

Reconsidering the Importance of the Association of Egg Consumption and Dietary Cholesterol With Cardiovascular Disease Risk

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Nutrition research, in contrast with randomized clinical trials that compare a drug with placebo, is more difficult for many reasons, including complexities in data gathering and changes in human behavior over time. In this issue of *JAMA*, Zhong and colleagues¹ report new insights about a controversial topic, the association of egg consumption and dietary cholesterol with cardiovascular disease (CVD) incidence and all-cause mortality. Clearly, the topic of this study is important to clinicians, patients, and the public at large because the association of egg consumption and dietary cholesterol with CVD, although debated for decades, has more recently been thought to be less important. Compared with the meta-analyses and reviews previously published, this report is far more comprehensive, with enough data to make a strong statement that eggs and overall dietary cholesterol intake remain important in affecting the risk of CVD and more so the risk of all-cause mortality.

In the 2014 Lifestyle Guidelines from the American College of Cardiology/American Heart Association² and the 2015-2020 Dietary Guidelines for Americans,³ the association of dietary cholesterol with CVD was minimized. This was because the independent relationship of dietary cholesterol from eggs and other foods with plasma levels of low-density lipoprotein cholesterol (LDL-C) and CVD remained unproven and was deemed to be much less important than the well-substantiated effect of dietary saturated fat on levels of LDL-C, a major risk factor for atherosclerotic CVD. This position was further supported by a meta-analysis⁴ in which the heterogeneous nature of the clinical trials made it difficult to support a relationship among dietary cholesterol, plasma levels of LDL-C, and CVD risk. In an accompanying editorial,⁵ some caution was raised using several lines of evidence. First, there are high-quality clinical research studies in humans,^{6,7} wherein all components of the diet other than the cholesterol content were well controlled. In these trials, increasing amounts of eggs and dietary cholesterol produced incremental increases in LDL-C. Second, a decrease in coronary heart disease (CHD) events following recommendations for dietary cholesterol reductions (from <300 mg to <200 mg daily) has been reported.⁸ Third, there is epidemiological evidence that dietary cholesterol intake in patients with diabetes may incur more CVD harm.^{8,9} Conversely, the limitations in applying the evidence of egg consumption on CVD risk and the need for future studies, including studies of the genetic basis of cholesterol intake on CVD risk, were also recently reviewed.¹⁰

In the report by Zhong et al,¹ a harmonized approach was used to analyze self-reported baseline nutritional data on macronutrient intake in 29 615 adults from 6 prospective US cohorts, a group with high racial and ethnic diversity, to examine cardiovascular disease outcomes over a median of 17.5 years. The main finding was that higher consumption of eggs and dietary cholesterol (which included eggs and meats) was significantly associated with incident CVD and all-cause mortality, with a dose-response relationship. Another important finding in the study was that associations between dietary cholesterol and incident CVD and all-cause mortality were no longer significant after adjusting for consumption of eggs and processed and unprocessed red meat. Moreover, the dietary cholesterol content of eggs fully explained the association between egg consumption and incident CVD and largely explained the association between egg consumption and all-cause mortality.

Despite the limitation of using only 1 set of baseline dietary intake data to predict observations up to 30 years later, a major strength of the analysis was the stringent categorization of dietary constituents to isolate the independent relationships of dietary cholesterol and eggs with CVD outcomes. Although all cohorts used different dietary assessment tools (except the 2 Framingham cohorts), this issue was addressed by implementing a rigorous methodology to harmonize dietary data, performing cohort-stratified analyses, and conducting several sensitivity analyses. The result is that other unhealthy behaviors associated with more egg consumption, such as variations in saturated vs monounsaturated and polyunsaturated fat consumption, tobacco use, physical activity *z* score, presence or absence of diabetes, body mass index, and dietary patterns were accounted for in the various models. Importantly, the recent emphasis on advocating dietary patterns (ie, the Mediterranean-style dietary pattern or Dietary Approaches to Stop Hypertension [DASH]) rather than specific foods to reduce CVD risk is not only sufficiently evidence based to be recommended by guidelines,^{2,3} but also these dietary patterns were recently ranked as best diets for 2019.¹¹ Yet, Zhong et al¹ found that the effect of egg and dietary cholesterol remained after considering the beneficial effect of a heart-healthy dietary pattern, an issue that hopefully will not discourage implementation or continuation of such healthful dietary patterns. In addition, although 4882 members of the study cohorts were excluded for missing data, their absence in the analysis failed to materially affect the findings.

