Circulation

AHA SCIENCE ADVISORY

Dietary Cholesterol and Cardiovascular Risk

A Science Advisory From the American Heart Association

ABSTRACT: The elimination of specific dietary cholesterol target recommendations in recent guidelines has raised questions about its role with respect to cardiovascular disease. This advisory was developed after a review of human studies on the relationship of dietary cholesterol with blood lipids, lipoproteins, and cardiovascular disease risk to address questions about the relevance of dietary cholesterol guidance for heart health. Evidence from observational studies conducted in several countries generally does not indicate a significant association with cardiovascular disease risk. Although meta-analyses of intervention studies differ in their findings, most associate intakes of cholesterol that exceed current average levels with elevated total or low-density lipoprotein cholesterol concentrations. Dietary guidance should focus on healthy dietary patterns (eg, Mediterranean-style and DASH [Dietary Approaches to Stop Hypertension]–style diets) that are inherently relatively low in cholesterol with typical levels similar to the current US intake. These patterns emphasize fruits, vegetables, whole grains, low-fat or fat-free dairy products, lean protein sources, nuts, seeds, and liquid vegetable oils. A recommendation that gives a specific dietary cholesterol target within the context of food-based advice is challenging for clinicians and consumers to implement; hence, guidance focused on dietary patterns is more likely to improve diet quality and to promote cardiovascular health.

Jo Ann S. Carson, PhD, RDN, FAHA, Chair
Alice H. Lichtenstein, DSc, FAHA, Vice Chair
Cheryl A.M. Anderson, PhD, MPH, MS, FAHA
Lawrence J. Appel, MD, MPH, FACP, FAHA
Penny M. Kris-Etherton, PhD, RD, FAHA
Katie A. Meyer, ScD, MPH
Kristina Petersen, PhD, APD
Tamar Polonsky, MD, MSCI
Linda Van Horn, PhD, RD, FAHA
On behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease; and Stroke Council

Key Words: AHA Scientific Statements ■ cholesterol ■ diet ■ eggs ■ risk factors

https://www.ahajournals.org/journal/circ

Historically, nutrition guidelines for reducing cardiovascular disease (CVD) risk and achieving optimal plasma lipoprotein profiles have included recommendations to limit dietary cholesterol.[1,2] However, contemporary guidelines for CVD risk reduction from the American Heart Association (AHA) and American College of Cardiology (ACC)[3,4] and the "2015–2020 Dietary Guidelines for Americans" (DGA)[5] have not issued explicit guidance for dietary cholesterol. Because of the inconsistencies in the evidence base and the inherent difficulty in conducting and interpreting studies to isolate the independent effect of dietary cholesterol on CVD risk, controversy has ensued about whether dietary cholesterol should be a target for CVD prevention and management. This science advisory has 2 aims: to review the key human studies to date that have assessed the relationship of dietary cholesterol with plasma and lipoprotein cholesterol concentrations and CVD risk, and to explore methodological issues that contribute to the continued controversy on this topic, including questions on the impact of egg intake.

CURRENT DIETARY CHOLESTEROL RECOMMENDATIONS

The "2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk" did not include a recommendation for dietary cholesterol and concluded, "There is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C [low-density lipoprotein cholesterol]."[3] Similarly, the 2015 Dietary Guidelines Advisory Committee did not recommend limiting dietary cholesterol to <300 mg/d as presented in prior editions of the DGA.[6] The 2015 Dietary Guidelines Advisory Committee, with a focus on dietary patterns, provided nuanced statements related to cholesterol intake:

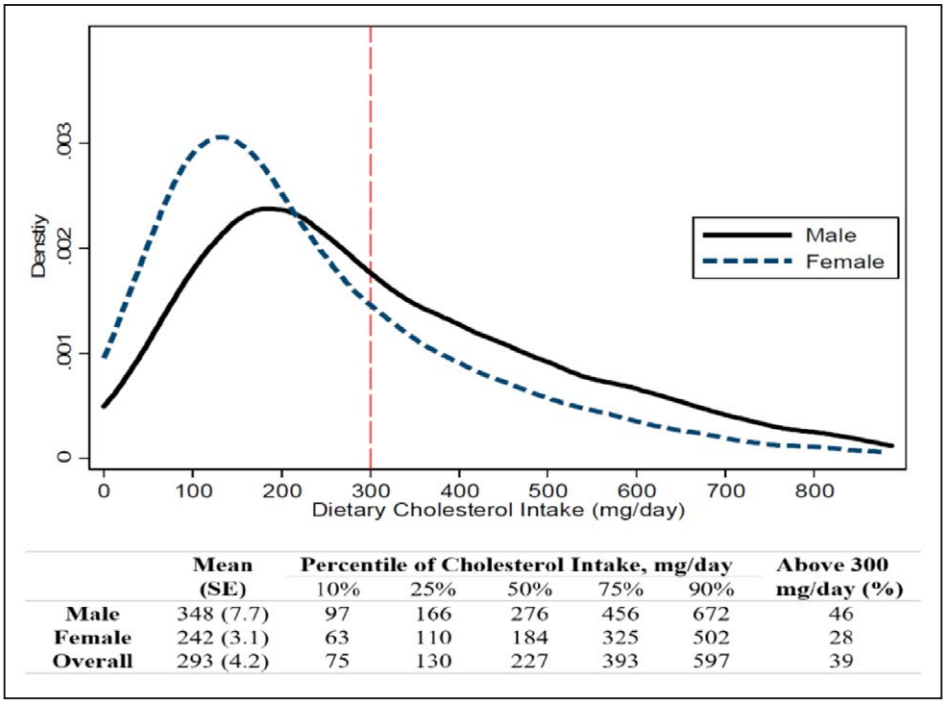
> *Previously, the Dietary Guidelines for Americans recommended that cholesterol intake be limited to no more than 300 milligrams per day. The 2015 DGAC [Dietary Guidelines Advisory Committee] will not bring forward this recommendation because available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol, consistent with the conclusions of the AHA/ACC report. Cholesterol is not a nutrient of concern for overconsumption.*[7]

At the time of the 2015 Dietary Guidelines Advisory Committee, the mean dietary intake in the United States for those ≥1 year of age was <300 mg/d. Because this level did not meet the criterion of a nutrient of concern, the importance of a numerical limitation was diminished. However, the 2015 DGA report stated that the lack of an explicit limit for dietary cholesterol did not imply that dietary cholesterol is unimportant in the adoption of healthy eating patterns. The report also emphasized that adherence to US Department of Agriculture–recommended eating patterns will naturally contribute to low amounts of dietary cholesterol because dietary cholesterol commonly coexists with major food sources of saturated fat. All of the US Department of Agriculture–recommended eating patterns included in the 2015 to 2020 report have <300 mg/d cholesterol across calorie levels ≤3200 kcal/d.[8] Similarly, the multisociety 2018 Guideline on the Management of Blood Cholesterol[4] brought forward the "2013 AHA/ACC Guideline on Lifestyle Management to Reduce Cardiovascular Risk,"[3] which did not include a recommendation for dietary cholesterol but recommended healthy eating patterns involving relatively low levels of dietary cholesterol.

Two recent guidelines, one for primary prevention and one for secondary prevention, have addressed the issue of dietary cholesterol. The "2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease" cited studies of the benefit of plant-based rather than animal-based protein and concluded, "A diet containing reduced amounts of cholesterol and sodium can be beneficial to decrease atherosclerotic CVD risk" without further distinction.[9] The 2015 "National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia," focused on individuals with established hypercholesterolemia, recommend limiting dietary cholesterol to <200 mg/d to lower LDL cholesterol and non–high-density lipoprotein (HDL) cholesterol concentrations.[10] The National Lipid Association Expert Panel concluded that "dietary cholesterol modestly increases total cholesterol, and LDL-cholesterol on average, although hypo- and hyper-responders do exist in the population."[10]

CURRENT CHOLESTEROL INTAKE IN THE UNITED STATES

According to the 2013 to 2014 NHANES (National Health and Nutrition Examination Surveys), the mean cholesterol intake in US adults ≥20 years of age was 293 mg/d (95% CI, 284–302), corresponding to a cholesterol density of 137 mg/1000 kcal. However, there are racial/ethnic differences. Mexican Americans have the highest intake with a mean of 338 mg/d (153 mg/1000 kcal), whereas the intake for non-Hispanic blacks and whites is 320 mg/d (142 mg/1000 kcal) and 282 mg/d (135 mg/1000 kcal), respectively. Mean cholesterol intake of the overall population has been relatively constant at ≈290 mg/d from 2001 to 2002 to 2013 to 2014. Intake varies by sex. Mean cholesterol intake was 242 mg/d (135 mg/1000 kcal) in women and 348 mg/d (144 mg/1000 kcal) in men (Figure 1).[11]



	Mean (SE)	Percentile of Cholesterol Intake, mg/day					Above 300 mg/day (%)
		10%	25%	50%	75%	90%	
Male	348 (7.7)	97	166	276	456	672	46
Female	242 (3.1)	63	110	184	325	502	28
Overall	293 (4.2)	75	130	227	393	597	39

Figure 1. Histogram of estimated cholesterol intake by sex for US adults ≥20 years of age, NHANES (National Health and Nutrition Examination Surveys), 2013 to 2014.
Truncated at 97.5th percentile of cholesterol intake. Reprinted from Xu et al.[11] Copyright © 2018, The Authors.

