption of eggs and dietary cholesterol (Table 2). Other national Heart Associations have in recent years loosened the restrictions on dietary cholesterol.[13] In 2000, the American Heart Association (AHA) still recommended restricting dietary cholesterol.[14] But the AHA's guidelines were further revised in 2014 giving the green light to enjoy eggs.[15] The British Heart Foundation states that 'it's a myth that eggs are bad for your heart. Eggs can form part of a balanced diet, despite their perceived 'bad' reputation due to their cholesterol content'.[16] The National Heart Foundation of Australia likewise states: 'Good news on eggs: Did you know that blood cholesterol levels are more influenced by the saturated and *trans* fat we eat than the cholesterol in foods? That's why it's OK to eat eggs - you can enjoy up to six eggs each week as part of a healthy balanced diet'.[17] The Danish Heart Association today says that 'eggs are a good source of protein and vitamins and can be included as part of a varied and heart-friendly diet, but be aware in that the egg yolk is high in both fat and cholesterol'.[18]

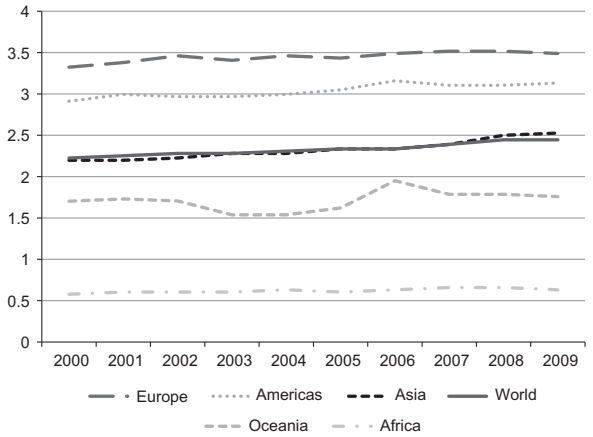

Figure 1. Egg consumption per person (eggs per week) in Europe compared with average for Africa, Americas, Asia, Oceania and Globally. Modified from Table 2, The Poultry Site.[4]

Atherosclerotic mechanism

Accumulation of low-density lipoprotein (LDL)-cholesterol from plasma in the subendothelial space of the coronary arteries is an important process in the development of CHD. The transfer of LDL-cholesterol into the arterial wall increases with increasing concentration of LDL-cholesterol in plasma, but is also dependent on the resistance of the endothethelial layer to macromolecular permeation. Cholesterol cannot be metabolized in the arterial wall. It can however be removed and brought to the liver by various processes of which some may involve high-density lipoprotein (HDL).

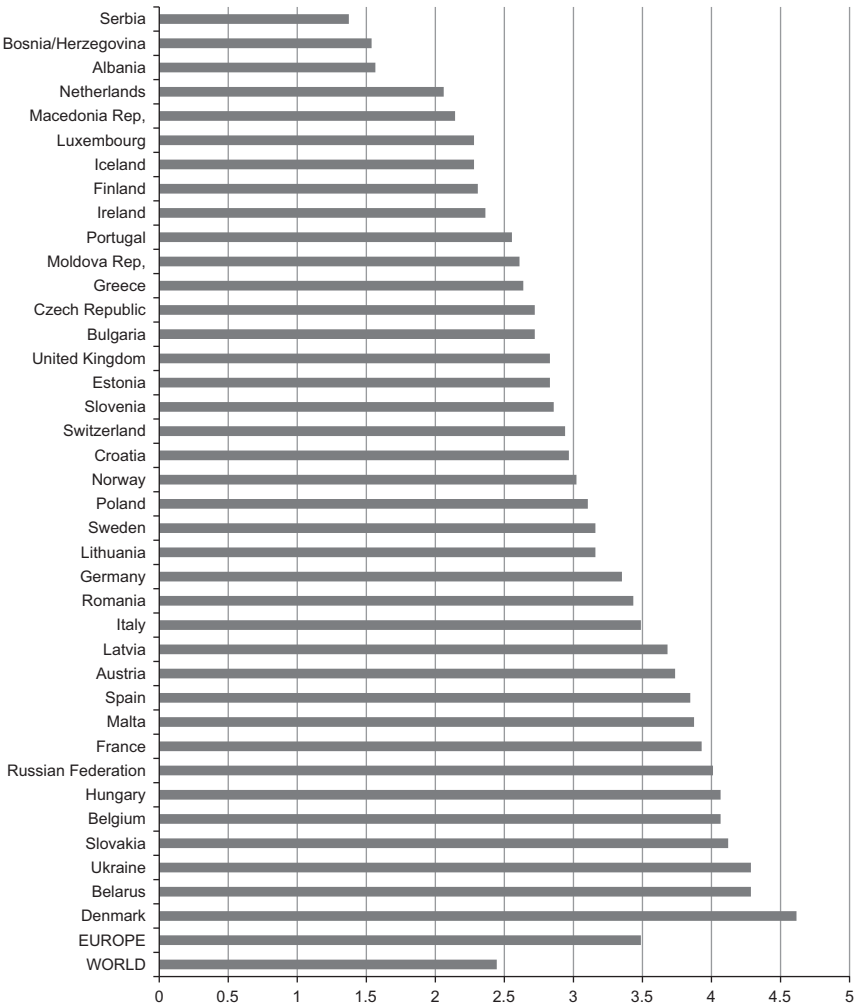

Figure 2. Egg consumption per person (eggs per week) in European countries compared with European and Global average. Modified from Table 3, The Poultry Site.[4]

