Scientists’ Comment on Dietary Cholesterol
To the Secretaries of the U.S. Department of Health and Human Services & the U.S. Department of Agriculture

The final Dietary Guidelines should advise Americans to limit their consumption of cholesterol-rich foods (primarily whole eggs and egg yolks) to lower their risk of heart disease and type 2 diabetes.

The 2015 DGAC’s conclusion that dietary cholesterol should no longer be considered a “nutrient of concern” has received considerable attention in the media and eggs are being trumpeted in an egg industry marketing campaign even before the 2015 DGA is released. However, we are concerned that the DGAC’s conclusion about dietary cholesterol is inconsistent with the AHA/ACC guidelines, evidence from clinical trials and cohort studies, and the overall dietary pattern recommended by the DGAC.

The DGAC states that it "will not bring forward [the recommendation in previous editions of the DGA to limit cholesterol to 300 mg/day] because available evidence shows no appreciable relationship between consumption of dietary cholesterol and serum cholesterol, consistent with the conclusions of the AHA/ACC report." However, the AHA/ACC did not conclude that there is no appreciable relationship between dietary and serum cholesterol. It concluded that “there is insufficient evidence to determine whether lowering dietary cholesterol reduces LDL-C.” The DGAC report did not present evidence to support its conclusion that there is “no appreciable relationship” between dietary cholesterol and serum cholesterol. In fact, that conclusion directly contradicts the AHA/ACC conclusion, which specifically states that “there are insufficient data to make a statement.”

The AHA/ACC’s conclusion is based on what it saw as insufficient research. In contrast, the DGAC’s conclusion misinterprets the alleged absence of evidence as the presence of evidence that high doses of cholesterol cause no harm. We question the scientific rigor and logic of that conclusion.

Contrary to the DGAC’s conclusion, dietary cholesterol is very much a “nutrient of concern,” because it increases LDL cholesterol, a well-established risk factor for coronary heart disease. Furthermore, the consumption of whole eggs is associated with the risk of type 2 diabetes and the risk of coronary heart disease (CHD) in people with diabetes. The Guidelines should clarify


that the healthy dietary pattern it recommends does not include one or more eggs per day. That message has been lost in the media frenzy over the DGAC’s decision to de-list cholesterol as a nutrient of concern. The Guidelines should counter the mistaken impression, created by the DGAC’s report, that consuming whole eggs in any quantity has been thoroughly investigated and deemed to be part of a healthy dietary pattern. In fact, the DGAC gave the public the green light to consume high levels of eggs based in part on cohort studies that never assessed those levels.

I. Dietary cholesterol increases the risk of heart disease and type 2 diabetes.

A. Risk of Heart Disease

1. Clinical studies

Clinical studies show that dietary cholesterol at levels that are commonly consumed by Americans raises serum LDL-cholesterol, a well-established risk factor for heart disease.

Weggemans et al. identified 17 studies—including 11 metabolic ward studies—involving 556 individuals conducted between 1974 and 1999. The diets were designed to maintain stable body weight. The authors’ meta-analysis found that for each additional 100 mg/day of dietary cholesterol, serum LDL cholesterol increased by roughly 2 mg/dL. Among the studies they included, 10 involved individuals who consumed an increase of 167 to 560 mg/day of cholesterol (see figure below). Those increases indicate that consuming one to three egg yolks per day would increase LDL by 4 to 12 mg/dL (0.10 to 0.31 mmol/l). The authors concluded that “the advice to limit the consumption of eggs and other foods rich in dietary cholesterol may still be important in the prevention of coronary heart disease.”

It should be noted that most participants in the studies included in the Weggemans et al. meta-analysis were normal-weight young adults. Few of those studies investigated the impact of dietary cholesterol on people who are middle-aged or older, who are overweight or obese, or who have diabetes, prediabetes, hypertension, or prehypertension, even though those groups comprise major segments of the U.S. population.

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In a 1997 meta-analysis of metabolic-ward studies, Clarke et al. concluded that 200 mg/day (equivalent to about one egg/day) of dietary cholesterol increases LDL cholesterol by roughly 4 mg/dL, a calculation that is consistent with Weggemans et al. (Only two studies on a total of 21 people were included in both meta-analyses).

The AHA/ACC report appeared to minimize the importance of the findings of Clarke et al. by noting that earlier meta-analyses were based on 6 studies on 128 participants and that “these studies predate our search.” There is absolutely no valid scientific justification for the AHA/ACC’s or DGAC’s ignoring studies that were done before 1997. Given the strict control of diets in metabolic-ward studies—and the relative paucity of recent metabolic ward studies—the results from those studies should be given extra credence.