The major contributors of dietary cholesterol, in descending order, were meat, eggs, grain products, and full-fat dairy products. On average, meat (including poultry, mixed dishes, red meat, processed meat, and seafood) contributed 42% of total cholesterol intake, eggs contributed 25% of total cholesterol, and other food groups contributed the additional third. However, the relative proportion of cholesterol from eggs varied substantially among the different quartiles of cholesterol intake. In the highest quartiles with a mean intake of 731 mg/d in men and 519 mg/d in women, eggs were the major contributor. Among men, the mean dietary cholesterol contributed by eggs alone ranged from 1 mg/d (1%) in quartile 1 to 307 mg/d (42%) in quartile 4; corresponding data in women were 0 mg/d (0%) and 223 mg/d (43%).[11]

OBSERVATIONAL STUDIES OF DIETARY CHOLESTEROL AND CVD RISK

Relationship Between Dietary Cholesterol and CVD Risk

Findings from observational studies have not generally supported an association between dietary cholesterol and CVD risk (Table 1; additional details available in Data Supplement 1). Seventeen prospective cohort studies meeting our inclusion and exclusion criteria have assessed the association between dietary cholesterol and CVD outcomes (coronary heart disease [CHD] and stroke). Twelve studies reported no significant association between stroke, CHD events, or CHD death and dietary cholesterol, regardless of the dietary assessment method.[12–14,16–20,24–27] There was appreciable variability in study population, design, and statistical analyses, including sociodemographic characteristics, the range of dietary cholesterol intakes, and control for covariates. Several studies, including those that reported a significant positive association, adjusted for serum cholesterol concentration, an important covariant.[17,18,21,22,25] In some studies, positive associations in unadjusted or semiadjusted analyses were attenuated after adjustment for other dietary components such as fiber[12,24] and saturated fat.[24] Furthermore, when energy intake was included as a covariate in the statistical models, no significant association was observed between dietary cholesterol and fatal or nonfatal CHD or stroke.[12–14,16–20,22,24] Positive associations were generally restricted to studies that did not adjust for energy intake.[15,21,23,28,29] These findings illustrate the sensitivity of findings when consideration is given to other dietary components, as well as methodological issues.

Two studies reported a significant association between dietary cholesterol and stroke, albeit in opposite directions. In the Swedish Mammography Cohort, high cholesterol intake (median, 302 mg/d in the highest quintile) was associated with a higher risk of total stroke and ischemic stroke (20% and 29%, respectively) compared with the lowest quintile (me-

Table 1. Prospective Cohort Investigations of Association of Dietary Cholesterol and CVD Risk

Study Author, Year, Cohort (US Unless Noted)	Population, n	Dietary Cholesterol, mg/d Unless Noted	Findings Reported as Relative Risk (95% CI) Unless Noted	Comments
Studies that assessed dietary cholesterol using food frequency questionnaires				
Ascherio et al,[12] 1996, HPFS	43 757 men	mg/1000 kcal Mean=152	Fatal or nonfatal MI, 1.03 (0.81–1.32) Fifth vs first quintile Adjusted for risk factors, energy, and fiber intake	Ascherio et al[12] and He et al[13] used the same cohort, with longer follow-up for the stroke outcomes in the 2003 He et al report.
He et al,[13] 2003, HPFS	43 732 men	mg/1000 kcal Median in first to fifth quintiles: 189–389	Ischemic stroke,1.02 (0.75–1.39) Hemorrhagic stroke,1.04 (0.58–1.88) Adjusted for risk factors, energy intake, and other nutritional factors	
Pietinen et al,[14] 1997, Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Finland)	21 930 men	Average of medians of quintiles, 560	Major coronary event,0.93 (0.79–1.10) Adjusted for risk factors and energy and fiber intake	
Larsson et al,[15] 2012, Swedish Mammography Cohort (Sweden)	34 670 women	Median in first to fifth quintiles, 161–319	Total stroke, 1.20 (1.00–1.44)* Ischemic stroke, 1.29 (1.05–1.58)* Hemorrhagic stroke, 0.96 (0.58–1.58) Adjusted for risk factors and nutritional factors	
Yaemsiri et al,[16] 2012, Women's Health Initiative–Observational Study	87 025 women	Average of medians of quintiles, 191	Ischemic stroke: HR=1.04 (0.81–1.33) Adjusted for risk factors, energy intake, and other nutritional factors	
Hu et al,[17] 1997, NHS	80 082 women	mg/1000 kcal Median in first to fifth quintiles, 132–273	Fatal/nonfatal CHD, 1.17 (0.92–1.50) Adjusted for risk factors, energy intake, and other nutritional factors	Hu et al[17] and Iso et al[18] used the same cohort with a focus on different outcomes.
Iso et al,[18] 2001, NHS	85 764 women	Median in first to quintiles, 212–465	Hemorrhagic stroke, 1.04 (0.46–2.38) Adjusted for risk factors, energy intake, and other nutritional factors	
Seino et al,[19] 1997, Shibata Study Japan	2283 men and women	393	Cerebral infarct, 1.11 (0.48–2.56) Adjusted for some risk factors, energy, and type of fat intake	
Studies that assessed dietary cholesterol using 24-h dietary recalls				
Posner et al,[20] 1991,Framingham Study	859 men (45–55 and 56–65 y of age)	530 in younger men 532 in older men	CHD incidence No significant association among those 45–55 y (P=0.92) or 56–65 y (P=0.364) of age Adjusted for risk factors and energy intake	
McGee et al,[21] 1984, Honolulu Heart Program	7088 men (Japanese ancestry)	mg/1000 kcal 243	CHD death Using logistic coefficient, mg cholesterol/1000 kcal, significant positive association (P<0.05)* Adjusted for risk factors	Adjusted for body weight but not for energy intake
Esrey et al,[22] 1996, Lipid Research Clinics Prevalence Follow-up Study (US and Canada)	4546 men and women	408	CHD death, 1.0 (10 mg) per 5000 kJ (0.99–1.02) Adjusted for risk factors and energy intake	
Mann et al,[23] 1997, UK	10 802 men and women	Median in first to third tertiles, 156–431 for men, 138–378 for women	Ischemic heart disease death, 3.53 (1.57–7.96)* Adjusted for age, sex, smoking, and social class	≈20% were vegetarians or semi-vegetarian Included wide range of ages, leaner population Did not adjust for energy intake
Xu et al,[24] 2006, Strong Heart Study	2938 male and female American Indians	333	Total CHD, 1.09 (0.77–1.54) Nonfatal CHD, 1.14 (0.76–1.70) Adjusted for risk factors and energy intake	A higher-risk population: 48% with diabetes mellitus, 44% with hypertension

(*Continued*)

Table 1. Continued

Study Author, Year, Cohort (US Unless Noted)	Population, n	Dietary Cholesterol, mg/d Unless Noted	Findings Reported as Relative Risk (95% CI) Unless Noted	Comments
Garcia-Palmieri et al,[25] 1980, Puerto Rico Heart Health Program	8218 rural and urban men	Age-adjusted mean, 356 (rural), 439 (urban)	CHD No significant difference in dietary cholesterol between participants with and those without incident CHD over 6 y of follow-up Adjusted for risk factors Numeric results not published	
Study that assessed dietary cholesterol using 24-h food diary				
Sauvaget et al,[26] 2004, Adult Health Study (Japan)	3731 men and women in Hiroshima and Nagasaki	Average of medians of tertiles of animal fat, 449	Cerebral infarct death, 0.34 (0.16–0.70) Adjusted for risk factors and radiation dose exposure	A leaner population than other cohorts
Studies that assessed dietary cholesterol using diet histories				
Kushi et al,[27] 1985, Ireland-Boston Diet-Heart Study (Ireland, US)	1001 men (brothers in Ireland and US and group in US with parents in Ireland)	mg/1000 kcal Irish, 233; Irish Bostonians, 273; first generation in US, 240	CHD death Cox proportional hazard coefficient, 0.0017 (P=0.10) Adjusted for risk factors	Mean kcal intake: Irish, 4033; Bostonians, 3099; first generation, 2946
Shekelle et al,[28] 1981, Western Electric Study	1900 men	mg/1000 kcal 241	CHD death logistic coefficient, 0.003 (P=0.008)* Adjusted for risk factors and type of fat intake	Mean kcal intake, 3183/d Adjusted for BMI
Shekelle and Stamler,[29] 1989, Western Electric Study	1824 men	755	CHD, 1.38 (1.00–1.90)*Other CVD, 1.8 (1.00–3.24)* Adjusted for age	Same cohort as in Shekelle et al[28] Highest daily cholesterol intake and 25 y of follow-up

BMI indicates body mass index; CHD, coronary heart disease; CVD, cardiovascular disease; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; MI, myocardial infarction; and NHS, Nurses' Health Study.

