Letters to the Editor

Nut consumption decreases risk of some diseases

Dear Sir:

We read with interest the recent meta-analysis of nut consumption and risk of cardiovascular disease and type 2 diabetes (1). The authors reported that high consumption of nuts decreased the risk of coronary artery disease and hypertension but not stroke or type 2 diabetes. A meta-analysis in this field is very important because the results have been inconsistent, and the authors clarified this association. However, 2 of the studies (2, 3) might not be suitable to be included in their meta-analysis because both reported the association between intake of nuts plus fruit and risk of coronary artery disease. However, after exclusion of those 2 studies, the pooled RR and 95% CI of a 1-serving/d increase did not substantially change the findings (RR: 0.76; 95% CI: 0.66, 0.88).

Neither of the authors declared a conflict of interest.

Min Zhao

Department of Nutrition and Food Hygiene
School of Public Health
Shandong University
44 Wenhuaxi Road
Jinan
China
E-mail: zhaomin1986zm@126.com

Wenhui Liu

Information and Data Analysis Laboratory
School of Public Health
Shandong University
Jinan
China

REFERENCES

1. Zhou D, Yu H, He F, Reilly KH, Zhang J, Li S, Zhang T, Wang B, Ding Y, Xi B. Nut consumption in relation to cardiovascular disease risk and type 2 diabetes: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2014;100:270–7.
2. Key TJ, Thorogood M, Appleby PN, Burr ML. Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. BMJ 1996;313:775–9.
3. Trichopoulou A, Bamia C, Trichopoulos D. Mediterranean diet and survival among patients with coronary heart disease in Greece. Arch Intern Med 2005;165:929–35.

doi: 10.3945/ajcn.114.091942.

Reply to M Zhao and W Liu

Dear Sir:

We thank Zhao and Liu for their comments. We agree that our published meta-analysis (1) included 2 potentially ineligible studies that used nuts and fruit in combination as the exposure variable. However, as stated by Zhao and Liu, the inclusion of both studies did not affect our results and the association was even stronger after exclusion of those 2 studies.

Neither of the authors declared a conflict of interest.

Donghao Zhou

Department of Endocrinology
Linyi People's Hospital
Linyi
China

Bo Xi

Department of Epidemiology and Health Statistics
School of Public Health
Shandong University
44 Wenhuaxi Road
Jinan
China
E-mail: xibo2007@126.com

REFERENCE

1. Zhou D, Yu H, He F, Reilly KH, Zhang J, Li S, Zhang T, Wang B, Ding Y, Xi B. Nut consumption in relation to cardiovascular risk and type 2 diabetes: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2014;100:270–7.

doi: 10.3945/ajcn.114.092239.

Vitamin D supplementation in African Americans: dose-response

Dear Sir:

We appreciate the important work from Ng et al (1) characterizing the dose-response relation between vitamin D intake and changes in serum 25-hydroxyvitamin D [25(OH)D] concentrations in African Americans. We are, however, concerned that their approach has resulted in considerable overestimation of the intake of vitamin D needed by this population group. Specifically, the researchers' a priori determination that vitamin D adequacy is achieved when 97.5% of the population achieves serum concentrations of 20 ng/mL—the

concentration linked to the Recommended Dietary Allowance (RDA) value of the Dietary Reference Intakes (DRIs)—is a misuse of the RDA reference value as outlined by the Institute of Medicine (2, 3) and as discussed by others (4–6).

In short, the definition of adequacy used by Ng et al is inappropriate for application to population groups. One cannot infer that persons with measures below the RDA—or in this case, the RDA-associated serum concentration—are inadequate, because, by definition, the RDA-associated serum concentration reflects a value that exceeds the needs of most individuals (2). Many persons below the RDA value have adequate status because a dose-response (or intake-adequacy) relation reflects a distribution of values across a population. Given this inherent variability, the appropriate approach to achieve a low prevalence of inadequacy within a population group—as verified by statistical modeling—is to shift the intake distribution so that most of the population (97.5%) has intakes above the Estimated Average Requirement (EAR), not above the RDA (3). The same approach applies to achieving serum values above the EAR-associated value, not above the RDA-associated value (6).

