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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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, strengths, 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 PREMIDED (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 PREMIDED, 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 PREMIDED; 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 PREMIDED 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 PREMIDED 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.

DM reported ad hoc honoraria or consulting fees from Bunge, the Haas Avocado Board, Amarin, Astra Zeneca, Boston Heart Diagnostics, Global Organization for EPA and DHA Omega 3s, and Life Sciences Research Organization (LSRO) and chapter royalties from UpToDate. LCDG received modest ad hoc consulting fees from LSRO to support the meta-analysis. MCF, RF, and KL received payment through LSRO (~5% of gross income) to conduct a review of nuts and cardiovascular health outcomes, which was funded through a contract with the International Tree Nut Council (ITNC). No author has stock or ownership in the ITNC. The ITNC (which was funded through a contract with the International Tree Nut Council (ITNC). No author has stock or ownership in the ITNC. The ITNC had no role in the study design, data collection and analysis, decision to publish, or preparation of the original article or this reply.

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Decrease in hunger and desire to eat: taste effect or the osmolar concentration?

Dear Editor:

Because the prevalence of obesity is increasing worldwide and it is an important risk factor for chronic diseases such as type 2 diabetes, cardiovascular diseases, and cancers, treatment of obesity has been an area of great interest. I am really interested in obesity treatment and novel methods to reduce weight. Van Avesaat et al. (1) proposed a new way to reduce food intake by intraduodenal infusion of noncaloric tastants that is a noteworthy way to achieve weight reduction. This study recommends the use of noncaloric tastants to reduce food intake. This is really interesting and researchers can study a variety of methods related to this strategy.

Although van Avesaat used similar volumes for each tastant solution, the osmolar concentration of the solutions were obviously different, or the rate of infusion was similar for all of the tastants with different osmolarities. If we investigate the concentrations and osmolarities, we observe that the osmolarity of umami and the combination of tastants (153 and 168 mOsmol/L, respectively) was significantly higher than that of bitter and sweet tastants (3 and 1 mOsmol/L, respectively). In the results, we saw that only umami and the combination of tastants had an effect on decreasing hunger and desire to eat and increasing satiety, and it may be that it was the effect of the concentrations and not of the tastant. Van Avesaat et al. did not mention this tip anywhere, despite its importance. So I think it is important to propose this important tip to researchers to design a new study and match the concentrations of tastant solutions or select a reasonable infusion rate according to variety of osmolarity. Perhaps the above-mentioned design will show new insight and provide new information about the effect of the concentration reached at every site in the gastrointestinal tract on hormone release and neural pathways or detect a novel signaling pathway for hunger, satiety, or other variables used in the study by van Avesaat et al.

I also have some comments about the study design and statistical analysis used by van Avesaat et al. First, it may be possible that hormone release or hormone response on the receptor area is affected by fat mass (2). We know that fat mass in individuals with normal BMI may exceed the range that is usually classified as normal-weight obesity or latent obesity. (3). Therefore, greater adiposity may interfere with hormone function, and we should consider fat mass in addition to BMI and waist circumference as adiposity indexes, considering that BMI alone is not a suitable index for assessing obesity in an individual. Second, smoking is a risk factor for taste receptors or their morphology (4, 5), and in future studies we should select study participants more carefully and clarify smoking status and history in detail. Third, Helicobacter pylori infection should be included in exclusion criteria, because it has an effect on taste perception (6). Fourth, van Avesaat et al. reported a period of 7 d before the beginning of the study and provided no information about this period. It would be better if a food record were used in this period in future studies to get information about participants’ dietary habits and habitual intake. Fifth, van Avesaat et al. used a simple test for evaluating the taste perception of the participants; it