*Significant positive association.

dian, 168 mg/d).[15] In contrast, in the Japanese Adult Health Study, a higher cholesterol intake was associated with lower risk of ischemic stroke.[22] However, this study should be interpreted with caution because the statistical models did not include many potential confounders that were adjusted for in the other studies reviewed, and thus, the results are likely influenced by residual confounding. Eight studies reported no significant association between dietary cholesterol and CHD or CHD mortality,[12,14,17,20,22,24,25,27] whereas 3 studies[21,23,28,29] showed a positive association with CHD or CHD mortality.

A meta-analysis that reviewed prospective cohort studies through December 2013 reported nonsignificant positive relationships between dietary cholesterol and risk of ischemic (1.13 [95% CI, 0.99–1.28]) or hemorrhagic (1.09 [95% CI, 0.79–1.50]) stroke. Effect estimates reflect comparisons of extreme quintiles (eg, quintile 5 versus 1), generally reflecting a difference in medians of 200 to 300 mg/d cholesterol intake. The insufficient number of cohort studies precluded conducting meta-analyses of other CVD-related outcomes.[30] In summary, the majority of published observational studies do not identify a significant positive association between dietary cholesterol and CVD risk.

Relationship of Egg Intake and CVD Risk

On average, eggs contribute 25% of dietary cholesterol in the United States.[11] A large egg contains ≈186 mg cholesterol.[31] Table 2 summarizes cohort studies meeting the inclusion and exclusion criteria that evaluated the relationship between egg intake and CVD risk (additional details available in Data Supplement 2). In general, egg intake was not significantly associated with CVD risk. Findings varied depending on subtypes of CVD considered.

- For stroke, no significant association was reported.[32,33,36,37,41,42] A meta-analysis of prospective cohort studies published through August 2016 reported that high egg consumption (≥7 eggs per week) was associated with a significantly lower risk of stroke (hazard ratio, 0.91 [95% CI, 0.85–0.98]) compared with low intake (<1 egg per week).[51]
- For CHD, in several US cohorts[32,36,37,40] and cohorts from Sweden,[41] Iran,[42] and Finland,[45] no significant association was observed between egg intake and CHD. A meta-analysis of prospective cohort studies also reported no significant association between egg intake and CHD risk.[51] However, among individuals with type 2 diabetes mellitus, 2 US studies

Table 2. Observational Studies of the Association of Egg Intake and Cardiovascular Disease Risk

Study Author, Year, Cohort (US Unless Noted)	Population, n	Association With					Comments
		CHD	Stroke	CVD Overall	CVD Mortality	HF	
Hu et al,[32] 1999, HPFS and NHS	HPFS: 37 851 men NHS: 80 082 women	None (both studies)	None (both studies)				Positive association with CHD among men and women with diabetes mellitus
Bernstein et al,[33] 2012, HPFS and NHS			None				Same cohort as in Hu et al[32]
Sauvaget et al,[34] 2003, Hiroshima/Nagasaki Life Span Study Japan	40 349 people enrolled in 1979		Inverse association for stroke mortality				
Nakamura et al,[35] 2006, Japan Public Health Center–based prospective study	1 cohort in 1990 and second cohort in 1993	None					
Qureshi et al,[36] 2007, National Health and Nutrition Examination I (1971–1975)	9734 participants	None	None				Positive association for CAD in diabetes mellitus
Djoussé and Gaziano, 2008,[37] observational study in PHS	21 327 US male physicians	None for MI	None				No association with MI or stroke among men with diabetes mellitus; positive association for all-cause mortality, more so among those with diabetes mellitus
Djoussé and Gaziano, 2008,[38] also PHS						Positive	No interaction with diabetes mellitus Same cohort as Djoussé and Gaziano[37]
Nettleton et al,[39] 2008, ARIC	14 153 participants without prevalent heart failure at baseline					Positive	No interaction with diabetes mellitus
Haring et al,[40] 2014, ARIC	12 066 participants	None					Same cohort as in Nettleton et al[39]
Larsson et al,[41] 2015, cohort of Swedish Men and Swedish Mammography Cohort (Sweden)	37 766 men 32 805 women	None for MI	None			Positive for men not women	
Farvid et al,[42] 2017, Golestan Cohort Study Iran	42 403 adults	None	None	None			
Nakamura et al,[43]2018, National Survey on Circulatory Disorders, Japan	4686 women randomly selected in 1990, age ≥30 y				None		
Diez-Espino et al,[44] 2017, observational study within the Prevention con Dieta Mediterranea (Spain)	7216 adults 55–80 y of age at high cardiovascular risk			None			No association in patients with diabetes mellitus
Virtanen et al,[45] 2016, Kuopio Ischaemic Heart Disease Risk Factor Study (Finland)	1032 men 42–60 y of age	None					Also listed below under Association of Measures of Atherosclerosis
Zazpe et al ,[46] 2011, Seguimiento Universidad de Navarra (Spain)	14 185 adults			None			

(*Continued*)

Table 2. Continued

		Association With Measures of Atherosclerosis			
		CIMT	CAC	Angiography	
Chagas et al,[47] 2012, Center for Cardiovascular Diagnosis and Intervention, São Lucas Hospital (Brazil)	382 adults referred for coronary angiogram			Positive	
Goldberg et al,[48]2013, Northern Manhattan Study	1429 participants	Inverse association			
Robbins et al,[49] 2014, the NHLBI Family Heart Study	1848 participants		None		
Choi et al,[50] 2015, Kangbuk Samsung Hospital Total Healthcare Centers(South Korea)	23417 adults referred for CAC		Positive		
Virtanen et al,[45] 2016, Kuopio Ischaemic Heart Disease Risk Factor Study (Finland)	1032 men 42–60 y of age	None			

Studies typically contrasted intake of ≥7 eggs per week with ≤1 eggs per week. Details of methods and relative risks for each study are available in Data Supplement 2. ARIC indicates Atherosclerosis Risk in Communities Study; CAC, coronary artery calcium; CAD, coronary artery disease; CHD, coronary heart disease; CIMT, carotid intima-media thickness; HPFS, Health Professionals Follow-up Study; MI, myocardial infarction; NHLBI, National Heart, Lung, and Blood Institute; NHS, Nurses' Health Study; and PHS, Physicians' Health Study I.

reported an association with CHD,[32,36] whereas 1 study did not find an association.[37]

- For heart failure, 2 cohort studies conducted in the United States[38,39] and 1 study in Sweden[41] reported that consumption of >1 egg per day was associated with 20% to 30% higher risk of heart failure compared with infrequent egg intake in men but not in women.

For both dietary cholesterol and egg consumption, the published literature does not generally support statistically significant associations with CVD risk. Still, several limitations of the current body of published literature merit mention. Studies of dietary cholesterol have spanned a broad time period, over which methods in nutritional epidemiology have appreciably changed, as is apparent in the heterogeneity in adjustment for total energy, other dietary components, and serum cholesterol concentrations. In addition, variations in study populations may correspond to important differences in confounding structure. For example, the significant inverse association between eggs and stroke was apparent in the meta-analysis only on inclusion of a study conducted in China,[51] where egg consumption is positively associated with socioeconomic indicators and physical activity, inversely associated with smoking, and generally correlated with other aspects of a healthy dietary pattern (ie, higher intake of fiber, vegetables, and fruit). With observational data, it is difficult to assess the relationship of any individual food independently of a dietary pattern. Thus, the observations for eggs may be confounded by other dietary components and lifestyle behaviors that covary with eggs.