Therefore, the approach taken by Ng et al (1) should have been to estimate how much vitamin D is needed to ensure a low prevalence of serum 25(OH)D concentrations below that specified as the EAR-associated value (ie, 16 ng/mL), not how much is needed to ensure that 97.5% of the population group achieves serum concentrations associated with a cutoff defined as the RDA-associated measure (ie, 20 ng/mL). The latter approach ''forces'' the majority of the population group to achieve serum concentrations that are greater, often considerably greater, than those needed to ensure adequacy, and in turn artificially inflates the needed increase in intakes of the group being studied. As can be seen in Figure 3 of Ng et al, a notably lower dose would have been suggested if the solid line had been drawn at 16 ng/mL, rather than at 20 ng/mL. The Ng et al analysis will be of much interest to those working in the vitamin D field and should therefore be corrected to reflect the intake amount needed to reduce the number of African Americans with serum 25(OH)D concentrations $<$16 ng/mL.

This misapplication of the RDA value is not unique to this research group (5), and clearly it is tempting to use the RDA-associated serum concentration as the goal to ensure adequacy for nearly all. This approach, however, is not only inconsistent with the Institute of Medicine–recommended methodology that considers the variability in requirements within a population, it also increases the possibility of adverse effects if it results in a proportion of the population's intakes above the Tolerable Upper Intake Level (UL). To illustrate this possibility, data published elsewhere for adults aged 19–70 y from NHANES 2005–2006 (6) are shown in **Figure 1**, which includes the DRI-established requirement distribution for serum 25(OH)D (dashed line) and the current observed serum 25(OH)D distribution for adults aged 19–70 y (solid line). Also shown in Figure 1 is the effect of shifting the current observed distribution so that all but 2.5% achieve the RDA-associated concentration (dotted line, without adjustment for a potential nonlinear relation between intake and serum increases). Some members of the population are likely to exceed the UL. Serum 25(OH)D concentrations approaching the UL may be of particular concern for African Americans. A recent publication (7) confirmed a reverse J-shaped association between 25(OH)D and all-cause mortality for NHANES participants and also showed an increased risk of mortality in non-Hispanic blacks that exceeded that for non-Hispanic whites at serum 25(OH)D concentrations of 40–47.6 ng/mL (RR: 2.1 in blacks compared with 1.1 in whites) and at $\geq$48 ng/mL (RR: 2.4 for blacks compared with 1.6 for whites; referent is 30–39.6 ng/mL). Although these risk estimates may not differ statistically (likely reflecting the small sample size of non-Hispanic blacks), the point estimates suggest a basis for concern for greatly increased serum 25(OH)D concentrations among this population group.

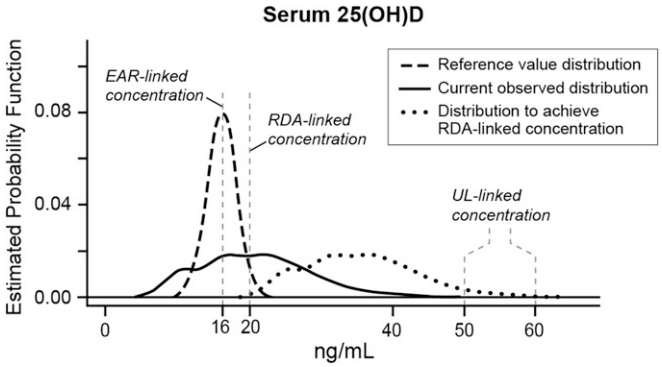

FIGURE 1. Serum 25(OH)D reference distribution with a comparison of observed serum 25(OH)D concentrations for adults aged 19–70 y in NHANES 2005–2006 (n = 3871) with the observed distribution shifted so that 97.5% of the sample achieve 20 ng/mL. The reference distribution was derived by using the mean (95th percentile) specified by the Institute of Medicine (2) with a calculated SD = 5.0 nmol/L on the basis of normality. The estimated probability function indicates the frequency of each concentration in the sample. Adapted from reference 6. EAR, Estimated Average Requirement; RDA, Recommended Dietary Allowance; UL, Tolerable Upper Level; 25(OH)D, 25-hydroxyvitamin D.