Table 1. Recommendations on egg and cholesterol consumption to healthy people

Source	*Recommendation*
Danish Technical University, FOOD[87]	Eat up to seven eggs a week, no limit for consumption of dietary cholesterol
Dietary Guidelines for Americans 2015[6]	Eat as little cholesterol as possible
French National Nutrition and Health Program[88,89]	1–2 servings of egg per day. No specific recommendations for consumption of dietary cholesterol
Mayo Clinic[11]	Consume no more than 300 mg of cholesterol a day
Mediterranean Diet Pyramid (Spain)[88]	Consume eggs 2-4 times weekly, serving size 50-100 g. No specific recommendations for consumption of dietary cholesterol
Nordic Nutrition Recommendations 2012[9]	No upper limit for either egg or dietary cholesterol
The Italian Dietary Guidelines[89]	No specific recommendations for eggs or dietary cholesterol

Table 2. Recommendations on egg and cholesterol consumption to patients diagnosed with cardiovascular disease

Source	*Recommendation*
American Heart Association[15]	No upper limit for either egg or dietary cholesterol.
Australian Heart Foundation[85]	Up to six eggs per week can be included as part of a varied and healthy diet
British Heart Association[16,90]	Eggs are a part of a balanced diet
Danish Heart Association (Hjerteforeningen)[91]	Eggs are a good source of protein and vitamins and can be included as part of a varied and heart-friendly diet, but be aware in that the egg yolk has is high in both fat and cholesterol
European Society of Cardiology[92]	When guidelines are followed to lower saturated fat intake, this usually also leads to a reduction in dietary cholesterol intake. Therefore, some guidelines (including this one) on healthy diet do not give specific guidelines on the intake of dietary cholesterol; others recommend a limited intake of, 300 mg/day
German Heart Association (Deutsche Herzstiftung)[12]	Do not exceed 250–300 mg cholesterol daily and no more than two eggs a week
Mayo Clinic 2016[11]	Limit cholesterol to maximum 200 mg daily
New Zealand Heart Foundation[86]	Up to six eggs per week can be included as part of a heart friendly diet
Swedish Heart Association (Hjärt-lungfonden)[93]	No upper limit for either egg or dietary cholesterol

LDL-cholesterol in the arterial wall is taken up by macrophages which eventually may develop to foam cells that constitute an important part of the atherosclerotic lesion. This simple description of the development of the atherosclerotic lesion demonstrates that there are several ways that atherogenesis can be affected: (1) by changes in plasma LDL cholesterol, (2) by changes in endothelial cells and (3) by changes in reverse cholesterol transfer from artery to plasma and further on to the liver. The risk related to the intake of eggs has so far relied on the increase of LDL-cholesterol in plasma, but it is possible that intake of eggs may interfere with the other processes involved in atherogenesis. The development of atherosclerotic lesions also depends on the propensity of the macrophages in the arterial wall to take up oxidized LDL-cholesterol ending up as foam cells. This process has recently attracted some attention since trimethylamine-N oxide (TMAO) seems to promote the formation of foam cells. Trimethylamine (TMA) is formed in the intestinal microbiota from choline-rich substances like phophatidylcholine, present in relatively large amounts in egg yolks. When TMA reach the liver it is oxidized to TMAO.[19] TMAO concentrations in plasma increase with increasing intake of eggs.[20,21] TMAO concentrations in plasma seem to be a powerful predictor of total mortality in patients with CHD even after adjustment for other known risk factors.[22,23] This theory makes eggs and other choline-containing food items, that is, all animal products pro-atherogenic, not because of their cholesterol content but because of their choline content being the precursor for the microbiota to form TMA. Several authors have however cautioned against letting the findings with egg ingestion and TMAO production have influence on dietary guidelines before further studies are done. This seems sensible due to phophatidylcholine is ubiquitous in our diet, thus eliminating phophatidylcholine would mean reducing the intake of many apparently healthy foods.

Literature search

Three literature searches on human studies within the past 10 years were performed during April–May 2015. The first search identified clinical trials with the terms: 'egg and cholesterol' ($n = 36$), 'egg and diabetes' ($n = 11$), 'egg and cardiovascular' ($n = 21$). After removing duplicates, 33 studies were evaluated. Twelve articles were excluded for the following reasons: irrelevant outcome ($n = 4$), multiple publications ($n = 6$) and only abstract available in English ($n = 2$). The second search identified observational studies with search terms: 'egg' and 'cholesterol' or 'diabetes' or 'cardiovascular' ($n = 18$). Two studies were excluded as being irrelevant to the outcome of interest (cancer and pregnancy). Twelve studies had CVD as outcome,[24–35] and four had diabetes as outcome.[36–39] The third search identified meta-analyses and systematic reviews with search terms: 'egg' and 'cholesterol' or 'diabetes' or 'cardiovascular'; four publications were identified, one being both a meta-analysis and systematic review.[40–43] Subsequent initial search two observational studies,[44–46] one clinical trial[47] and three meta-analyses have been identified.[48–50]