An important reminder is that the data and findings in the study by Zhong et al¹ are observational and reflect associations

only, not cause and effect. Nonetheless, of interest is how these data relate to current consumption of eggs and free cholesterol in the United States. Considering that the average individual in the United States consumes approximately 295 mg of cholesterol daily, including 3 to 4 eggs per week,¹² the adjusted hazard ratio (HR) for incident CVD (1.06; 95% CI, 1.03-1.10) and for all-cause mortality (1.08; 95% CI, 1.04-1.11) associated with an additional one-half egg per day were modest, raising the question of whether these levels of statistical significance are clinically important. However, excessive egg and cholesterol intake appear to be more important in individuals who consume many more eggs and much higher amounts of dietary cholesterol. For instance, for those who consumed 2 eggs per day rather than 3 to 4 eggs per week, the HR for incident CVD was 1.27 (95% CI, 1.10-1.45) and for all-cause mortality was 1.34 (95% CI, 1.15-1.52). For individuals who consumed 600 mg of cholesterol per day, the HR for CVD was 1.37 (95% CI, 1.19-1.59) and for all-cause mortality was 1.38 (95% CI, 1.22-1.58). Estimating from Figure 1 in the article by Zhong et al,¹ approximately 2% of individuals in the study consumed at least 600 mg of cholesterol daily, and approximately 2% had intakes of at least 2 eggs per day.

However, the relationships between egg consumption or cholesterol intake with plasma lipids and lipoproteins were not assessed, yet the presumed increase in CVD risk would be secondary to higher levels of LDL-C. When healthy young men consumed 0, 1, 2, or 4 eggs per day for 8 weeks in a clinical trial in which daily cholesterol intake ranged from 128 to 858 mg, total plasma cholesterol and LDL-C increased in parallel by 1.5 mg/dL for every 100 mg of dietary cholesterol added to the diet.⁶ In women, the effect was greater, with increases in LDL-C of 2.1 mg/dL per 100 mg of dietary cholesterol per day when 0, 1, or 3 eggs per day were consumed and dietary cholesterol intakes ranging from 108 to 667 mg per day were provided.⁷

Zhong et al¹ also examined the association of egg consumption and dietary cholesterol with all-cause mortality. Not surprisingly, dietary cholesterol consumption was significantly associated with CVD mortality (adjusted HR, 1.22 [95% CI, 1.07-1.39]). However, an unanswered question remains: to what mechanism was the association between dietary cholesterol intake and non-CVD causes of death (adjusted HR, 1.16 [95% CI, 1.08-1.26]) attributable? In this study, an adjudication process was not used to define this important and statistically meaningful relationship. Because some cohorts included a small percentage of patients with cancer, it is of interest that an association of dietary cholesterol intake with colon cancer mortality has been documented, and this association was independent of dietary fat quantity and quality.¹³ However, in the study by Zhong et al,¹ there were no data on cancer death or types of malignancy.

The authors suggest that the meaning of their work is that “among US adults, higher consumption of dietary cholesterol or eggs was significantly associated with higher risk of incident CVD and all-cause mortality in a dose-response manner.” Overall, the strength of these relationships is modest, but higher consumption of cholesterol or eggs substantially above the median was associated with a monotonic increase in CVD incidence and all-cause mortality. At the population level, this is an important finding. The association between egg consumption and dietary cholesterol with CVD events and mortality may be mediated by higher levels of LDL-C, but such an increase is not always seen,¹⁴ and the mechanism of the observed association with non-CVD mortality remains to be defined. Considering the negative consequences of egg consumption and dietary cholesterol in the setting of heart-healthy dietary patterns, the importance of following evidence-based dietary recommendations, such as limiting intake of cholesterol-rich foods, should not be dismissed.

ARTICLE INFORMATION

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