appear to contradict the results from a meta-analysis of long-term observational studies that showed that the benefits of nuts may be saturated at certain amounts (3). It would be more informative to further show the curves by restricting the analyses to the RCTs instead of all trials, given the fact that nonrandomized trials showed greater effects in most of their subanalyses.

In sum, the study by Del Gobbo et al. (5) represents an interesting and important study that showed a cholesterol-lowering effect of nut consumption, a mechanism by which nuts may exert their health effects. However, it is notable that the trials included in the meta-analysis are of relatively short durations, and a recent Cochrane systematic review (10) that considered RCTs of ≥3 mo claimed “very limited evidence for the effects on CVD risk factors.” Thus, additional long-term, well-designed RCTs that investigate the effects of nut supplementation on risk factors for, and primary prevention of, CVD are still required.

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Guo-Chong Chen
Zhong-Xiao Wan
Li-Qiang Qin

From the Department of Nutrition and Food Hygiene, School of Public Health (G-CC, Z-XW; L-QQ, e-mail: qinliqiang@suda.edu.cn), Soochow University, Suzhou, China.

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Reply to G-C Chen et al.

Dear Editor:

We concur with Chen and colleagues that observational studies have potential limitations that might limit inference on cause and effect. All study designs, including randomized trials and experimental studies, have potential limitations. Because the limitations across these study designs are different and complementary, strong evidence for causal effects is derived not from any single study design but when concordant findings are seen across diverse types of investigations (1). This reflects true “evidence-based medicine” in which all of the evidence, including consistency, strength, and limitations of diverse individual studies, is considered to derive conclusions on cause and effect. In this case, our meta-analysis of controlled trials provides additional convincing evidence that tree nut consumption lowers the risk of coronary artery disease (CAD) (2, 3).

Our results, long-term prospective cohorts, or the PREDIMED (Prevención con Dieta Mediterránea) trial do not suggest that such benefits are limited to subjects with dyslipidemia. We identified no significant differences in the effects of nuts on blood lipids or lipoproteins among subjects with or without dyslipidemia. Similarly, in PREDIMED, both Mediterranean diet arms (supplemented with tree nuts or extra-virgin olive oil) showed reduced cardiovascular events, without significant heterogeneity among participants with dyslipidemia, hypertension, or adiposity (Table S10 in reference 3). Chen and colleagues focus on selected nonsignificant findings from subgroup analyses in PREDIMED; such observations are speculative and should be undertaken with great caution.

We are uncertain why Chen and colleagues cite the meta-analysis on nuts and incident CAD by Afshin et al. (2) as evidence that benefits may saturate at certain levels. A potential nonlinear effect was not evaluated in that investigation, and visual inspection of individual study results in that report does not suggest any apparent threshold effect for CAD (2). In our present study, dose-response analyses suggested a nonlinear effect of nut consumption on total and LDL cholesterol, with stronger effects at >60 g/d (4). However, we highlighted that 4 of 5 trials that had such high intakes were nonrandomized and that additional randomized trials that use such doses were required for confirmation.

In the meta-analysis by Afshin et al. (2) on nuts and incident CAD, the median observed consumption in the highest categories was ~24 g/d, and in PREDIMED it was ~41 g/d (5). Given that the average global nut consumption is only ~9 g/d, and that only 26 countries (representing <10% of the global adult population) even have average consumption amounts as high as 16 g/d (four 1-ounce servings/wk) (6), the immediate public health relevance of much higher intakes (e.g., ≥60 g/d) appears to be small.

In our present study (4), we calculated the estimated CAD benefit of tree nuts on the basis of the identified LDL-lowering effect to represent a risk reduction of ~4% per daily serving (similar to Chen et al.’s calculations). Notably, the estimated CAD benefit on the basis of our identified apolipoprotein B–lowering effect was 50% larger: ~6% lower risk per daily serving. Both of these predicted effects are smaller than benefits observed in PREDIMED and prospective studies (2, 3). These larger effect sizes in studies of clinical
events are consistent with additional, nonlipid benefits of tree nut consumption, as previously summarized (2, 4).

Chen and colleagues correctly surmise that the trials in our meta-analysis were short in duration (range: 3–26 wk; median: ~4 wk). These intervention periods are sufficiently long, however, to establish stable endpoint measurements for plasma lipids and lipoproteins (7); and long-term studies of nut intake and clinical events have already been performed (2, 3, 5). On the basis of our findings and this earlier body of evidence, CAD benefits of nut consumption are well established. Additional studies of the effects of nuts on other risk pathways and other clinical endpoints, as well as experimental elucidation of specific active ingredients and relevant molecular mechanisms, are a priority for future investigations.

G. K. Stein, S. M. Molnar, J. M. Menkes, D. M. Mozaffarian

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From the Stanford School of Medicine (LCDG, e-mail: delgobbo@stanford.edu), Palo Alto, CA; the Life Sciences Research Organization, Bethesda, MD (MCF, RF, and KL); and the Friedman School of Nutrition Science and Policy, Tufts University, Boston, MA (DM).

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