Of the intervention studies investigating the effect of egg consumption on risk markers of CVD or diabetes among subjects not at high risk of—and without established—heart disease 12 studies were randomized controlled trial,[51–60] 8 were crossover trials[61–65] and 1 intervention was non-randomized controlled[66] (Table 3). Five interventions were conducted in people with high risk of CVD or with established artery disease; two were randomized controlled trial[67,68] and three were crossover[47,69,70] studies. All interventions were evaluated as 'good', 'fair' or 'poor' using the 'Quality Assessment of Controlled Intervention Studies from National Institutes of Health' 2014 and GRADE system (grading quality of evidence and strength of recommendations).[71,72] Only five studies, all randomized

Table 3. Trials investigating egg consumption and risk markers of cardiovascular disease and type 2 diabetes

Reference	*N and type*	*Duration*	*Intervention*	*Variables*	*Results*	*Evaluation*
Healthy subjects[a]*, RCT*						
Harman *et al.*[52]	45 healthy	12 weeks	Energy restriction and either 2 eggs/day OR no eggs	Body composition Lipids Lipoproteins	No difference	Good (randomized, baseline equal, no ITT)
van der Made *et al.*[53]	101 early AMD	1 year	Buttermilk drink + 1.5 egg yolk/day OR + egg substitution	Lipids Lutein	No effect on lipids	Good (long study period, no ITT, baseline equal, good cholesterol outcome assessment)
Vander *et al.*[54]	152 BMI: 25–50	8 weeks 5 days/week	Egg diet (−1000 kcal) Egg Bagel diet (−1000 kcal) Bagel	Satiety (body composition lipids)	ED vs BD ↑weight loss ↓WC ↓FM No difference in lipids	Good (block randomization, no ITT, baseline equal, thorough outcome assessment)
Vislocky *et al.*[55]	12 healthy	8 weeks	2 eggs/day 0 eggs/day +endurance training in both groups	Lipids	Lipids improved in both groups No effect of diet	Good (small sample size, no dropouts, thorough outcome assessment, baseline equal)
Bunger *et al.*[57]	100 healthy	6 weeks	Control beverage Egg yolk+Lutein drink Dried yolk+lutein Dried yolk+lutein as beverage	Serum lutein (Lipids)	No effect	Poor (investigation focused on lutein Lipid results poorly described)
Baumgartner *et al.*[58]	97	12 weeks	3 arms Control regular diet 1 egg extra/day 1buttermilk+yolk/day	Lipids lipoproteins low-grade systemic inflammation Endothelial activity Liver function	Egg-group: ↑total cholesterol ↑LDL No difference in other variables	Poor (not equal randomization No data on difference in baseline lipidprofile Sexes are calculated separately which make the groups very small No ITT analysis)
Mayurasakorn *et al.*[74]	417 6–15 years	12 weeks	3 eggs/week 10 eggs/week	Albumin Lipids	No difference in groups Both showed: ↑HDL ↑Albumin ↓Total cholesterol ↓LDL ↓LDL:HDL ratio	Poor (only abstract available, no actual control group)
Iglay *et al.*[59]	36 elderly	12 weeks Training 3days/week	HPHchol (incl eggs) LPLchol (excl eggs) +resistance training in both groups	Strength Body composition Skeletal muscle fiber type and size Urinary creatinine Lipids	↑LBM ↓FM ↓total cholesterol ↓LDL No difference between groups	Poor (28% dropout, baseline equal, no ITT, primary variable muscle and body composition)
Wenzel *et al.*[60]	24 women	12 weeks	Pill (sugar) 6 eggs/week with either 331 mg (EGG 1) or 964 mg (EGG 2) of lutein and zeaxanthin/yolk	Lutein zeaxanthin, macular pigment (lipids)	Egg group ↑zeaxanthin Pills: ↑total cholesterol ↑TG	Poor (assignment, small sample size, baseline lipid and anthropometrics equal)

Table 3. (Continued)

Reference	*N and type*	*Duration*	*Intervention*	*Variables*	*Results*	*Evaluation*
Healthy subjects[a], crossover						
Green *et al.*[61]	42 elderly	1 month (3 weeks washout)	3 large eggs/day OR eggSUB	Lipids	No difference in variables	Fair (outcome assessment, baseline equal between sexes)
Nissinen *et al.*[62]	29 men	6 weeks (3 months washout)	Normal diet OR Low cholesterol/low fat High cholesterol/low fat Low cholesterol/high fat	Lipis Surrogate cholesterol markers, sterols	Lower lipids after test diets than normal diet. Regulation of cholesterol synthesis	Fair
Burns-Whitmore *et al.*[63]	20 (Vegetarians)	8 weeks (4 weeks washout)	standard eggs n-3 eggs walnuts	Lipids Erythrocyte membrane Fatty acids Inflammatory markers	Walnuts: ↑Membrane alanine n-3eggs: ↑Membrane docosahexaenoic acid No negative effect	Poor (Egg-group = reference No ITT Few participants)
Knopp *et al.*[73]	197 ± BMI 27.5 ± insulin resistant	1 month (1 month washout)	0 egg yolk/day 2 egg yolk/day 4 egg yolk/day	Lipids	In all groups: ↑HDL, highest in insulin sensitive and least in obese and insulin resistant 4 egg yolks/day: ↑LDL	Poor (allocated, large baseline difference between groups, dropout not described)
Goodrow *et al.*[64]	33 AMD	5 weeks	1 egg eggSUB	Lipids Lutein Zeaxanthin	Egg-group: ↑Lutein ↑Zeaxanthin No effect on lipids	Poor (short duration, no description of randomization)
Vishwanathan *et al.*[65]	56	5 weeks (4 weeks washout)	2 egg yolks/day OR 4 egg yolks/day	Zeaxanthin Lutein (Lipids)	Both eggs: ↑zeaxanthin and lutein ↑HDL No effect on LDL cholesterol	Poor (all subjects taking cholesterol reducing medication, no ITT, lipids only secondary results)
Healthy subjects[a], non-randomized controlled interventions						
Rueda and Khosla[66]	73 healthy	14 weeks 5*/week	Breakfast, either with 2 eggs OR no eggs	Energy intake and composition Lipids	Equal energy intake Egg-group: higher protein and fat No difference in lipids	Poor (subjects assigned, sig. diff in baseline weight, BMI)
Healthy subjects[a], non-controlled interventions						
Mayurasakorn *et al.*[74]	56	12 weeks	1 egg extra/day	Lipids	↑Total cholesterol ↑HDL No effect on LDL and TG	Only abstract available
Subjects with diabetes or impaired glucose tolerance, RCT						
Fuller *et al.*[51]	140 preT2D/T2D and overweight	12 weeks	Weight maintenance High egg 2 eggs/day 6 days/week Low egg < 2eggs/week	Glycemic index Lipids VAS hunger satiety	No effect of diet on lipids Egg-group: ↓Hunger ↑Satiety	Good (GCP, 1:1 randomization)
Pearce *et al.*[56]	65 T2D/impaired glucose tolerance	12 weeks	Energy restriction (6-7 mj) and either HPHchol (eggs) OR HPLchol (meat)	Weight Lipids BP Insulin, glucose	Both groups ↓weight and BP Egg-group ↑HDL ↑ folate and lutein Meat group ↓ HDL	Fair (matched allocation, no ITT, baseline equal, fair outcome assessment)