In addition, we note that Ng et al (1) did not take into account another key component in the setting of DRIs. That is, the nutrient dose-response relation must reflect the total exposure rather than an added exposure superimposed on an undefined underlying exposure. Their study as designed focused only on the contribution from the supplements administered; it failed to account for the ''background'' intake from dietary sources. Background vitamin D intake is not insignificant [estimated at 200–428 IU/d for age groups $\geq$1 y (6)] and, importantly, baseline vitamin D intake appears to alter the dose-response relation (8).

Finally, in considering the issues raised by Ng et al (1), it is important to keep in mind that African Americans are an understudied population group for whom target serum concentrations of vitamin D are unclear, especially because the DRI was established on the basis of bone health, for which African Americans have an advantage relative to white populations (9). Furthermore, as shown by the recent report from Powe et al (10) concerning vitamin D binding protein among blacks, they may also experience genetic variation and other differences relative to the metabolism or bioavailability of vitamin D that have not been clearly elucidated. More research is needed in this population to discern vitamin D requirements; in the meantime, available research should at least appropriately apply the DRI constructs, and include contributions of diet, to build this literature.

The authors had no conflicts of interest to disclose.

Patsy M Brannon

Division of Nutritional Sciences
Cornell University
Ithaca, NY

Susan T Mayne

Yale School of Public Health
New Haven, CT

Suzanne P Murphy

Cancer Research Center of Hawaii
Honolulu, HI (retired)

Christine L Taylor

Office of Dietary Supplements, NIH
6100 Executive Boulevard
Bethesda, MD 20892-7517
E-mail: taylorcl3@od.nih.gov

REFERENCES

1. Ng K, Scott JB, Drake BF, Chan AT, Hollis BW, Chandler PD, Bennett GG, Giovannucci EL, Gonzalez-Suarez E, Meyerhardt JA, et al. Dose response to vitamin D supplementation in African Americans: results of a 4-arm, randomized, placebo-controlled trial. Am J Clin Nutr 2014;99:587–98.
2. Institute of Medicine. Dietary Reference Intakes: applications in dietary assessment. Washington, DC: The National Academies Press, 2000.
3. Institute of Medicine. Dietary Reference Intakes: applications in dietary planning. Washington, DC: The National Academies Press, 2003.
4. Murphy SP, Barr SI. Practice paper of the American Dietetic Association: using the Dietary Reference Intakes. J Am Diet Assoc 2011;111:762–70.
5. Trumbo PR, Barr SI, Murphy SP, Yates AA. Dietary Reference Intakes: cases of appropriate and inappropriate uses. Nutr Rev 2013; 71:657–64.
6. Taylor CL, Carriquiry AL, Bailey RL, Sempos CT, Yetley EA. Appropriateness of the probability approach with a nutrient status biomarker to assess population inadequacy: a study using vitamin D. Am J Clin Nutr 2013;97:72–8.
7. Sempos CT, Druazo-Arvizu RA, Dawson-Hughes B, Yetley EA, Looker AC, Schleicher RL, Cao G, Burt V, Kramer H, Bailey RL, et al. Is there a reverse J-shaped association between 25-hydroxyvitamin D and all-cause mortality? Results from the U.S. nationally representative NHANES. J Clin Endocrinol Metab 2013;98:3001–9.
8. Institute of Medicine. Dietary Reference Intakes: calcium and vitamin D. Washington, DC: The National Academies Press, 2011.
9. Barrett-Connor E, Siris ES, Wehren LE, Miller PD, Abbott TA, Berger ML, Santora AC, Sherwood LM. Osteoporosis and fracture risk in women of different ethnic groups. J Bone Miner Res 2005;20:185–94.
10. Powe CE, Evans MK, Wenger J, Zonderman AB, Berg AH, Nalls M, Tamez H, Zhang D, Bhan I, Karumanchi A, et al. Vitamin D-binding protein and vitamin D status of black Americans and white Americans. N Engl J Med 2013;369:1991–2000.

doi: 10.3945/ajcn.114.090605.