In contrast to those meta-analyses, Griffin and Lichtenstein reviewed studies on the effect of dietary cholesterol on lipids conducted only between 2003 and 2013. They included only four studies that they categorized as assessing “dietary cholesterol supplementation while controlling for background diet” without weight loss, which applies to the vast majority of Americans. However, unlike the metabolic ward studies included in Clarke et al. and 11 of the 17 studies included in Weggemans et al., Griffin and Lichtenstein considered the background diet in those studies “controlled” if subjects were only told to follow a diet (e.g., an NCEP Step 1 diet or a “lacto-vegetarian” diet). Those diets are far

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7 The critical importance of dietary cholesterol in the induction of atherosclerosis was established in landmark animal studies by Anitschkow in 1933. Stamler, J., & Shekelle, R. (1988). Dietary cholesterol and human coronary heart disease. The epidemiologic evidence. *Archives of Pathology & Laboratory Medicine, 112*(10), 1032-1040.
less controlled than diets in studies where researchers provide all meals throughout the study. Furthermore, the studies had other limitations. One study tested egg consumption along with an endurance-training program.\textsuperscript{9} Another had a crossover design but no washout period.\textsuperscript{10} Two were funded by the egg industry, which could influence the results.\textsuperscript{11} The studies in that review should carry far less weight than the earlier, controlled, metabolic-ward studies, regardless of their date of publication.

Some researchers (often with ties to the egg industry) have claimed that 70% of the population are hypo-responders to dietary cholesterol.\textsuperscript{12,13} However, some studies classify subjects as hypo- or hyper-responders based on a single experiment.\textsuperscript{14} In fact, when Dutch researchers retested people who were classified as hypo- or hyper-responders after a single 2-week experiment, they found that much of the initial variation in response was due to chance intra-individual fluctuation.\textsuperscript{15} These results do not support sweeping claims that most Americans are hypo-responders to dietary cholesterol.

The findings of controlled trials on the effects of lipids on total and LDL-cholesterol are utilized in an online calculator constructed by Martijn Katan, a leader in the field of lipid research.\textsuperscript{16} The calculator shows that, based on clinical trials, one DV’s worth of cholesterol (300 mg) has about half the effect on LDL-cholesterol as one DV’s worth of saturated fat (20 grams). That estimate, and the well-controlled feeding studies that the calculator relies on, indicate that dietary cholesterol still is a significant contributor to coronary heart disease—and a “nutrient of concern.” Furthermore, recent evidence suggests that egg yolks may also cause cardiovascular disease because their phosphatidylcholine leads to the production of TMAO (trimethylamine-N-oxide), which promotes atherosclerosis.\textsuperscript{17}

2. Cohort studies (general population)

A number of cohort studies have examined the relationship between the consumption of dietary cholesterol or eggs and cardiovascular disease, and two meta-analyses have been conducted on cohort studies on egg consumption and the risk of heart disease, stroke, and diabetes.\textsuperscript{18,19} Neither meta-analysis found an association with eggs and stroke or heart disease. However, those cohort studies have serious limitations.

First, the range of egg consumption between the lowest- and highest-exposure groups was small, with people in the highest intake group typically consuming only one or more eggs per day. For example, in one U.S. study, only 6 percent of 37,851 men and 9 percent of 80,082 women consumed \textit{at least} 1 egg per day, and only 1.6 percent of women reported consuming 2 eggs or more per day.\textsuperscript{20} That narrow range limits the sensitivity of the studies. Furthermore, it means that the DGAC’s cholesterol conclusion, which was widely interpreted as a go-ahead to eat unlimited quantities of eggs, was based in part on cohort studies that never examined the impact of eating more than 1 egg per day. The DGAC has therefore sanctioned an egg-rich diet without acknowledging that it lacks evidence on the consequences of eating egg-rich diets.

Second, it is a tall order to expect that in cohort studies any single food is potent enough to have a marked effect on the risk of disease. Other studies have documented an association between disease or mortality and an entire category of foods, such as red meat. However, few studies attempt to discern an association between a single food, say hamburgers, and cardiovascular disease. If subjects are consuming a diet containing significant amounts of cholesterol and/or saturated fat from other sources (meat, poultry, seafood, dairy, baked goods), the cholesterol in eggs may not have sufficient impact to alter the risk of disease, just as the saturated fat in, say, butter may not have sufficient impact to alter the risk of disease. Furthermore, cohort studies rely on inexact dietary intake data, which reduces their sensitivity.

Despite those limitations, a 20-year cohort study of roughly 21,000 U.S. male physicians reported a 22 percent increased risk of all-cause mortality among men who did not have diabetes and who consumed at least 7 eggs per week.\textsuperscript{21} The same authors reported a 28 percent higher risk of heart failure among physicians who ate one egg per day and a 64 percent higher risk among those who ate at least two eggs per day.\textsuperscript{22} Similarly, when researchers tracked more than 14,000 African-American and white adults in the


\textsuperscript{20} Hu, F. B., Stampfer, M. J., Rimm, E. B., Manson, J. E., Ascherio, A., Colditz, G. A., et al. (1999). A prospective study of egg consumption and risk of cardiovascular disease in men and women. \textit{JAMA}, 281(15), 1387-1394. The median intake in the highest quintile was 0.79 eggs per day for men and 0.67 eggs per day for women.