Table 3. (Continued)

Reference	*N and type*	*Duration*	*Intervention*	*Variables*	*Results*	*Evaluation*
Subjects at high risk or with established cardiovascular disease, RCT						
Mutungi *et al.*[67]	28 overweight (18 MetS)	12 weeks	Low CHO diet and 1 egg/day OR 1 placebo/day	Body composition Lipids	Egg-group: ↑HDL	Fair (no baseline comparison, randomized, no description of dropouts)
Blesso *et al.*[68]	37 MetS	12 weeks	25–30E% CHO and one of +3eggs/day OR +3yolk free substitution	Lipids LCAT CEPT Apolipoproteins Oxidized LDL Insulin, HOMA-IR	Egg-group: ↑HDL ↑Large HDL ↑LCAT ↑in LDL size ↓VLDL total and medium ↓insulin and HOMA-IR	Poor (description of randomization No ITT analyses Difference in energy in test diets No data on difference in baseline values)
Subjects at high risk or with established cardiovascular disease, crossover						
Katz *et al.*[69]	32 CAD	6 weeks (4 weeks washout)	3 types breakfast: 2 eggs ½ cup egg beaters High CHO	Endothelial function (lipids BP Weight)	No difference	Fair (randomized, no baseline comparison, good efficacy outcome assessment)
Njike *et al.*[70]	40 hyperlipidemic	Single dose 6 weeks (4 weeks washout)	Breakfast with either 3 eggs OR Sausage and cheese 2 eggs/day OR ½ cup eggSUB/day	Endothelial function (lipids) Endothelial function (lipids)	No effect Subgroup (vs egg): ↑endothelial function ↓Total cholesterol ↓LDL Egg-group: no effect	Fair (ITT analyses, randomization, flow chart, no baseline comparison, good efficacy outcome assessment)
Njike *et al.*[47]	34 T2D	12 weeks (6 weeks washout)	2 eggs per day No eggs	Glycemic control (as glycated hemoglobin) Anthropometry Blood pressure Diet quality	No effect on glycated hemoglobin and systolic blood pressure Reduction of BMI, visceral fat mass, waist circumference, percent body fat	Fair (ITT analyses, randomization, flow chart, no baseline comparison, good efficacy outcome assessment)

Abbreviations: AMD, age-related macular degeneration; BP, blood pressure; CAD, coronary artery disease; CEPT: cholesteryl ester transfer protein; CHO, carbohydrate; FA, fatty acids, FM, fat mass; GCP, good clinical practice; HDL, high-density lipoprotein; HOMA-IR, insulin resistance index; IGT, impaired glucose tolerance; ITT, intention to treat; LCAT, lecithin-cholesterol acyltransferase; LDL: low-density lipoprotein; MetS, metabolic syndrome; RCT: randomized controlled trial; TG, triglyceride; T2D, type 2 diabetes; VLDL, very low-density lipoprotein; VAS, visual analogue scale. [a]That is, subjects without diabetes, not at high risk of or already established cardiovascular disease.