A meta-analysis[52] of individual participant data from 6 ethnically diverse US prospective cohorts concluded that there was a positive association between both dietary cholesterol and egg consumption and CVD risk (1.17 [95% CI, 1.09–1.26]). The authors estimated that each additional half-egg consumed per day was associated with a significant increase in CVD risk (1.06 [95% CI, 1.03–1.10]). After adjustment for dietary cholesterol, the association between egg intake and CVD was no longer significant.[52] More recently, the relationship between foods of animal origin and ischemic heart disease was examined by the use of data from 9 prospective European countries (pan-European EPIC [*European* Prospective Investigation Into Cancer and Nutrition] cohort). With respect to egg intake, a negative association was observed with ischemic heart disease (0.93 [95% CI, 0.88–0.99]) that was attenuated and became nonsignificant after the first 4 years of follow-up were eliminated. In further analysis, substitution of 100 kcal/d of red and processed meat with an equivalent amount of egg was associated with a 24% lower ischemic heart disease risk.[53]

INTERVENTION STUDIES OF DIETARY CHOLESTEROL AND CVD RISK

Although evidence from observational studies examining the relationship between dietary cholesterol and CVD risk is inconsistent, the discrepant results are likely heavily contributed to by residual confounding. It is difficult to distinguish between the effect of dietary cholesterol per se and the effect of dietary patterns high in cholesterol or satu-

Table 3. Controlled Feeding Studies Examining the Effect of Dietary Cholesterol on Total, LDL, and HDL Cholesterol

Study	Design	Duration of Study Period, wk	Sample Characteristics	n*	Background Diet	Cholesterol Content of Intervention Group
Bowman et al,[56] 1988	Randomized, 2×2 factorial, controlled feeding	5	Nonsmoking, healthy men (mean age, 22±3 y)	19	Low-fat diet (31% kcal)	504 mg/d
					Usual-fat diet (46% kcal)	
Chenoweth et al,[57] 1981	2×2, crossover, controlled feeding study	4	Healthy men with total cholesterol >190 mg/dL (mean age, 25 y)	32	Control diet (44% kcal fat, 17% kcal saturated fat)	Control diet: 894 mg/d
					Modified-fat diet (35% kcal fat, 9% kcal saturated fat)	Modified-fat diet: 728 mg/d
Connor et al,[58] 1964	4-period, crossover, controlled feeding study	4	Men 24–48 y of age who were healthy inpatients on a metabolic ward	6	Low P/S, 40% fat from saturated fat and 10% PUFA	Low P/S: 729 mg/d
					High P/S, 19% fat from saturated fat and 31% PUFA	High P/S: 725 mg/d
Fielding et al,[59] 1995	4-group parallel, controlled feeding study	4	Healthy, nonsmoking, normolipidemic men (age, 25–35 y)	84	High-PUFA diet (9%–10% kcal)	High PUFA: 603 mg/d
					High saturated fat (16%–17% kcal)	High saturated fat: 635 mg/d
Flaim et al,[60] 1981	2-group parallel, controlled feeding study	4	Healthy men (mean age, 23 y)	23	Average American diet (≈40% kcal fat, 14% kcal saturated fat)	1415 mg/d
Ginsberg et al,[61] 1995	3-period, crossover, controlled feeding study	8	Healthy, normolipidemic women (mean age, 24 y)	13	AHA diet (28% kcal fat, 8% kcal saturated fat)	1 egg/d: 277 mg/d
						3 eggs/d: 667 mg/d
Ginsberg et al,[62] 1994	4-period, crossover, controlled feeding study	8	Healthy, normolipidemic men (mean age, 25 y)	20	AHA Step 1 diet (30% kcal fat, 9% kcal from saturated fat)	1 egg/d: 283 mg/d
						2 eggs/d: 468 mg/d
						4 eggs/d: 858 mg/d
Illingworth et al,[63] 1995	3-period, crossover, controlled feeding study	4	Patients with hypocholesterolemia	30	Diet containing 30% kcal from fat	350 mg/d
						650 mg/d
			Patients with normal cholesterol levels			350 mg/d
						650 mg/d
			Patients with primary hypercholesterolemia			350 mg/d
						650 mg/d
Johnson and Greenland,[64] 1990	2-period crossover, controlled feeding study	4	Healthy male athletes (mean age, 27±5 y)	10	Diet containing 30% kcal fat	600 mg/d
Quig et al,[65] 1983	2×2 factorial, crossover, controlled feeding study‡	4	Healthy, nonsmoking men (mean age, 23±2 y)	12‡	Average American diet (≈40% kcal fat, 14% kcal saturated fat)	1400 mg/d
Reaven et al,[66] 2001	4-period, partial crossover, controlled feeding study	4	Nondiabetic, postmenopausal women who were insulin sensitive or insulin resistant with TC <280 mg/dL	65	NCEP Step 1 diet (30% kcal fat, 9% kcal saturated fat)	319 mg/d
						523 mg/d
						941 mg/d

(*Continued*)

rated fat, for example, sausage or bacon eaten with eggs. Randomized controlled trials provide a means of examining the question in a controlled setting. A meta-analysis of 17 intervention trials that ranged from 4 to 12 weeks long reported an increase in total cholesterol (11.2 mg/dL), LDL cholesterol (6.7 mg/dL), and HDL cholesterol (3.2 mg/dL) concentrations in the intervention group compared with the control group.[30] In the intervention group of the included studies, dietary cholesterol ranged from 501 to 1415 mg/d compared with 0 to 415 mg/d in the referent group. This is equivalent to ≈3 to 7 compared with 0 to 2 eggs per day. In this meta-analysis, the fatty acid composition of the diets was not factored into the analyses.

Methodological Issues

A relevant issue with regard to the study of dietary cholesterol is the influence of dietary fat type. In many intervention studies, the fatty acid composition of the diets was not matched; likewise, because the major-

Table 3. Continued

Cholesterol Content of Referent Group	Source of Dietary Cholesterol	P/S	Outcomes†	Between-Group Difference (Intervention–Referent), mg/dL (mean±SE)		
				TC	LDL-C	HDL-C
193 mg/d	Egg	0.4	TC, LDL-C, HDL-C	19.0±2.63	21.0±1.87	1.0±2.19
				6.0±3.01	5.0±2.79	1.0±2.03
Control diet: 340 mg/d	Egg	Control diet: 0.4–0.6	TC	21.0±5.67		
Modified-fat diet: 186 mg/d		Modified-fat diet: 1.1–1.4		13.0±3.50		
Low P/S: 0 mg/d	Egg	Low P/S: 0.2	TC	38.0±12.36		
High P/S: 0 mg/d		High P/S: 1.7		28.0±8.44		
High PUFA: 176 mg/d	Not reported	High PUFA: 0.8	TC	21.0±8.03		
High saturated fat: 203 mg/d		High saturated fat: 0.3–0.4		27.7±8.47		
415 mg/d	Egg	0.6	TC, LDL-C, HDL-C	17.0±11.07	13.0±10.77	−1.0±4.24
0 eggs/d: 108 mg/d	Egg	0.9	TC, LDL-C, HDL-C	6.19±3.83	3.9±4.13	1.6±3.0
				15.85±4.05	11.6±3.94	3.5±2.84
0 eggs/d: 128 mg/d	Egg	0.9	TC, LDL-C, HDL-C	5.5±4.76	7.0±4.58	−0.2±1.82
				6.3±4.67	6.6±4.52	−0.5±1.81
				11.1±5.07	11.2±5.02	1.2±1.87
50 mg/d	Not reported	0.8	TC, LDL-C, HDL-C	4.0±10.58	2.0±5.67	1.0±4.74
				12.0±10.40	10.0±5.87	1.0±4.74
				8.0±6.54	6.0±6.5	2.0±3.91
				18.0±6.54	15.0±7.29	3.0±4.07
				10.0±9.96	9.0±9.59	2.0±2.28
				20.0±8.70	20.0±8.10	3.0±2.58
200 mg/d	Egg	1.5	TC, LDL-C, HDL-C	10.05±4.25	8.9±3.48	1.2±8.89
400 mg/d	Egg	0.6	TC, LDL-C, HDL-C	26.0±13.71	14.0±8.73	8.0±2.88
113 mg/d	Egg	1.0	TC, LDL-C	11.0±6.0	7.0±5.0	
				6.0±8.54	4.0±7.0	
				8.0±6.0	6.0±5.0	

AHA indicates American Heart Association; HDL, high-density lipoprotein; HDL-C, high density lipoprotein cholesterol; LDL, low-density lipoprotein; LDL-C, low density lipoprotein cholesterol; NCEP, National Cholesterol Education Program; P/S, polyunsaturated to saturated fat ratio; PUFA, polyunsaturated fatty acid; and TC, total cholesterol.

*Included in data analysis.

†Outcomes are reported in a way that enabled inclusion in the meta-regression.

‡Only the sedentary group is included in the meta-regression analyses.

§SE derived according to the methods outlined in Data Supplement 3.

ity of observational studies do not adjust for saturated, monounsaturated, and polyunsaturated fat, it can be difficult to distinguish between the independent effects of dietary cholesterol and dietary fat type.

Meta-Regression Analyses

A recent meta-regression analysis[54] including 55 randomized controlled dietary intervention studies identified a dose-response relationship between dietary

cholesterol and LDL cholesterol concentrations after adjustment for dietary fatty acid composition using predicted lipoprotein changes derived from the Mensink et al[55] equation. Controlling for saturated, monounsaturated, and polyunsaturated fat, the meta-regression model indicated that every 100–mg/d increase in dietary cholesterol predicted an LDL cholesterol concentration increase of 1.90 mg/dL (based on a linear model), 4.46 mg/dL (based on a low-dose linear model derived from the Michaelis-Menten equation), and 4.58 mg/dL (based on a nonlinear model). These results suggest that dietary cholesterol is directly associated with LDL cholesterol concentration, and this relationship persisted after adjustment for dietary fat type.