Atherosclerosis Risk in Communities Study for 13 years, they found a 23 percent increased risk of heart failure for each serving of eggs consumed per day.\textsuperscript{23}

3. Cohort studies (people with type 2 diabetes)

Cohort studies have consistently reported that egg consumption is associated with a higher risk of heart disease or mortality in people with type 2 diabetes. For example, in a study of 1,941 adults aged 70 to 79, those who had type 2 diabetes and consumed eggs (possibly more than one per occasion) at least three times per week had five times the risk of incident CVD compared to those who consumed eggs less than once a week.\textsuperscript{24} Similarly, in a study that tracked 37,851 men for 8 years and 80,082 women for 14 years, men with diabetes who consumed one or more eggs per day had twice the risk of coronary heart disease—and women with diabetes had a 49 percent higher risk—than those who consumed less than one egg per week.\textsuperscript{25} When researchers tracked 21,327 male physicians for 20 years, the risk of all-cause mortality among those with diabetes was twice as high if they consumed at least five to six eggs per week versus if they ate less than 1 egg per week.\textsuperscript{26} And among 5,672 women with type 2 diabetes, every 200 mg of cholesterol per 1,000 calories was associated with a 37 percent higher risk of cardiovascular disease.\textsuperscript{27}

In two meta-analyses of those and/or other studies, Shin et al. reported that among people with diabetes, those who consumed the most eggs (at least one per day) had a 69 percent higher risk of CVD than those who consumed the least (less than 1 egg per week or never), while Rong et al. reported that people with diabetes who consumed the most eggs had a 54 percent higher risk of coronary heart disease than those who consumed the least.\textsuperscript{28}

The DGAC’s failure to describe the impact of dietary cholesterol on people with diabetes is irresponsible given that they comprise a large and growing segment of the population and have a greater risk of heart disease than others. Since 2001, health authorities including the National Heart, Lung, and Blood Institute have considered people with diabetes to have the same elevated risk of a cardiovascular event as those who have existing coronary heart disease. The risk of cardiovascular disease is 70 percent higher among people aged 20 or older with diagnosed diabetes than among others, according to

\textsuperscript{25} Hu et al., 1999.
\textsuperscript{26} Djoussé & Gaziano, 2008 (\textit{AJCN}).
\textsuperscript{28} Shin et al., 2013; Rong et al., 2013.
the CDC. Accordingly, cholesterol goals for people with diabetes (e.g., LDL less than 100 mg/dL) are far stricter than those for people without the disease.

Furthermore, diabetes is remarkably prevalent in the United States. An estimated 14 percent of men and 11 percent of women aged 20 or older have diabetes. However, an estimated 28 percent of these people are undiagnosed, according to the National Diabetes Statistics Report. Even if the Dietary Guidelines were to warn people with diabetes to limit their intake of whole eggs, the 8.1 million Americans with undiagnosed disease would have no way of knowing that frequent eating of eggs might raise their risk of CVD. That’s a reason to encourage the general population to limit their egg (yolk) intake.

Furthermore, an estimated 37 percent of adults aged 20 years or older—and 51 percent of those aged 65 or older—have prediabetes. To our knowledge, studies have not examined the association between egg consumption and risk of CVD in people with prediabetes. However, the sheer size of this at-risk group and the “diabetes tsunami” that experts predict in the coming years are cause for concern and another reason why the Dietary Guidelines should encourage the entire population to reduce consumption of cholesterol.

B. Risk of Diabetes

Egg consumption is consistently associated with a higher risk of type 2 diabetes. When researchers tracked 20,703 men in the Physicians’ Health Study for 20 years, those who consumed at least 7 eggs per week had a 58 percent higher risk of type 2 diabetes than those who consumed no eggs. Similarly, among 36,295 women who were followed for 12 years in the Women’s Health Study, those who consumed at least 7 eggs per week had a 77 percent higher risk of type 2 diabetes. In a meta-analysis of those and other studies that tracked more than 69,000 people for nearly 15 years, Shin et al. found that the people in the highest category of egg consumption (at least 1 egg per day) had a 42 percent higher risk of type 2 diabetes than those in the lowest category of consumption (less than 1 egg per week).