Table 4. Observational studies investigating egg consumption and risk of cardiovascular diseases and type 2 diabetes

Reference	*Design*	*N*	*Method of dietary assessment*	*Mean length follow-up, years*	*End points (cases)*	*Results*
Cardiovascular disease as end point						
Bernstein *et al.*[24]	Prospective	43 150 male	Questionnaire	22	Stroke (1397)	No association of egg consumption on risk of stroke
	Prospective	84 019 female	Questionnaire	26	Stroke (2633)	
Chagas *et al.*[34]	Observation	382 adults referred to undergo coronary angiography	Direct individual interviews	0	Dyslipidemia Coronary atherosclerotic burden	Egg consumption inversely associated with dyslipidemia and more than one egg per week was associated with a lower atherosclerotic burden
Choi *et al.*[33]	Cross sectional	23 417	FFQ	0	Coronary artery calcium	Positive association with egg and subclinical coronary artery calcium
Djoussé and Gaziano (2008)[94]	Prospective cohort	21 327 male	FFQ	20	Myocardial infarction (1550) Stroke (1342) Death (5169)	Egg intake had no influence on MI or stroke Mortality was higher with higher egg intake, even more in diabetic subjects
Djoussé and Gaziano[25]	Prospective cohort	21 275	FFQ	20.4	HF (1084)	Egg intake up to 6/week was not associated with HF More than 7 eggs/week increased risk of HF, hazard risk was 1.28 (1.02–1.61) and 1.64 (1.08–2.49) for 1 and $\geqslant$ 2 eggs / day vs $<$1 egg/day
Goldberg *et al.*[35]	Prospective cohort	1429	FFQ	11	Vascular events Incident stroke Incident MI Vascular death	Consumption of 1 egg/month–1 egg/week was inversely related to several markers of carotid atherosclerosis. No association with clinical vascular events, including stroke, was detected.
Hu *et al.*[26]	Prospective cohort	37 851 male	FFQ	8	CHD (866) Stroke (258)	No associations between egg and CHD or stroke No higher risk as responds to increased egg consumption Subgroup analysis: diabetic subjects with high egg intake had higher risk of CHD $>$1 vs $<$1 egg/day, RR 2.02 (1.05–3.87), $P=0.04$)
	Prospective cohort	80 082 female	FFQ	14	CHD (939) Stroke (563)	
Nakamura *et al.*[27]	Prospective	5185 female	FFQ	14	IHD mortality (41) All-cause mortality (107)	Lower all-cause mortality in women consuming 1–2 eggs/week vs 1 egg/day
	Prospective	4077 male	FFQ	14	IHD mortality (39) All-cause mortality (112)	
Nakamura *et al.*[28]	Prospective	90 735 (43 319 male 47 416 female)	Questionnaire on egg intake	10.2	Lipids CHD (462)	CDH had high cholesterol High egg intake not correlated with cholesterol High egg intake group had lower cholesterol

Table 4. (Continued)

Reference	*Design*	*N*	*Method of dietary assessment*	*Mean length follow-up, years*	*End points (cases)*	*Results*
Larsson *et al.*[44]	Prospective cohort	37 766 male	FFQ	13	HF (1628) MI (3262) Ischemic stroke (2039) Hemorrhagic stroke (405)	Daily egg consumption not associated with MI or stroke, $\geqslant 1$ egg/day associated with increased risk of HF
	Prospective cohort	32 805 female	FFQ	13	HF (1207) MI (1504) Ischemic stroke (1561) Hemorrhagic stroke (294)	Daily egg consumption not associated with HF, MI or stroke
Qureshi *et al.*[29]	Cohort	9734	Questionnaire	20	Egg consumption CHD	No effect of egg consumption on stroke, ischemic stroke or coronary artery disease Subgroup analysis: >6 eggs/week in diabetic RR 2.0 for coronary artery disease
Sauvaget *et al.*[30]	Prospective	40 349	FFQ	16	Stroke mortality (1462)	Egg, dairy, fish were independently associated with decreased risk of stroke mortality, especially intracerebral hemorrhage
Scrafford *et al.*[31]	Cross-sectional NHANESIII	6833 male	FFQ	8.8	CHD (198) Stroke (63)	No correlation between egg and CHD Inverse correlation between egg and stroke
	Cross-sectional NHANESIII	8113 female	FFQ	8.9	CHD (168) Stroke (74)	
Spence *et al.*[32]	Retrospective (post egg yolk consumption and present carotid plaque)	1262 Consecutive patients referred to CVD prevention clinic	Questionnaire: egg yolk-years, pack-years until investigation	–	Total plaque area	Linear increase of carotid artherosclerotic plaque after 40 years Exponential increase in plaque area with egg consumption. Plaque area 125 ± 129.62 vs 132.26 ± 142.48 mm^2 with consumption of $\leqslant$2eggs/week and >3 eggs/week, respectively Only data on egg consumption and a non-healthy cohort
Virtanen *et al.*[46]	Prospective	1032 men	4-day food record	20.8	CAD (230)	Egg or dietary cholesterol intakes were not associated with increased CAD risk, even in highly susceptible individuals
Type 2 diabetes as end point						
Djoussé *et al.*[95]	Prospective cohort	20 703 male	FFQ	20	T2D (1921)	Increased risk of T2D with high egg intake
	Prospective cohort	36 295 female	FFQ	11.7	T2D (2112)	
Djoussé *et al.*[36]	Cross-sectional	4568 African-American non-diagnosed T2D at entry 64% women	FFQ	0	T2D (1004)	Egg consumption at time of measure was positively ass with prevalent T2D
	Prospective	3564 African-American with T2D	FFQ	7.3	T2D (531)	Egg consumption not associated with T2D development

Table 4. (Continued)