To further isolate the effects of dietary cholesterol on blood lipoprotein concentrations, we conducted a meta-regression analysis of controlled feeding studies, limiting included trials to those with similar ratios of dietary polyunsaturated fatty acid to saturated fatty acid in the randomized groups of the trials. Eligible studies included adults only, had ≥2 diets differing in dietary cholesterol content but similar ratio of polyunsaturated fatty acid to saturated fatty acid, intervened for ≥4 weeks, and reported total, LDL, or HDL cholesterol concentration. Detailed methodology is presented in Data Supplement 3.

In total, 11 feeding studies met the inclusion criteria, contributing 25 comparisons[56–66] (Table 3). Seven studies had a crossover design,[57,58,61–65] and 4 studies had a parallel design.[56,59,60,66] Differences in dietary cholesterol ranged from 155 to 1000 mg/d. A significant positive relationship was identified between dietary cholesterol and total cholesterol concentrations (Figure 2). This relationship remained significant when studies that had a dietary cholesterol difference >1000 mg/d were removed from the analyses, resulting in a cholesterol intake ranging from 155 to 828 mg/d (Data Supplement 3, Table S6). (These analyses excluded trials with a difference of 1000 mg/d because a difference in dietary cholesterol of 1000 mg/d was deemed implausible in free-living populations.) No significant association was identified between dietary cholesterol and total cholesterol concentrations when only studies with a difference in dietary cholesterol of ≤300 or >300 mg/d were included in the regressed models separately (Data Supplement 3, Table S6). Leave-one-out sensitivity analysis showed that individual removal of 3 studies[58,61,63] attenuated the association to nonsignficant (P<0.082); removal of any one of the other 9 studies did not change the relationship (Data Supplement 3, Table S7).

LDL cholesterol concentration is a stronger predictor of CVD risk than total cholesterol.[4] No significant association was observed between dietary cholesterol and LDL cholesterol or HDL cholesterol concentrations (Figure 2). However, the positive relationship between

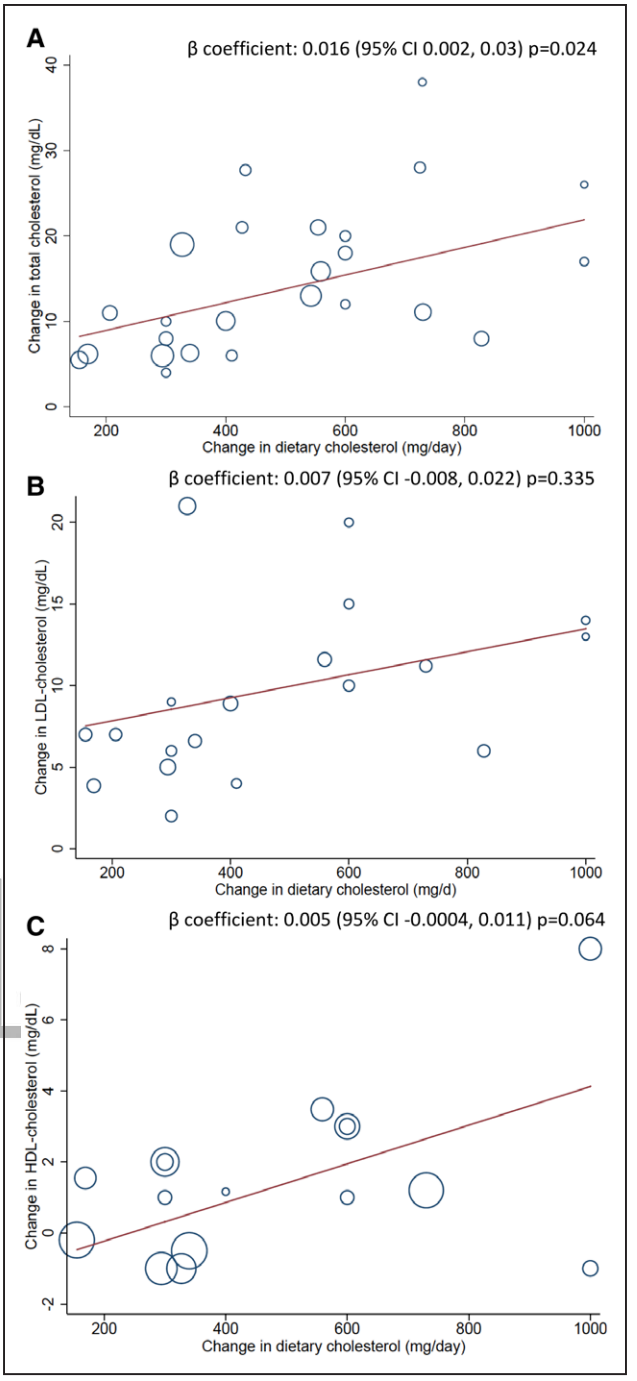


Figure 2. Meta-regression plots represent the relationship between a change in dietary cholesterol and serum lipids.
Section (**A**) represents relationship to total cholesterol, (**B**) represents the relationship with low-density lipoprotein (LDL) cholesterol, and (**C**) represents the relationship with high-density lipoprotein (HDL) cholesterol. The size of the data points represents the weight of the study in the fitted random-effects meta-regression model.

dietary cholesterol and HDL cholesterol approached significance (P=0.064), and the leave-one-out sensitivity analysis indicated that after removal of 1 study,[60] the relationship reached statistical significance (Data Supplement 3, Table S8). The results for LDL cholesterol remained robust in analyses by study design and cutoffs

Table 4. Food Sources of Dietary Cholesterol Within Categories Shown to be the Greatest Contributors to Dietary Cholesterol*

Food Source	Dietary Cholesterol, mg	Saturated Fat, g
Eggs		
1 large egg cooked	186	2.0
Meat		
3 oz pork spareribs	89	7.9
3 oz tenderloin steak trimmed 1/8 in, broiled	82	5.7
3 oz pork tenderloin, broiled	80	1.9
3 oz tenderloin steak trimmed, grilled (lean)	79	2.8
3 oz ground beef 70/30,† broiled	75	6.2
3 oz ground beef 80/20,† broiled	75	5.7
3 oz ground beef 95/5,† broiled	75	2.5
3 oz ground beef 97/3,† broiled	75	1.9
Poultry		
3 oz chicken drumstick, skin on, roasted	110	2.3
3 oz chicken drumstick, skin removed, cooked	75	1.3
3 oz lean chicken breast, skin removed, roasted	72	0.86
3 oz chicken breast, skin on, roasted	71	1.9
Milk and milk products		
1 cup whole milk	24	4.6
1 cup 2% milk	20	3.0
1 cup 1% milk	12	1.5
1 cup nonfat milk	5	0.3
Seafood		
3 oz shrimp, cooked	161	0.05
3 oz lobster, cooked	124	0.18
3 oz pollock, cooked	77	0.15
3 oz crab, cooked	65	0.14
3 oz salmon, cooked	60	1.1
3 oz tilapia, cooked	48	0.80

*Food categories shown to be the greatest source of dietary cholesterol in analyses by Xu et al[11]; dietary cholesterol and saturated fat values extracted from the US Department of Agriculture Food Composition Databases; standard reference values are used.[50]

†Ratios represent the percent lean to percent fat by weight in the ground beef before cooking.

for dietary cholesterol (Data Supplement 3, Table S9). A log-linear model was explored, and the association between LDL-cholesterol and dietary cholesterol did not fit a log-linear model (P=0.69).

Meta-regression analyses assessing the relationship among dietary cholesterol, LDL cholesterol, and HDL cholesterol concentrations were limited by the number of comparisons available for analysis and the small sample sizes of most trials. Thus, less power was available for the analyses of LDL cholesterol and HDL cholesterol compared with total cholesterol, which may have contributed to the lack of a significant association with these specific lipoproteins.

Implementation Within the Context of the American Diet

These analyses explored changes in blood cholesterol concentrations in response to dietary cholesterol when the ratio of polyunsaturated fatty acid to saturated fatty acid of the diet was held constant. From an implementation perspective in an American diet, dietary cholesterol and saturated fat for the most part increase in parallel.[11] In addition, many intervention studies tested implausibly high cholesterol intakes that are well above the consumption levels of 95% of the population.[30,54] In addition, in examinations of the intake of dietary cholesterol in the context of typical eating patterns, the effects of fatty acid composition must be taken into consideration. This is of particular concern in the United States, where eggs are frequently accompanied by bacon or sausage. Thus, estimating the independent effect of dietary cholesterol with theoretical or experimental methods (predictive calculations and feeding studies) is not representative of actual eating patterns and limits the generalizability to dietary patterns (Table 4).

