Nut consumption, lipid profile, and health outcomes

Dear Editor:

Nuts are nutritionally rich foods. Accumulating evidence from prospective observational studies has shown significant inverse associations of nut consumption with various health outcomes including all-cause mortality (1, 2), and total and fatal ischemic heart disease (1–3), although the associations with risks of stroke (1–3), type 2 diabetes (2, 3), and cancer (2) are less consistent. Yet, observational studies lack the random allocation of an intervention that is necessary to prove a causal link between exposure and outcome and are subject to the problems of measurement error, dilution bias, and in particular, potential confounders (4).

Recently, Del Gobbo et al. (5) evaluated the effects of tree nut consumption on several potential risk factors for CVD in adults without prevalent CVD in their meta-analysis of 42 randomized controlled trials (RCTs) and 19 nonrandomized trials, with interventions ranging from 3 to 26 wk (median: 4 wk). They reported that nut consumption significantly reduced total cholesterol, LDL cholesterol, apolipoprotein B, and triglycerides (restricted to nonrandomized trials), with no effects on blood pressure (BP) and other outcomes. Also in a recent issue of the Journal, Mohammadifard et al. (6) reported no overall effects of nuts on BP, despite a slight reduction in systolic BP among subjects without type 2 diabetes by consumption of all types of nuts, and reductions in both systolic and diastolic BP by pistachios. A third report by Flores-Mateo et al. (7) showed neutral effects of nut consumption on adiposity indexes, including body weight, BMI, and waist circumference.

In a large Spanish trial [PREDIMED (Prevención con Dieta Mediterránea)] (8) in 7447 participants at high risk of CVD, a Mediterranean diet supplemented with 30 g mixed nuts/d was found to be significantly associated with a 28% lower risk of CVD after a median follow-up of 4.8 y. Accordingly, the observed cardiovascular benefits appeared to be limited to the subjects with dyslipidemia (P-interaction = 0.07), whereas the differences were less pronounced when considering hypertension status (P-interaction = 0.15) and other baseline characteristics such as BMI (P-interaction = 0.94), waist circumference (P-interaction = 0.93), or diabetes status (P-interaction = 0.88). These observations may further indicate that nut consumption may reduce CVD through a cholesterol-lowering effect.

Del Gobbo et al. (5) reported that the reductions in LDL cholesterol associated with nut consumption of 1 serving/d were 4.8 mg/dL in all participants and 4.4 mg/dL in the participants with higher baseline LDL cholesterol (>130 mg/dL). According to data on subgroups of participants without CVD from the Cholesterol Treatment Trialists' Collaborators study (9), a meta-analysis of individual data from 27 randomized trials evaluating the efficacy and safety of statins treatment, we estimated that this reduction in LDL cholesterol could confer a 1.1% reduction in all-cause mortality, a 3.2% reduction in total CVD, and a 1.8% reduction in CVD mortality among subjects with high LDL cholesterol (**Table 1**).

Del Gobbo et al. (5) further highlighted nonlinear dose-response relations between nut consumption and total and LDL cholesterol, with curves for the associations becoming steeper after the consumption of 60 g nuts/d. These observations make sense, but they

TABLE 1
Estimated reductions in all-cause mortality, total CVD, and CVD mortality corresponding to reductions in LDL cholesterol associated with nut consumption of 1 serving/d[1]

	CTT Collaboration (9)	Del Gobbo et al. (5)
Design	Meta-analysis of individual data from 27 randomized trials	Meta-analysis of 61 controlled trials
Interventions	Regular statin therapy	Nuts per 1 serving/d
Subgroups	Participants without CVD[2]	Adults without CVD but with higher LDL cholesterol[3]
Mean/median duration	4.8 y	4 wk
Baseline LDL cholesterol, mmol/L	3.70[4]	≥3.362
Reductions in LDL cholesterol, mmol/L	1.00	0.113
RR (95% CI)		
All-cause mortality	0.91 (0.85, 0.97)[5]	0.989 (0.982, 0.997)[6]
Total CVD	0.75 (0.70, 0.80)[5]	0.968 (0.960, 0.975)[6]
CVD deaths	0.85 (0.77, 0.95)[5]	0.982 (0.971, 0.994)[6]

[1] CTT, Cholesterol Treatment Trialists'; CVD, cardiovascular disease.
[2] To be comparable with the meta-analysis by Del Gobbo et al. (5), results from subgroups of participants without CVD were selected.
[3] To be comparable with the CTT Collaboration, results from subgroups of participants with higher baseline LDL cholesterol (>130 mg/dL) were selected.
[4] Mean value for all participants (SD: 0.7 mmol/L).
[5] Reported risk estimates for participants without history of CVD.
[6] Estimated RRs corresponding to reductions in LDL cholesterol associated with nut consumption of 1 serving/d.

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.

None of the authors had a conflict of interest.

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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 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