Reference	Design	N	Method of dietary assessment	Mean length follow-up, years	End points (cases)	Results
Kurotani *et al.*[37]	Prospective	27 248 male 36 218 female	147-item FFQ	5	T2D (1,165) registration self reported	Men: No correlation of cholesterol and T2D Women: Highest quintile of egg intake had 23% lower OR of T2D
Radzeviciene and Ostrauskas[38]	Case-control	234 cases 468 controls	Questionnaire		T2D	Both: no correlation between egg and T2D 3–4.9 egg/week OR 2.6 (1.34, 5.08) ⩾ 5 eggs/week OR 3.02 (1.14, 7.89) vs < 1 egg/week
Shi *et al.*[78]	Cross-sectional	1308 male 1541 female	FFQ FFQ		T2D T2D	No association Intake of ⩾ 1 egg/day increased risk of T2D Women: ⩾ 7 eggs/week OR 3.01 (95% CI 1.12–8.12)
Virtanen *et al.*[39]	Prospective	2332 male	4 days food record	19.3	T2D (432)	Subjects with highest intake of egg (> 40 g/day) vs lowest (< 14 g/day) had 38% lower risk of developing T2D. Inverse association with egg intake and glucose and CRP, but not with insulin

Abbreviations: CAD, coronary artery disease; CHD, coronary heart disease; CVD, coronary vascular disease; FFQ, food frequency questionnaire; HF, heart failure; IHD, ischemic heart disease; MI, myocardial infarct; T2D, type 2 diabetes. [a]That is, subjects without diabetes, not at high risk of or already established cardiovascular disease.

controlled trials, were evaluated as of good quality[51–55] (Table 3), the remaining studies were either of fair or poor quality.

Observational studies

During the past decade many of the numerous investigations of 'the diet-heart hypothesis' have been included in systematic reviews and meta-analysis (Table 4).[41–43,48–50] They include data on the associations of egg consumption and the risk of CVD and cardiac mortality as well as the incidence of type 2 diabetes (T2D) in the general population, and also the relationship between egg consumption and CVD risk in patients with known T2D.

Only three studies have included subjects with established CVD, not included in any meta-analysis.[32–34]

Healthy people

Among the reviews and meta-analysis including healthy subjects, there is no consensus of an association of egg consumption and the risk of CVD and T2D (Table 4). In a meta-analysis of prospective cohort studies, Shin *et al.*[43] found that egg consumption was not associated with the risk of CVD, cardiac mortality or total mortality in the general population. They did however, in a subanalysis, find that the highest compared with lowest egg consumption was associated with an increased hazard ratio (HR) of T2D (1.42 95% CI: 1.09–1.86). Li *et al.*[41] included 14 studies involving 320 778 subjects and found a dose–response relationship between egg consumption and the risk of CVD and T2D. An increment of four eggs per week increased the relative risk (RR) for CVD and T2D of 1.06 (95% CI: 1.03–1.10) and 1.29 (95% CI: 1.21–1.37), respectively. Rong *et al.*[42] performed a dose–response meta-analysis of prospective cohort studies with 17 reports including subgroups of diabetics (four reports) to quantify the association between egg consumption and risk of CVD and stroke. They found no evidence of an association between egg consumption and risk of CHD or stroke. In a meta-analysis including 17 cohorts of healthy adults, Berger *et al.*[48] found no association between dietary cholesterol and the relative risk of ischemic stroke 1.13 (95% confidence interval (CI): 0.99–1.28) or hemorrhagic stroke 1.09 (95% CI: 0.79–1.50). In a meta-analysis including 12 cohorts, Djoussé *et al.*[49] found increased risk of T2D with consumption of three or more eggs per week, but only in US studies. In a meta-analysis including 14 studies with healthy subjects, Alexander *et al.*[50] found 12% decreased risk of stroke (0.88 (95% CI: 0.81–0.97)) and no association of CHD (0.97 (95% CI: 0.88–1.07)) with consumption of one egg per day compared with less than two eggs per week.

Three newly published observational studies are not included in any meta-analysis.[33,44,45] In a cohort including approximately 70 000 Swedish men and women, Larsson *et al.*[44] found no association with egg consumption and risk of myocardial infarction and stroke. They did find that consumption of more than one egg a day, but not less frequent consumption, was associated with increased risk of heart failure in men, but not in women (RR for men 1.30 (95% CI: 1.01, 1.67)). Among subjects included in the NHLBI (National Heart, Lung, and Blood Institute) Family Heart Study with no established CVD, Robbins *et al.*[45] found no association between egg consumption and prevalence of coronary-artery calcium content. Choi *et al.*[33] investigated the association between egg consumption and coronary artery calcium content in healthy South Korean subjects. In a multi-variable adjusted model they found higher prevalence of detectable coronary artery calcium in subjects consuming seven or more eggs per week than in subjects consuming less than one egg per week (1.80 (95% CI: 1.14–2.83)). The authors conclude that egg consumption is positively associated with coronary atherosclerosis and that this may be mediated by the cholesterol in eggs.[33] The association was more pronounced in subjects with high body mass index and in those with low vegetable intake.