The available evidence suggests that within the context of eating patterns, replacing saturated fat with unsaturated fat is expected to produce greater reductions in LDL cholesterol concentrations than reducing dietary cholesterol alone.[3,4,7,67] Within the range of dietary cholesterol and dietary fats available from common food sources (Table 4), there is greater potential to optimize plasma lipoprotein profiles by improving the ratio of dietary saturated fatty acid to polyunsaturated fatty acid than by reducing dietary cholesterol. For example, replacing full-fat milk with fat-free milk would lower saturated intake by 4.3 g/1 cup; however, this replacement would yield only a 19-mg reduction in dietary cholesterol. Replacing 3 oz lean ground beef with 3 oz chicken breast would lower saturated fat by 4.84 g but dietary cholesterol by only 3 mg (Table 4). (From a clinical perspective, if a patient were consuming 10% of energy from saturated fat on a 2000-kcal diet and then made these 2 changes, that patient's saturated fat intake would be ≈6% of energy as recommended by the 2013 AHA/ACC lifestyle guideline.[3]) The calorie deficit should be filled with an unsaturated fat rather than carbohydrate, particularly refined carbohydrate. Of unique consideration is shellfish, which are relatively high in dietary cholesterol but very low in saturated fat.

SUMMARY

Consideration of the relationship between dietary cholesterol and CVD risk cannot ignore 2 aspects of diet. First, most foods contributing cholesterol to the US diet are usually high in saturated fat or consumed

with foods high in saturated fat. Second, heart-healthy dietary patterns (eg, Mediterranean-style[68] and DASH-style[69] diets) are inherently low in cholesterol, with typical menus containing <300 mg/d cholesterol, similar to the current US intake.

An extensive evidence base, including many well-designed studies, reflects mixed results. Most observational studies, conducted in several countries, generally reported no significant association of dietary cholesterol or egg intake with CVD outcomes in terms of CHD, myocardial infarction, and stroke risk. In contrast, a recent meta-analysis of individual participant data from ethnically diverse US cohorts concluded that half an egg per day was associated with a 6% increase in CVD risk. Three studies specifically addressed individuals with type 2 diabetes mellitus, eggs, and CHD risk. Two of 3 studies reported a positive association with CHD. Three other studies reported an association with increased risk for heart failure in the general population. The possibility of observational data on eggs being confounded by other dietary components must be considered.

More convincing are data from intervention studies that show a modest effect on CVD risk factors and lipid and lipoprotein concentrations. Two meta-analyses of studies with substantial heterogeneity report that dietary cholesterol increased total and LDL cholesterol concentrations. Our meta-regression analysis using data from controlled feeding studies in which the ratio of polyunsaturated fatty acid to saturated fatty acid in the comparison diets was matched indicated that dietary cholesterol significantly increased total cholesterol, but the findings were not significant for the stronger predictor of CVD risk, LDL cholesterol, or HDL cholesterol concentration.

CONCLUSIONS

Dietary guidance to achieve cardiovascular health should remain focused on adopting a healthy dietary pattern, as recommended by the 2015 to 2020 DGA and current AHA/ACC guidelines. Healthy dietary patterns are inherently relatively low in cholesterol, with typical levels similar to the current US intake. These patterns emphasize fruits, vegetables, whole grains, low-fat or fat-free dairy products, lean protein sources, nuts, seeds, and liquid vegetable oils. A recommendation that gives a specific dietary cholesterol target within the context of food-based advice is challenging for clinicians and consumers to implement; hence, guidance focused on dietary patterns is more likely to improve diet quality and to promote cardiovascular health.

SUGGESTIONS FOR CLINICAL PRACTICE AND CONSUMERS

To achieve healthy dietary patterns, consumers are advised to eat a dietary pattern characterized by fruits, vegetables, whole grains, low-fat or fat-free dairy products, lean protein sources, nuts, seeds, and vegetable oils, consistent with those recommended in the 2015 to 2020 DGA. These patterns have a relatively high ratio of polyunsaturated fatty acid to saturated fatty acid and are low in cholesterol, achieved by minimizing the intake of major sources of saturated fat intake (animal fats) and including liquid nontropical vegetable oils. Choosing plant-based protein sources will limit cholesterol intake.

Given the relatively high content of cholesterol in egg yolks, it remains advisable to limit intake to current levels. Healthy individuals can include up to a whole egg or equivalent daily. A 3-oz serving of shrimp is equivalent to about a whole egg. Shrimp and other shellfish can be incorporated into a heart-healthy dietary pattern when paired with other lean or plant-based protein sources. Caveats exist for the following subgroups:

- Vegetarians (lacto-ovo) who do not consume meat-based cholesterol-containing foods may include more dairy and eggs in their diets within the context of moderation discussed herein.
- Patients with dyslipidemia, particularly those with diabetes mellitus or at risk for heart failure, should be cautious in consuming foods rich in cholesterol.
- For older normocholesterolemic patients, given the nutritional benefits and convenience of eggs, consumption of up to 2 eggs per day is acceptable within the context of a heart-healthy dietary pattern.

Additional dietary guidance can be found online.[70,71]

Acknowledgments

The authors appreciate the contributions of Alan Remaley, MD, PhD, representing the Arteriosclerosis, Thrombosis and Vascular Biology Council, and Jennifer Dearborn, MD, representing the Stroke Council, in the planning of this science advisory.

ARTICLE INFORMATION

The Data Supplements are available with this article at https://www.ahajournals.org/doi/suppl/10.1161/CIR.0000000000000743.

The American Heart Association requests that this document be cited as follows: Carson JAS, Lichtenstein AH, Anderson CAM, Appel LJ, Kris-Etherton PM, Meyer KA, Petersen K, Polonsky T, Van Horn L; on behalf of the American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Arteriosclerosis, Thrombosis and Vascular Biology; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Peripheral Vascular Disease; and Stroke Council. Dietary cholesterol and cardiovascular risk: a science advisory from the American Heart Association. *Circulation*. 2019;140:●●●– ●●●. doi: 10.1161/CIR.0000000000000743.

Disclosures

Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Jo Ann S. Carson	University of Texas Southwestern Medical Center	None	None	None	None	None	None	None
Alice H. Lichtenstein	Tufts University, Jean Mayer USDA Human Nutrition Research Center on Aging	None	None	None	None	None	None	None
Cheryl A.M. Anderson	University of California at San Diego	None	None	None	None	None	None	None
Lawrence J. Appel	Johns Hopkins University	None	None	None	None	None	None	None
Penny M. Kris-Etherton	Pennsylvania State University	None	None	None	None	None	None	None
Kate A. Meyer	University of North Carolina at Chapel Hill, Nutrition Research Institute	None	None	None	None	None	None	None
Kristina Petersen	Pennsylvania State University	None	None	None	None	None	None	None
Tamar Polonsky	University of Chicago	None	None	None	None	None	None	None
Linda Van Horn	Northwestern University	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Robert C. Bauer	Columbia University	None	None	None	None	None	None	None
Ervin R. Fox	University of Mississippi	None	None	None	None	None	None	None
Frank M. Sacks	Harvard University	None	None	None	None	None	None	None
Connie M. Weaver	Purdue University	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