30 Rates increase with age, to 26 percent among adults aged 60 years and older, and are higher in African Americans (18 percent) and Hispanics (19 percent) than in non-Hispanic whites (10 percent). These percentages include people whose diabetes is undiagnosed. Scientific Report of the 2015 Dietary Guidelines Advisory Committee. Table D1.27, p. 92.
31 CDC, 2014
32 *Id.*
35 Egg consumption has not been linked to a higher risk of type 2 diabetes in Finnish and Japanese studies, possibly because the consumption of eggs in those populations is associated with unmeasured factors that lower the risk of diabetes. Virtanen, J. K., Mursu, J., Tuomainen, T. P., Virtanen, H. E., & Voutilainen, S. (2015). Egg consumption.
Those findings are especially troubling given the current prevalence of type 2 diabetes, which imposes an enormous economic and human toll. Diabetes increases the risk not just of heart disease and stroke but also of blindness, kidney disease, and amputations. Experts estimate that in 2012, the disease cost the nation $176 billion in direct medical expenses and $69 billion in indirect costs (disability, work loss, premature death). Despite these excessive costs, the DGAC ignored the evidence that dietary cholesterol may raise the risk of type 2 diabetes.

II. The DGAC’s dismissal of concerns about dietary cholesterol undermines its advice on healthy dietary patterns.

The DGAC’s conclusion that dietary cholesterol is not a nutrient of concern threatens to undermine the DGAC’s advice on dietary patterns. The key dietary pattern recommended by the DGAC is “rich in vegetables, fruit, whole grains, seafood, legumes, and nuts; moderate in low- and non-fat dairy products and alcohol (among adults); lower in red and processed meat; and low in sugar-sweetened foods and beverages and refined grains.” Although the pattern doesn’t include an unlimited quantity of whole eggs, many people may now believe that it does because of publicity following the release of the DGAC’s report.

The DGAC’s report provides “three USDA Food Patterns (Healthy U.S.-style, Healthy Vegetarian, and Healthy Mediterranean-style) at the 2000 calorie level.” Those patterns include only 3 eggs (3 oz.) per week. The patterns presumably limit eggs to conform to the DASH and OmniHeart clinical trials that provide strong evidence for the AHA/ACC’s and DGAC’s dietary pattern guidelines. The 2,100-calorie DASH and OmniHeart diets contained less than 150 mg of cholesterol per day. Similarly, the USDA Healthy Mediterranean-Style Pattern contains only 232 mg of cholesterol for a 2,000-calorie diet and the Healthy Vegetarian

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36 CDC, 2014.
37 Id.
39 DGAC Report, Table D1.32; Table 3, Appendix E-3.7.
40 The USDA Healthy Vegetarian Pattern allows 4 eggs per week for those who consume 2,800 calories per day and 1 to 2 eggs for those who consume 1,000 to 1,400 calories per day. DGAC Report, Table A1, Appendix E-3.7.
Pattern contains only 120 mg of cholesterol in a 2,000-calorie diet. USDA’s Food Patterns presumably limit eggs to leave room for the fruits, vegetables, and other foods in the DGAC’s healthy dietary pattern. Eggs are also limited in the Healthy Eating Index and in most variations of a Mediterranean diet, which, like DASH/OmniHeart diets, have been associated with a lower risk of disease. Therefore, it is critical that the DGA clarify that a healthy dietary pattern would contain only about three whole eggs per week.

Conclusion

In summary, the DGAC’s conclusion that dietary cholesterol is not a “nutrient of concern” is not based on the best scientific evidence available—that is, controlled clinical studies, especially metabolic-ward studies, demonstrating that dietary cholesterol raises LDL cholesterol, a known risk factor for heart disease. Furthermore, the DGAC relied on the AHA/ACC, rather than conduct its own review of studies on dietary cholesterol, yet the DGAC’s conclusion (i.e., there is “no appreciable relationship” between dietary and serum cholesterol) contradicts that of the AHA/ACC (i.e., there is “insufficient evidence” to determine whether lowering dietary cholesterol lowers LDL).

Moreover, the DGAC’s conclusions about dietary cholesterol have misled the public about a healthy intake of whole eggs. The DGAC ignored consistent evidence from cohort studies reporting that people who consume one or more eggs per day have an increased risk of type 2 diabetes and an increased risk of cardiovascular disease if they already have diabetes. By ignoring this evidence, the DGAC has led the public to believe that a healthy dietary pattern could contain an unlimited quantity of eggs, even though the DGAC’s own healthy dietary patterns allow only 3 whole eggs per week. It is crucial that the DGA correct these misconceptions.

Sincerely,

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43 The cholesterol levels in a Healthy Mediterranean-Style Pattern range from 92 mg/day for a 1,000-calorie diet to 300 mg/day for a 3,200-calorie diet. Cholesterol levels in a Healthy Vegetarian-Style Pattern range from 78 mg per day for a 1,000-calorie diet to 160 mg/day for a 3,200-calorie diet. DGAC Report, Tables B1, B2, Appendix E-3.7.
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