Diabetic subjects

Dietary cholesterol and egg intake have been associated with increased risk of CVD in people with T2D, in most studies that have assessed them (Table 4). The meta-analysis by Shin *et al.*[43] included a database of 7549 diabetic patients in four cohorts. Patients with diabetes who ate eggs more than once per day were 1.69 times as likely to develop a CVD comorbidity than patients who never ate eggs or ate less than once per week (pooled HR: 1.69 (95% CI: 1.09–2.62)). However, egg consumption was not significantly associated with risk of overall mortality. In a review by Tran *et al.*[40] they find no consistency in egg consumption of the risk of T2D. The authors, however, found the cohort studies significantly incomparable in study design and having limitations, not suitable for a meta-analysis. In the meta-analysis by Li *et al.*,[41] it was found that the association between egg consumption and the risk of CVD seemed even more obvious in diabetic patients. For each increment of four eggs per week the relative risk of CVD increased by 1.40 (95% CI: 1.25, 1.57). Among diabetic patients consuming two or more eggs per day compared with less than one egg per week, Rong *et al.*[42] found higher relative risk of CHD and lower risk of developing hemorrhagic stroke, 1.54 (95% CI: 1.14, 2.09) and 0.75 (95% CI: 0.57 to 0.99) respectively. One study included in the meta-analysis by Rong *et al.* found no association among diabetics,[31] and the other does not describe a diabetic subgroup.[27]

Djoussé *et al.*[36] found positive association between egg consumption and prevalence of T2D in African-American subjects (prevalence ratio for $\geqslant 5$ eggs/week vs < 1 egg/month was 1.52 (95% CI: 1.17, 1.97). Among subjects without T2D they found no association with biomarkers of diabetes nor did they find an association between egg consumption and development of T2D after 7.3 years follow-up (HR for $\geqslant 5$ eggs/week vs < 1 egg/month was 1.17 (95% CI: 0.81, 1.70)). In a subgroup analysis including subjects with T2D, Robbins *et al.*[45] found no association between egg consumption and coronary-artery calcium content.

High CVD risk subjects

Among 1262 at risk patients Spence *et al.*[32] found carotid plaque area to increase exponentially with egg-yolk years ($P < 0.0001$); this remained significant after adjusting for coronary risk factors. Due to numerous confounding factors in the study, for example, recall of food ingestion, standard deviations exceeding mean in both groups, age difference between groups (for editorials following its publication please see refs 73–75), these results should however be interpreted with caution. Among 382 adults referred to undergo coronary angiography Chagas *et al.*[34] found egg consumption inversely associated with dyslipidemia ($P = 0.031$) and that those who ate more than one egg per week had a lower atherosclerotic burden ($P = 0.033$). Among 1032 men, where 32.5% were carriers of the apolipoprotein E gene 4 (i.e. highly susceptible individuals), Virtanen *et al.*[46] found no association between consumption of egg or cholesterol and the risk of coronary artery disease; HR of 1.17 (95% CI: 0.85, 1.61) in the noncarriers and an HR of 0.93 (95% CI: 0.50, 1.72) in the carriers.

INTERVENTION STUDIES

In total, 23 interventions have assessed the effect of egg consumption on cardiovascular risk markers; 17 including healthy subjects (i.e. subjects without T2D, not at high risk of or already established CVD), 2 including diabetics and 4 including subjects at high risk of or with already established CVD (Table 3).

Among healthy subjects two studies found egg consumption to increase LDL cholesterol; Baumgartner *et al.*[58] found that adding an extra egg a day to the habitual diet of healthy subjects increased total and LDL cholesterol after 12 weeks. But when examining the mean results there is a higher increase of total and LDL cholesterol in the control group compared with the egg group. Further, these results should be interpreted with caution due to the quality of this study. Subjects were not equally randomized, the groups were very small, and there was no intention to treat analysis. Knopp *et al.*[76] found increased LDL and HDL after one month's consumption of four egg yolks a day among insulin-resistant subjects with habitual low intake of cholesterol. Including four egg yolks in the daily diet will most likely change the habitual dietary pattern, but no data on total dietary intake are presented in the paper.

All other interventions found no adverse effects on blood lipids of a high versus low egg consumption.[52,54,61,69] Even up to 1 year of intervention with 1.5 egg yolk a day had no effect on blood lipids among 101 elderly subjects.[53] On the contrary, consumption of 1–3 eggs daily during 8–12 weeks increased HDL in healthy adults.[65,77] In an 8-week weight loss intervention, an energy-restricted diet containing egg increased weight loss and reduced waist circumference and fat mass compared with a diet with no eggs.[54]

Among subjects diagnosed with T2D consumption of two eggs a day for 12 weeks increased satiety, reduced hunger and increased HDL compared with a low egg diet (less than two eggs per week).[51,56]

Among subjects at high risk of heart disease (metabolic syndrome) consumption of up to three eggs a day during 12 weeks increased HDL and in one study also reduced VLDL and insulin levels.[67,68] Among subjects with hyperlipidemia or diagnosed coronary artery disease a single dose of three eggs or consumption of two eggs daily during 6 weeks had no effect on endothelial function nor on blood lipids.[69,70] Thirty-four adults with T2D had improvements in their anthropometric measurements after two eggs a day during 12 weeks; there was no effect on glycated hemoglobin or systolic blood pressure.[47]

A recent meta-analysis including 17 intervention studies by Berger *et al.*[48] found dietary cholesterol until 900 mg/day to increase concentrations of total, LDL and HDL cholesterol but not triglycerides or very low-density lipoproteins. With dietary cholesterol above 900 mg/day, HDL persisted to increase but total and LDL cholesterol did not, this suggests a plateauing effect when dietary cholesterol increases,[48] which is consistent with previous observations.[78]

DISCUSSION

In 1971 the data on initial serum cholesterol and the risk of CHD after 14 years in The Framingham Study were published.[79] The study found that elevated cholesterol was associated with an increased risk of CHD. Though not aiming at any specific cause of elevated serum cholesterol in the article, the results lead to a further establishment of the 'diet-heart disease hypothesis'. This hypothesis proposed that elevated serum cholesterol was a direct cause of excess dietary cholesterol and saturated fat intake, and that egg consumption consequently should be limited to achieve a low intake of cholesterol.[80] A later analysis of the data from The Framingham Study found however no association between egg consumption and serum cholesterol, all cause death, total CHD, myocardial infarction or angina pectoris.[80] In spite of this, egg consumption has been the focus of investigation in many studies, and limited egg consumption has been recommended to minimize CHD risk, and in dietary recommendations to people with T2D.