REFERENCES

1. US Department of Agriculture and US Department of Health and Human Services. *Dietary Guidelines for Americans*. 7th ed. Washington, DC: US Government Printing Office; 2010.
2. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497. doi: 10.1001/jama.285.19.2486
3. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, Lee IM, Lichtenstein AH, Loria CM, Millen BE, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [published corrections appear in Circulation. 2014;129:S100–S101 and *Circulation*. 2015;131:e326]. *Circulation*. 2014;129(suppl 2):S76–S99. doi: 10.1161/01.cir.0000437740.48606.d1
4. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: executive summary [published correction appears in *Circulation*. 2019;139:e1178–e1181]. *Circulation*. 2019;139:e1082–e1143. DOI: CIR0000000000000624.
5. US Department of Health and Human Services. 2015–2020 Dietary Guidelines for Americans. 8th ed. December 2015. https://health.gov/dietaryguidelines/2015/guidelines/. Accessed December 2, 2018.
6. Jahns L, Davis-Shaw W, Lichtenstein AH, Murphy SP, Conrad Z, Nielsen F. The history and future of dietary guidance in America. *Adv Nutr*. 2018;9:136–147. doi: 10.1093/advances/nmx025
7. Dietary Guidelines Advisory Committee. Scientific report of the 2015 Dietary Guidelines Advisory Committee: advisory report to the Secretary of Health and Human Services and the Secretary of Agriculture. 2015. https://health.gov/dietaryguidelines/2015-scientific-report/. Accessed June 14, 2019.
8. US Department of Agriculture. Nutrients in healthy US-style food pattern at each calorie level, 2015. https://www.cnpp.usda.gov/sites/default/files/usda_food_patterns/NutrientsInHealthyUS-StyleFoodPattern.pdf. Accessed January 17, 2019.
9. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, Himmelfarb CD, Khera A, Lloyd-Jones D, McEvoy JW, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2019;140:e646–e650]. *Circulation*. 2019;140:e596–e646. doi: 10.1161/CIR.0000000000000678
10. Jacobson TA, Maki KC, Orringer CE, Jones PH, Kris-Etherton P, Sikand G, La Forge R, Daniels SR, Wilson DP, Morris PB, et al; NLA Expert Panel. National Lipid Association recommendations for patient-centered management of dyslipidemia: part 2. *J Clin Lipidol*. 2015;9(suppl):S1–S122.e1. doi: 10.1016/j.jacl.2015.09.002
11. Xu Z, McClure ST, Appel LJ. Dietary cholesterol intake and sources among U.S adults: results from National Health and Nutrition Examination Surveys (NHANES), 2001-2014. *Nutrients*. 2018;10:E771. doi: 10.3390/nu10060771
12. Ascherio A, Rimm EB, Giovannucci EL, Spiegelman D, Stampfer M, Willett WC. Dietary fat and risk of coronary heart disease in men: cohort follow up study in the United States. *BMJ*. 1996;313:84–90. doi: 10.1136/bmj.313.7049.84
13. He K, Merchant A, Rimm EB, Rosner BA, Stampfer MJ, Willett WC, Ascherio A. Dietary fat intake and risk of stroke in male US healthcare professionals: 14 year prospective cohort study. *BMJ*. 2003;327:777–782. doi: 10.1136/bmj.327.7418.777
14. Pietinen P, Ascherio A, Korhonen P, Hartman AM, Willett WC, Albanes D, Virtamo J. Intake of fatty acids and risk of coronary heart disease in a cohort of Finnish men: the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. *Am J Epidemiol*. 1997;145:876–887. doi: 10.1093/oxfordjournals.aje.a009047
15. Larsson SC, Virtamo J, Wolk A. Dietary fats and dietary cholesterol and risk of stroke in women. *Atherosclerosis*. 2012;221:282–286. doi: 10.1016/j.atherosclerosis.2011.12.043
16. Yaemsiri S, Sen S, Tinker L, Rosamond W, Wassertheil-Smoller S, He K. Trans fat, aspirin, and ischemic stroke in postmenopausal women. *Ann Neurol*. 2012;72:704–715. doi: 10.1002/ana.23555
17. Hu FB, Stampfer MJ, Manson JE, Rimm E, Colditz GA, Rosner BA, Hennekens CH, Willett WC. Dietary fat intake and the risk of coronary heart disease in women. *N Engl J Med*. 1997;337:1491–1499. doi: 10.1056/NEJM199711203372102
18. Iso H, Stampfer MJ, Manson JE, Rexrode K, Hu F, Hennekens CH, Colditz GA, Speizer FE, Willett WC. Prospective study of fat and protein intake and risk of intraparenchymal hemorrhage in women. *Circulation*. 2001;103:856–863. doi: 10.1161/01.cir.103.6.856
19. Seino F, Date C, Nakayama T, Yoshiike N, Yokoyama T, Yamaguchi M, Tanaka H. Dietary lipids and incidence of cerebral infarction in a Japanese rural community. *J Nutr Sci Vitaminol (Tokyo)*. 1997;43:83–99. doi: 10.3177/jnsv.43.83
20. Posner BM, Cobb JL, Belanger AJ, Cupples LA, D'Agostino RB, Stokes J 3rd. Dietary lipid predictors of coronary heart disease in men: the Framingham study. *Arch Intern Med*. 1991;151:1181–1187.
21. McGee DL, Reed DM, Yano K, Kagan A, Tillotson J. Ten-year incidence of coronary heart disease in the Honolulu Heart Program: relationship to nutrient intake. *Am J Epidemiol*. 1984;119:667–676. doi: 10.1093/oxfordjournals.aje.a113788
22. Esrey KL, Joseph L, Grover SA. Relationship between dietary intake and coronary heart disease mortality: Lipid Research Clinics Prevalence Follow-Up Study. *J Clin Epidemiol*. 1996;49:211–216. doi: 10.1016/0895-4356(95)00066-6
23. Mann JI, Appleby PN, Key TJ, Thorogood M. Dietary determinants of ischaemic heart disease in health conscious individuals. *Heart*. 1997;78:450–455. doi: 10.1136/hrt.78.5.450
24. Xu J, Eilat-Adar S, Loria C, Goldbourt U, Howard BV, Fabsitz RR, Zephier EM, Mattil C, Lee ET. Dietary fat intake and risk of coronary heart disease: the Strong Heart Study. *Am J Clin Nutr*. 2006;84:894–902. doi: 10.1093/ajcn/84.4.894
25. Garcia-Palmieri MR, Sorlie P, Tillotson J, Costas R Jr, Cordero E, Rodriguez M. Relationship of dietary intake to subsequent coronary heart disease incidence: the Puerto Rico Heart Health Program. *Am J Clin Nutr*. 1980;33:1818–1827. doi: 10.1093/ajcn/33.8.1818
26. Sauvaget C, Nagano J, Hayashi M, Yamada M. Animal protein, animal fat, and cholesterol intakes and risk of cerebral infarction mortality in the Adult Health Study. *Stroke*. 2004;35:1531–1537. doi: 10.1161/01.STR.0000130426.52064.09
27. Kushi LH, Lew RA, Stare FJ, Ellison CR, el Lozy M, Bourke G, Daly L, Graham I, Hickey N, Mulcahy R. Diet and 20-year mortality from coronary heart disease: the Ireland-Boston Diet-Heart Study. *N Engl J Med*. 1985;312:811–818. doi: 10.1056/NEJM198503283121302
28. Shekelle RB, Shryock AM, Paul O, Lepper M, Stamler J, Liu S, Raynor WJ Jr. Diet, serum cholesterol, and death from coronary heart disease: the Western Electric study. *N Engl J Med*. 1981;304:65–70. doi: 10.1056/NEJM198101083040201
29. Shekelle RB, Stamler J. Dietary cholesterol and ischaemic heart disease. *Lancet*. 1989;1:1177–1179. doi: 10.1016/s0140-6736(89)92759-1
30. Berger S, Raman G, Vishwanathan R, Jacques PF, Johnson EJ. Dietary cholesterol and cardiovascular disease: a systematic review and meta-analysis. *Am J Clin Nutr*. 2015;102:276–294. doi: 10.3945/ajcn.114.100305
31. US Department of Agriculture, Agricultural Research Service, Nutrient Data Laboratory. USDA National Nutrient Database for Standard Reference, Legacy. April 2018.
32. Hu FB, Stampfer MJ, Rimm EB, Manson JE, Ascherio A, Colditz GA, Rosner BA, Spiegelman D, Speizer FE, Sacks FM, et al. A prospective study of egg consumption and risk of cardiovascular disease in men and women. *JAMA*. 1999;281:1387–1394. doi: 10.1001/jama.281.15.1387
33. Bernstein AM, Pan A, Rexrode KM, Stampfer M, Hu FB, Mozaffarian D, Willett WC. Dietary protein sources and the risk of stroke in men and women. *Stroke*. 2012;43:637–644. doi: 10.1161/STROKEAHA.111.633404
34. Sauvaget C, Nagano J, Allen N, Grant EJ, Beral V. Intake of animal products and stroke mortality in the Hiroshima/Nagasaki Life Span Study. *Int J Epidemiol*. 2003;32:536–543. doi: 10.1093/ije/dyg151
35. Nakamura Y, Iso H, Kita Y, Ueshima H, Okada K, Konishi M, Inoue M, Tsugane S. Egg consumption, serum total cholesterol concentrations and coronary heart disease incidence: Japan Public Health Center-based prospective study. *Br J Nutr*. 2006;96:921–928. doi: 10.1017/bjn20061937
36. Qureshi AI, Suri FK, Ahmed S, Nasar A, Divani AA, Kirmani JF. Regular egg consumption does not increase the risk of stroke and cardiovascular diseases. *Med Sci Monit*. 2007;13:CR1–CR8.
37. Djoussé L, Gaziano JM. Egg consumption in relation to cardiovascular disease and mortality: the Physicians' Health Study. *Am J Clin Nutr*. 2008;87:964–969. doi: 10.1093/ajcn/87.4.964
38. Djoussé L, Gaziano JM. Egg consumption and risk of heart failure in the Physicians' Health Study. *Circulation*. 2008;117:512–516. doi: 10.1161/CIRCULATIONAHA.107.734210

