Egg consumption: to eat or not to eat?

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Hypercholesterolemia has been recognized as a key risk factor for cardiovascular disease (CVD) (1). Up to 70% of circulating cholesterol is synthesized endogenously, while the remainder comes from dietary sources (2). Whether eating foods rich in cholesterol is independently associated with CVD and mortality has been the subject of intensive research for many years, with a plethora of observational studies reporting equivocal results (3-5). Several meta-analyses tried to shed light on this vexing topic, but were flawed by major methodological drawbacks, leading ultimately to inconsistent conclusions (6,7). The heterogeneous nature of the observational studies, which made the quantitative synthesis of their results problematic, and the potential for significant residual confounding (i.e., tobacco use, unhealthy dietary patterns) have rendered the results of those meta-analyses prone to bias. Therefore, the association between dietary cholesterol and CVD has been an open question.

Recently, Zhong *et al.* circumvented the inherent limitations of meta-analyses based on aggregate data by pooling together individual-level data from 6 US based cohorts and exploring the association of dietary cholesterol with CVD and mortality in the pooled data (8). A standardized protocol was used to harmonize self-reported diet data obtained from 29,615 participants, who were followed-up for mortality or incident CVD over a median of 17.5 years. The major finding of this study was that consuming more eggs or dietary cholesterol was associated with higher risk of CVD. Specifically, after adjusting for important confounders, the adjusted hazard ratio (HR) was 1.06 (95% CI, 1.03–1.10) for each additional half an egg consumed daily and 1.17 (95% CI, 1.09–1.26) for each additional 300 mg of dietary cholesterol consumed daily. The corresponding adjusted HRs for all-cause mortality were 1.08 (95% CI, 1.04–1.11) and 1.18 (95% CI, 1.10–1.26). The authors observed a dose-response association between the exposures of interest and outcomes. Interestingly, egg consumption was not an independent predictor of CVD or mortality when models were adjusted for dietary cholesterol. This intriguing finding could be explained by the qualitative characteristics of non-egg cholesterol sources, as egg-derived cholesterol was less than 25% of total dietary cholesterol. We will further elaborate on this interesting observation below.

Zhong and colleagues should be commended for performing an individual-level data meta-analysis with a comprehensive statistical approach (i.e., cohort-stratified, cause-specific hazard models, sensitivity analyses) which allows to draw more solid conclusions. The authors nicely evaluated the independent association of dietary cholesterol with incident CVD and all-cause mortality, adjusting for demographic, socioeconomic, and behavioral-lifestyle factors (e.g., variations in saturated *vs.* monounsaturated and polyunsaturated fat consumption, low physical activity, tobacco use and diabetes mellitus) in a number of comprehensive multivariate models (8). Notably, the unfavorable effects of eggs and dietary cholesterol were similar between patients who consumed a higher quality diet and those who did not. This important and novel

information further supports the recommendation that dietary cholesterol intake should be minimized, even when a healthier dietary pattern is adopted.

However, the study by Zhong *et al.* has some limitations that merit discussion (8). First, a meta-analysis of observational data is still observational evidence and therefore causality should not be lightly inferred from these data, especially considering that dietary patterns are complex behavioral exposures and isolation of a single dietary element is challenging. Second, only a single assessment of egg and dietary cholesterol consumption was used to predict mortality and cardiovascular outcomes after a considerably long follow-up period (up to 30 years). Although eating habits are difficult to break, and despite the fact that the authors performed sensitivity analysis by censoring participants at different time points, this long-term follow-up may have introduced a degree of misclassification bias. Of note, left- or right-truncating follow-up cannot remedy this type of bias. Third, the impact of dietary cholesterol on circulating lipoproteins [e.g., low-density lipoprotein (LDL)] was not assessed and was not accounted for in multivariate analysis. A recent meta-analysis showed a significant increase in both serum cholesterol and LDL cholesterol when comparing intervention with control doses of dietary cholesterol (net change: 11.2 mg/dL and 6.7 mg/dL, respectively) (6). Finally, although an association between dietary cholesterol and circulating LDL cholesterol can partially explain the higher risk for CVD experienced by patients who consume more eggs or dietary cholesterol, it cannot explain the association between dietary cholesterol and non-cardiovascular mortality reported by Zhong *et al.* This intriguing observation merits a deeper discussion.

Recently, research has convincingly demonstrated the effect of nutrition on human gut microbiota, which has been implicated in the pathogenesis of various cardiovascular and non-cardiovascular conditions (e.g., atherosclerosis, obesity) through a number of metabolites (9). Interestingly, dietary phosphatidylcholine, which mainly comes from eggs, has been shown to exert negative effects on all-cause and cardiovascular mortality via increased circulating levels of microbiome-derived metabolites such as the atherogenic metabolite trimethylamine-N-oxide (TMAO) (10). In addition, carnitine, which is an abundant nutrient in red meats, provides to gut microbiota another important substrate for the production of TMAO (11). Similarly, the long known association of dietary heme from red meats with carcinogenesis has been recently shown to be mediated by intestinal microbiota that proliferate in the presence of heme

and cause hyperplasia and hyperproliferation (12). Therefore, gut microbiome and its nutrition-driven metabolites may be a missing link that can explain both the superseding impact of dietary cholesterol on CVD and mortality reported by Zhong and colleagues as well as the reported association with non-cardiovascular mortality. Based on these observations, it is reasonable to conclude that sources of dietary cholesterol should be explicitly recorded in future clinical studies evaluating the association of nutrition with outcomes.

From a clinical perspective, moderation of egg consumption, along with other sources of dietary cholesterol, seems prudent for adults of all ages based on the findings of the study of Zhong and colleagues. Future studies should elucidate the interplay between sources of dietary cholesterol and other nutrients that may moderate the impact of these sources on cardiovascular morbidity and mortality in what is considered a healthy diet, e.g., a Mediterranean-type diet. For example, in the Spanish European Prospective into Cancer and Nutrition (EPIC-Spain) study, moderate egg consumption, up to 1 egg per day, was not associated with mortality from CVD or cancer. Finally, it is important to stress that precautions about eggs and dietary cholesterol do not apply to children and adolescents, as eggs are an excellent and accessible source of nutrients for growth and development. Early introduction of eggs leads to significantly improved growth (13).

Despite these limitations, Zhong and colleagues convincingly demonstrated a strong association between dietary cholesterol and CVD and mortality in the U.S population. Further studies are needed to evaluate whether such conclusions can be extrapolated to other populations as dietary patterns are difficult to disentangle. Until more definitive data is available, future guidelines should stress the importance of a well-balanced diet as an important and inextricable part of a healthy lifestyle, albeit without strict limitations until more evidence becomes available.

Acknowledgments

Footnote

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