In the observational studies including a mix of healthy persons and diabetics, the subjects have been categorized according to number of eggs consumed per month or week with the group with lowest intake set as reference.[33,36,81] When reviewing the baseline study characteristics of anthropometry and dietary intake, subjects with the highest egg consumption (five or more or seven or more per week) share several characteristics known to influence

the development of heart diseases and diabetes, different from the reference group. A greater proportion is typically males, smokers and persons with higher body mass index; a higher intake of energy, total fat/saturated fat, and of red and processed meat, and a lower intake of fruit and vegetables.[25,33,36,37,81] Out of the observational studies investigating the association of egg consumption on CVD and T2D only two measured intake of *trans* fatty acids at baseline.[36,39] One study, a study of African American, found a positive association between egg and prevalent T2D, the subjects with high egg consumption had a daily 2 g higher intake of *trans* fat.[36] The other, a study of Finnish men, found a 38% lower risk among those consuming more eggs than those consuming little. In this study there was no difference in intake of *trans* fat among groups.[39] It is well recognized that dietary saturated and especially *trans*-fat have an adverse effect on LDL-cholesterol and the risk of CHD.[82–84] Intake of *trans*-fat should therefore be measured and controlled for in all the observational studies.

A recent randomized controlled trial of high quality investigated the effect of a 3-month high-egg diet on blood lipids among obese subjects with T2D.[51] The only differences between the groups were that the high-egg group had a 2-year longer history of T2D, and slightly higher total-, LDL- and HDL cholesterol. The diets were energy and nutrient matched. After intervention there were no differences between the groups on any risk markers of T2D or CVD, nor in body weight or fat-free mass. The high-egg group had reduced hunger and increased satiety.

As opposed to several prospective studies and meta-analyses[41] high-quality intervention studies do not support that there is any adverse effect of egg consumption of up to two eggs per day on risk markers of CVD or T2D (Table 3).[51–53,55,56,67,69,70] Studies investigating the effect of increased egg consumption and restricted energy intake found either no difference in plasma lipids between groups or increased HDL after egg consumption.[52,54,56] These studies also assessed anthropometry and found egg consumption to promote weight loss and reduce waist circumference.[54,56] This correlates well with egg consumption increasing satiety and reducing hunger as found by Fuller *et al*.[51] The effect of egg consumption on reducing energy intake is likely to be attributed by the high content of protein that is well acknowledged to improve weight loss, weight loss maintenance and reduce obesity-related comorbidities.[85,86] Berger *et al*.[48] concludes in their meta-analysis, including both observational and intervention trials, that there is lack of longitudinal data to support a limitation of dietary cholesterol.

The statistical approach to interpret the data from prospective studies is crucial to the outcome. A study including the data from 18 987 participants, including data on egg consumption, measures of adiposity and cardiovascular risk factors, examined the potential association between egg consumption and adiposity through two different statistical models.[87] In the first they found egg consumers to have both higher body mass index and waist circumference than non-egg consumer. In the other they identified eight clusters among those consuming eggs, where only two patterns drove an association between egg consumption and body mass index and waist circumference before controlled against standard covariates. After adjustment one pattern remained associated with increased diastolic blood pressure and serum LDL; but after adjustment for intake of junk food and medication no associations were present. These results underscore the significance of not only assessing a single dietary component when seeking to find dietary factors enhancing the risk of development of CVD and T2D.

The suggestion of egg consumption by itself promotes the risk and development heart disease and diabetes seems improbable compared with the general complexity of the dietary pattern, physical activity and genetic predisposition. The risk of developing heart diseases is more likely to be attributed to a lifestyle and dietary pattern often accompanying high egg intake or the cluster of other risk factors that differ in people with high egg consumption compared with those with lower egg consumption. The lack of control for *trans*-fat intake in most studies is of concern.

Although some observational studies have found association between egg consumption and the risk of CVD, results from intervention trials have not been able to substantiate this. In high-quality intervention studies including healthy or patients with TD2 or hyperlipidemia, dietary cholesterol, primarily from eggs, does not have a clinically relevant effect on the concentration of serum cholesterol. Thereby there does not seem to be a mechanistic explanation as to why eggs should increase the risk of CVD or T2D. The lack of scientific consensus on eggs for patients at high risk for CVD or diagnosed with CVD or diabetes, has led some countries' health organizations to refrain from a dietary recommendation on eggs to these groups. Australia and New Zealand have chosen to recommend all up to six eggs a week, but with the modification that the high-risk groups are well-treated (Table 2).[88,89] This appears for us a sensible strategy that to some extent excludes the bad reputation eggs have without the risk of putting the health at stake among patients at high risk for CVD or T2D.

In conclusion, If not for the dietary recommendations against the consumption of dietary cholesterol during the past half century, the current knowledge would most likely not be sufficient to restrict the intake of a nutrient rich basic food as eggs. Taken together up to seven eggs per week can safely be consumed, but in patients with established CVD or T2D only with special emphasis on a prudent diet and proper medical treatment.

CONFLICT OF INTEREST

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