JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 70, NO. 20, 2017
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.09.1082

EDITORIAL COMMENT

Eat Nuts, Live Longer*

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In the early 1990s, investigators from Loma Linda University published 2 landmark studies that placed nuts in the limelight as heart-healthy foods: the prospective Adventist Health Study (1), which for the first time related nut consumption to a reduced risk of coronary heart disease (CHD); and a randomized clinical trial (RCT) showing that a diet enriched with walnuts lowered blood cholesterol compared with a healthy control diet (2). Since then, epidemiological and clinical research on the health effects of nuts has increased exponentially, and results have supported the cardioprotective properties of nuts (3). Cohort studies have consistently shown that nut consumption relates to reduced rates of CHD, particularly fatal CHD, but evidence on stroke has been inconsistent (3–5). However, in the PREDIMED (PREvención con DIeta MEDiterránea [Prevention with Mediterranean Diet]) trial, a Mediterranean diet supplemented with 1 daily serving (30 g) of mixed nuts resulted in a 30% reduction in incident CVD, including a 46% reduction in stroke, thus providing first-level evidence of the cardiovascular benefit of nuts (6). Remarkably, cohort studies have also uncovered an inverse association between nut consumption and total cancer risk (4). Prospective studies have also provided suggestive evidence that nut consumption reduces total mortality and, in particular, cardiovascular and cancer mortality (4,5,7,8). Residual confounding is possible because in most of these studies nut eaters tend to have healthier lifestyles. Many RCTs have demonstrated beneficial effects of all nut types on blood lipids, with a dose-dependent reduction of total and low-density lipoprotein cholesterol, but no effects on blood pressure (9). Nut diets are also beneficial for metabolic syndrome, by showing modest decreases in triglycerides and fasting glucose and a tendency to smaller waist circumference (10). The optimal nutrient composition of nuts probably explains their salutary effects.

Like whole grains and legumes, nuts are nutrient-dense seeds, made of complex matrices in the outer layer and the germ, rich in vitamins, minerals, and bioactive phytochemicals destined to protect the plant's DNA from oxidative stress and facilitate perpetuation of the species, whereas macronutrients stored in the endosperm sustain the growth of the future seedling. Seed components synergize to influence metabolic and vascular physiology pathways positively, leading to protection from cardiovascular disease (CVD) (11). Most energy in nuts derives from their large fat content, but fatty acids are mainly unsaturated, predominantly oleic acid but also polyunsaturated fatty acids (PUFAs). Nuts also contain complex carbohydrate, fiber, protein, tocopherols, nonsodium minerals, phytosterols, and polyphenols (12). Of note, natural phytosterols in nuts may be responsible in part for their cholesterol-lowering effect (13).

The term *nuts* encompasses tree nuts (almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios, and walnuts); it also includes peanuts, which botanically are legumes but have a nutrient profile similar to that of tree nuts. Although most tree nut types and peanuts have been tested in RCTs for lipid effects and found to lower blood cholesterol effectively (9,13), most prospective studies have assessed effects of total nuts on CVD risk, hence there is little information on specific nut types. In this issue of the *Journal*, Guasch-Ferré et al.

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the author and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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(14) report findings from 3 seminal Harvard prospective cohorts assessing nut consumption in relation to CVD that partly fill this gap. With 210,836 study subjects and 14,136 incident CVD cases after follow-up for up to 32 years, this large cohort study provides robust evidence of the association between nut consumption and incident CVD. Results show that participants consuming nuts ≥5 times/week had a 14% lower risk of CVD and a 20% lower risk of CHD, but not a lower risk of stroke, compared with participants with the lowest nut consumption, thereby confirming findings of a recent meta-analysis of 12 cohort studies (4). The consistency of findings strongly suggests a causal association between nut consumption and CVD and CHD protection.

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Interestingly, total nut consumption was more strongly associated with lower rates of fatal CVD (−24%) than nonfatal CVD (−9%), the inverse association being driven by apparent protection from fatal CHD (−31%), not from nonfatal myocardial infarction (−3%) (14). This finding suggests that some nut components may have antiarrhythmic properties preventive of sudden cardiac death akin to those of n-3 PUFAs from fish oil, the best candidate being α-linolenic acid, the vegetable n-3 PUFAs (15), particularly abundant in walnuts (12). Specifically, a finding of the study by Guasch-Ferré et al. (14) is the analysis of the association of walnut consumption with CVD risk independent of other nuts. Consuming walnuts 1 or more times/week related to a 19% lower risk of CVD, a 21% lower risk of CHD, and a 17% lower risk of stroke. The fact that sparingly consuming walnuts is associated with lower CVD and CHD rates to a similar extent than frequent consumption of total nuts, while also reducing stroke risk, suggests a stronger antiatherogenic effect of walnuts. This may reflect their unique richness in α-linolenic acid and the fact that they are usually consumed raw, hence they keep the outer skin, whereas most other nuts are consumed roasted and lose the peel in which most antioxidants reside (12). Isolated consumption of peanuts ≥2 times/week, but not of peanut butter, was also associated with a modestly lower risk of CVD (13%) and CHD (10%) and a nonsignificant reduction in stroke risk. Peanut butter may not be cardioprotective because it is often processed with the addition of salt, honey, or simple sugars.

Given that they are high-fat foods, nuts are often perceived as promoting weight gain. However, there is no epidemiological or RCT evidence of weight gain ensuing from nut consumption (3,16). Furthermore, the PREDIMED RCT showed that participants allocated to an unrestricted-calorie Mediterranean diet supplemented with 1 daily serving of nuts for 5 years experienced a small decrease in body weight, not weight gain, and less gain in central adiposity compared with a lower-fat control diet (17). Mechanistically, the lack of weight gain after consuming nuts is mainly the result of their prominent satiating effect, together with incomplete digestion and a reduction of metabolizable energy (16).

Accumulating evidence on the cardiovascular benefit and safety of nuts has prompted the inclusion of this food group in many guidelines, including the 2013 American College of Cardiology/American Heart Association document on lifestyle management to reduce CVD risk (18). Further proof of the healthy properties of nuts has been provided by a report on mortality from cardiometabolic causes ascribable to 10 dietary factors in the United States in 2012, wherein the second cause of the largest numbers of estimated diet-related fatal cardiometabolic outcomes (8.5% of 702,308 deaths) was low nut or seed consumption (the first cause was high dietary sodium) (19). Research is ongoing into other putative health properties of nuts, such as delaying age-related cognitive decline and macular degeneration (20). Ideally, further investigations should test the effects of long-term consumption of nuts supplemented in the usual diet on hard cardiometabolic events. In the meantime, raw nuts, if possible unpeeled and otherwise unprocessed, may be considered as natural health capsules that can be easily incorporated into any heart-protective diet to further cardiovascular well-being and promote healthy aging.

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KEY WORDS cardiovascular disease, cohort studies, nuts