Reply to PM Brannon et al

Dear Sir:

We thank Brannon et al for their thoughtful comments on our study (1), and greatly appreciate the opportunity to reply. In their correspondence, they incorrectly state that we defined vitamin D adequacy as 97.5% of the population achieving a 25-hydroxyvitamin D [25(OH)D] concentration of 20 ng/mL and raise concern about potential misapplication of the Recommended Dietary Allowance (RDA) for vitamin D intake in our analysis. They discuss that the RDA should not be used to assess vitamin D adequacy in populations or groups, because, by definition, the RDA-associated concentration of 20 ng/mL reflects a value that exceeds the needs of most individuals. They suggest that the correct approach is to estimate how much vitamin D is needed to ensure a low prevalence of plasma 25(OH)D below the estimated average requirement (EAR) of 16 ng/mL (2).

Although we agree with their statement on appropriate applications of the RDA, it is clear that Brannon et al misinterpreted the intent of our analysis. The EAR of 400 IU and RDA of 600 IU for adults up to age 70 y calculated by the Institute of Medicine (IOM) to be associated with plasma 25(OH)D concentrations of 16 and 20 ng/mL, respectively, are based on dose-response curves from studies in white populations. Given the lower baseline concentrations of 25(OH)D among African Americans, differences in lifestyle behaviors, and differences in germline genetic variation and vitamin D metabolism that have not yet been fully characterized, it is important to reexamine the vitamin D requirement associated with these target 25(OH)D concentrations by using dose-response curves that are actually constructed from studies in African Americans, rather than extrapolating from curves from whites. Until now, there have been very few studies evaluating a variety of vitamin D intakes in a large-enough cohort of African Americans with minimal UV-B radiation exposure to reliably construct such a dose-response curve. Our trial randomly assigned 328 community-based African Americans in Boston, MA, to receive placebo or 1000, 2000, or 4000 IU of vitamin D_3/d for 3 mo during the winter, with plasma 25(OH)D concentrations assayed at baseline and at 3 and 6 mo. By using the resulting robust dose-response curve, we found a vitamin D requirement of 1640 IU/d to be the amount that corresponded to the RDA-associated 25(OH)D concentration of 20 ng/mL in African Americans. In fact, even when we consider the lower EAR-associated 25(OH)D concentration of 16 ng/mL as our target, as recommended by Brannon et al, the vitamin D intake required to reach that value in $\geq$97.5% of African Americans is still 1200 IU/d (95% CI: 1130, 1420 IU/d) (**Figure 1**).

A similar approach to determine the vitamin D intake corresponding to the RDA-associated 25(OH)D concentration was undertaken by Gallagher et al (3), who randomly assigned 163 postmenopausal white women with 25(OH)D $\leq$20 ng/mL to 7 doses of vitamin D_3 compared with placebo for 12 mo. By using the dose-response curve that resulted from this study in whites, the authors were able to confirm the IOM RDA of 600–800 IU/d, supporting the appropriateness of the methodology. No concerns have been published about misuse of the RDA in that study.

Brannon et al also state that we did not account for "background" intake of dietary vitamin D. However, all subjects in our study were administered dietary and lifestyle questionnaires, and Table 1 in our article clearly shows that in this representative cohort of African Americans, the contribution of vitamin D from dietary sources was extremely low at $<$200 IU/d at baseline (1). Moreover, plasma 25(OH)D concentrations reflect contributions from all sources of vitamin D, including diet; therefore, our determination of the vitamin D_3 dose associated with specific target 25(OH)D concentrations can be interpreted as the amount of vitamin D_3 needed in addition to underlying dietary intake.

Finally, Brannon et al raise concerns about vitamin D toxicity at doses near or above the Tolerable Upper Intake Level; however, we did not see any evidence of clinically significant hypercalcemia in our African American cohort, including those treated with 4000 IU vitamin D_3/d for 3 mo (1). They also claim that high doses of vitamin D supplementation may pose special concerns for African Americans; they cite a study from the NHANES cohort that reported a reverse J-shaped relation between 25(OH)D concentrations and all-cause mortality, with an adjusted RR of 2.4 for blacks with serum 25(OH)D $\geq$48 ng/mL compared with ~30–40 ng/mL, whereas the adjusted RR was 1.6 for the same comparison in whites (4). However, Brannon et al fail to point out that blacks comprised only 10% of the population in that study, for which the abstract explicitly states, "the study was too small to evaluate the association in non-Hispanic black . . . adults." This statement is supported by a very telling, extremely wide 95% CI