39. Nettleton JA, Steffen LM, Loehr LR, Rosamond WD, Folsom AR. Incident heart failure is associated with lower whole-grain intake and greater high-fat dairy and egg intake in the Atherosclerosis Risk in Communities (ARIC) study. *J Am Diet Assoc.* 2008;108:1881–1887. doi: 10.1016/j.jada.2008.08.015
40. Haring B, Gronroos N, Nettleton JA, von Ballmoos MC, Selvin E, Alonso A. Dietary protein intake and coronary heart disease in a large community based cohort: results from the Atherosclerosis Risk in Communities (ARIC) study [corrected]. *PLoS One.* 2014;9:e109552. doi: 10.1371/journal.pone.0109552
41. Larsson SC, Åkesson A, Wolk A. Egg consumption and risk of heart failure, myocardial infarction, and stroke: results from 2 prospective cohorts. *Am J Clin Nutr.* 2015;102:1007–1013. doi: 10.3945/ajcn.115.119263
42. Farvid MS, Malekshah AF, Pourshams A, Poustchi H, Sepanlou SG, Sharafkhah M, Khoshnia M, Farvid M, Abnet CC, Kamangar F, et al. Dietary protein sources and all-cause and cause-specific mortality: the Golestan Cohort Study in Iran. *Am J Prev Med.* 2017;52:237–248. doi: 10.1016/j.amepre.2016.10.041
43. Nakamura Y, Okamura T, Kita Y, Okuda N, Kadota A, Miura K, Okayama A, Ueshima H; NIPPON DATA90 Research Group. Re-evaluation of the associations of egg intake with serum total cholesterol and cause-specific and total mortality in Japanese women. *Eur J Clin Nutr.* 2018;72:841–847. doi: 10.1038/s41430-017-0051-4
44. Díez-Espino J, Basterra-Gortari FJ, Salas-Salvadó J, Buil-Cosiales P, Corella D, Schröder H, Estruch R, Ros E, Gómez-Gracia E, Arós F, et al; PREDIMED Investigators. Egg consumption and cardiovascular disease according to diabetic status: the PREDIMED study. *Clin Nutr.* 2017;36:1015–1021. doi: 10.1016/j.clnu.2016.06.009
45. Virtanen JK, Mursu J, Virtanen HE, Fogelholm M, Salonen JT, Koskinen TT, Voutilainen S, Tuomainen TP. Associations of egg and cholesterol intakes with carotid intima-media thickness and risk of incident coronary artery disease according to apolipoprotein E phenotype in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Am J Clin Nutr.* 2016;103:895–901. doi: 10.3945/ajcn.115.122317
46. Zazpe I, Beunza JJ, Bes-Rastrollo M, Warnberg J, de la Fuente-Arrillaga C, Benito S, Vázquez Z, Martínez-González MA; SUN Project Investigators. Egg consumption and risk of cardiovascular disease in the SUN Project. *Eur J Clin Nutr.* 2011;65:676–682. doi: 10.1038/ejcn.2011.30
47. Chagas P, Caramori P, Galdino TP, da Silveira de Barcellos S, Gomes I, Schwanke CH. Egg consumption and coronary atherosclerotic burden. *Atherosclerosis.* 2013;229:381–384. doi: 10.1016/j.atherosclerosis.2013.05.008
48. Goldberg S, Gardener H, Tiozzo E, Ying Kuen C, Elkind MS, Sacco RL, Rundek T. Egg consumption and carotid atherosclerosis in the Northern Manhattan Study. *Atherosclerosis.* 2014;235:273–280. doi: 10.1016/j.atherosclerosis.2014.04.019
49. Robbins JM, Petrone AB, Ellison RC, Hunt SC, Carr JJ, Heiss G, Arnett DK, Gaziano JM, Djoussé L. Association of egg consumption and calcified atherosclerotic plaque in the coronary arteries: the NHLBI Family Heart Study. *ESPEN J.* 2014;9:e131–e135. doi: 10.1016/j.clnme.2014.04.004
50. Choi Y, Chang Y, Lee JE, Chun S, Cho J, Sung E, Suh BS, Rampal S, Zhao D, Zhang Y, et al. Egg consumption and coronary artery calcification in asymptomatic men and women. *Atherosclerosis.* 2015;241:305–312. doi: 10.1016/j.atherosclerosis.2015.05.036
51. Xu L, Lam TH, Jiang CQ, Zhang WS, Zhu F, Jin YL, Woo J, Cheng KK, Thomas GN. Egg consumption and the risk of cardiovascular disease and all-cause mortality: Guangzhou Biobank Cohort Study and meta-analyses. *Eur J Nutr*. 2018.
52. Zhong VW, Van Horn L, Cornelis MC, Wilkins JT, Ning H, Carnethon MR, Greenland P, Mentz RJ, Tucker KL, Zhao L, et al. Associations of dietary cholesterol or egg consumption with incident cardiovascular disease and mortality. *JAMA.* 2019;321:1081–1095. doi: 10.1001/jama.2019.1572
53. Key TJ, Appleby PN, Bradbury KE, Sweeting M, Wood A, Johansson I, Kühn T, Steur M, Weiderpass E, Wennberg M, et al. Consumption of meat, fish, dairy products, and eggs and risk of ischemic heart disease. *Circulation.* 2019;139:2835–2845. doi: 10.1161/CIRCULATIONAHA.118.038813
54. Vincent MJ, Allen B, Palacios OM, Haber LT, Maki KC. Meta-regression analysis of the effects of dietary cholesterol intake on LDL and HDL cholesterol. *Am J Clin Nutr.* 2019;109:7–16. doi: 10.1093/ajcn/nqy273
55. Mensink RP, Zock PL, Kester AD, Katan MB. Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am J Clin Nutr.* 2003;77:1146–1155. doi: 10.1093/ajcn/77.5.1146
56. Bowman MP, Van Doren J, Taper LJ, Thye FW, Ritchey SJ. Effect of dietary fat and cholesterol on plasma lipids and lipoprotein fractions in normolipidemic men. *J Nutr.* 1988;118:555–560. doi: 10.1093/jn/118.5.555
57. Chenoweth W, Ullmann M, Simpson R, Leveille G. Influence of dietary cholesterol and fat on serum lipids in men. *J Nutr.* 1981;111:2069–2080. doi: 10.1093/jn/111.12.2069
58. Connor WE, Stone DB, Hodges RE. The interrelated effects of dietary cholesterol and fat upon human serum lipid levels. *J Clin Invest.* 1964;43:1691–1696. doi: 10.1172/JCI105044
59. Fielding CJ, Havel RJ, Todd KM, Yeo KE, Schloetter MC, Weinberg V, Frost PH. Effects of dietary cholesterol and fat saturation on plasma lipoproteins in an ethnically diverse population of healthy young men. *J Clin Invest.* 1995;95:611–618. doi: 10.1172/JCI117705
60. Flaim E, Ferreri LF, Thye FW, Hill JE, Ritchey SJ. Plasma lipid and lipoprotein cholesterol concentrations in adult males consuming normal and high cholesterol diets under controlled conditions. *Am J Clin Nutr.* 1981;34:1103–1108. doi: 10.1093/ajcn/34.6.1103
61. Ginsberg HN, Karmally W, Siddiqui M, Holleran S, Tall AR, Blaner WS, Ramakrishnan R. Increases in dietary cholesterol are associated with modest increases in both LDL and HDL cholesterol in healthy young women. *Arterioscler Thromb Vasc Biol.* 1995;15:169–178. doi: 10.1161/01.atv.15.2.169
62. Ginsberg HN, Karmally W, Siddiqui M, Holleran S, Tall AR, Rumsey SC, Deckelbaum RJ, Blaner WS, Ramakrishnan R. A dose-response study of the effects of dietary cholesterol on fasting and postprandial lipid and lipoprotein metabolism in healthy young men. *Arterioscler Thromb.* 1994;14:576–586. doi: 10.1161/01.atv.14.4.576
63. Illingworth DR, Hatcher LF, Pappu AS, Newcomb KC, Connor WE. Role of dietary cholesterol in the optimal diet for the treatment of hypercholesterolemia. *Can J Cardiol.* 1995;11(suppl G):115G–117G.
64. Johnson C, Greenland P. Effects of exercise, dietary cholesterol, and dietary fat on blood lipids. *Arch Intern Med.* 1990;150:137–141.
65. Quig DW, Thye FW, Ritchey SJ, Herbert WG, Clevidence BA, Reynolds LK, Smith MC. Effects of short-term aerobic conditioning and high cholesterol feeding on plasma total and lipoprotein cholesterol levels in sedentary young men. *Am J Clin Nutr.* 1983;38:825–834. doi: 10.1093/ajcn/38.6.825
66. Reaven GM, Abbasi F, Bernhart S, Coulston A, Darnell B, Dashti N, Kim H, Kulkarni K, Lamendola C, McLaughlin T, et al. Insulin resistance, dietary cholesterol, and cholesterol concentration in postmenopausal women. *Metabolism.* 2001;50:594–597. doi: 10.1053/meta.2001.22559
67. Mensink R. Effects of saturated fatty acids on serum lipids and lipoproteins: a systematic review and regression analysis. Geneva, Switzerland: World Health Organization; 2016.
68. Fung TT, McCullough ML, Newby PK, Manson JE, Meigs JB, Rifai N, Willett WC, Hu FB. Diet-quality scores and plasma concentrations of markers of inflammation and endothelial dysfunction. *Am J Clin Nutr.* 2005;82:163–173. doi: 10.1093/ajcn.82.1.163
69. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, Bray GA, Vogt TM, Cutler JA, Windhauser MM, et al. A clinical trial of the effects of dietary patterns on blood pressure: DASH Collaborative Research Group. *N Engl J Med.* 1997;336:1117–1124. doi: 10.1056/NEJM199704173361601
70. American Heart Association. Healthy living. https://www.heart.org/en/healthy-living. Accessed November 17, 2019.
71. American Heart Association. Cholesterol. https://www.heart.org/en/health-topics/cholesterol. Accessed November 17, 2019.