HHS Public Access

Author manuscript

Circ Res. Author manuscript; available in PMC 2020 March 15.

Published in final edited form as:

Circ Res. 2019 March 15; 124(6): 825–826. doi:10.1161/CIRCRESAHA.119.314752.

Nuts, Cardiovascular Health, and Diabetes: Will a Nut a Day Keep the (Heart) Doctor Away?

Ravi Shah, MD[1], **Venkatesh Murthy, MD, PhD**[2], and **Jane E. Freedman, MD**[3]

[1]Cardiology Division, Massachusetts General Hospital, Harvard Medical School, Boston, MA;

[2]Division of Cardiovascular Medicine, Department of Medicine and Frankel Cardiovascular Center, University of Michigan, Ann Arbor, Ann Arbor, MI;

[3]University of Massachusetts Medical School, Department of Medicine, Division of Cardiovascular Medicine, Worcester, MA

Keywords

Diabetes mellitus; diet; cardiovascular disease; risk factors; non-pharmacological therapy

Along with physical activity, a high-quality diet plays a critical and modifiable role in achieving and maintaining ideal cardiovascular health. Over the past two decades, there has been an explosion in nutritional epidemiology advocating various diet composition strategies to mitigate risks of atherosclerotic cardiovascular disease (CVD) and heart failure. As part of a strategy to target reductions in stroke and heart disease by 2020, the American Heart Association has put forth recommendations on a diet consistent with ideal health, emphasizing fruits, vegetables, whole grains, low-fat dairy, proteins (via nuts, legumes, and specific meats), and polyunsaturated oil consumption (part of "Life's Simple 7"[1]). Given the putative nutritional benefits of nut consumption on inflammation and CVD outcomes[2], there is scientific and public health interest in the role of nut consumption as part of a high-quality cardiovascular "friendly" diet[3]. Indeed, peanut and tree nut intake have been associated with better control of cardiometabolic risk factors[4, 5], less incident diabetes and lower fatal CVD.[2] However, the causal role of nut intake on CVD among individuals with diabetes remains largely unknown.

In this context, Liu and colleagues examine the association of dietary nut intake in individuals with type 2 diabetes (T2D) in two large, prospective observational cohorts.[6] In over 16,000 participants from the Nurses' Health Study and the Health Professionals Follow-Up Study with prevalent or incident T2D during follow-up, the investigators found that increased nut intake (particularly tree nuts) correlated with a lower risk of incident CVD and all-cause mortality.[6] Interestingly, in the cohort of individuals who developed T2D

Address for correspondence: Jane E. Freedman, University of Massachusetts Medical School, AS7-1051, 368 Plantation St., Worcester, MA 01605-4319 USA, jane.freedman@umassmed.edu.

Author Disclosures: Dr. Shah receives grants from the National Institutes of Heath and within the last 12 months has received funds from Amgen (scientific advisory board), Myokardia (consulting), and Best Doctors (consulting). Dr. Shah is a co-inventor on a patent for ex-RNAs signatures of cardiac remodeling. Dr. Murthy receives grants from the National Institutes of Health, and has minor stock holdings in GE. Dr. Freedman receives grants from the National Institutes of Health and American Heart Association.

(before a CVD outcome) during follow-up, individuals who ate more nuts after being diagnosed with T2D had a lower hazard of CVD and death. The authors acknowledge the limitations of an observational study design, predominantly Caucasian population, incomplete covariate ascertainment (e.g., severity of T2D), and potential for residual confounding. Strengths of this study include large size, serial measures and sub-classification of nut intake, comprehensive adjustment for (and stratification by) potential metabolic confounders, and standard adjudication of CVD events over a long period. The investigators conclude that incorporation of specific nut intake in dietary recommendations may forestall early mortality in individuals with T2D.

In addition to the epidemiologic data supporting the association between nut ingestion, T2D and CVD, there is mechanistic plausibility to the associations observed by Liu and co-workers, though specific limitations remain. As the authors point out, specific micronutrients within nuts (e.g., phytonutrients, unsaturated fatty acids, and vitamin content) may mediate improvement in dysglycemia, gut microbial remodeling, oxidative stress, and epigenetics[6] (Figure). Certainly, long-standing concerns over nut consumption increasing weight are not necessarily supported by data. Despite their high caloric value, greater nut intake has been associated with minor weight loss or weight neutral[7, 8]. In addition, tree nuts improved dysglycemia in a small prospective trial of nut supplementation in individuals with T2D[9], and nut consumption as a replacement for carbohydrate intake improved dysglycemia and lipid profile.[10] Unfortunately, dietary interventions in large populations have usually included intake of multiple beneficial foods (including nuts[11]), which may have shared micronutrient content and exerted interrelated impacts on molecular physiology central to heart and vascular disease. Furthermore, while careful observational studies like those of Liu *et al.* may adjust for dietary patterns and general metabolic health in modeling, hidden confounding (not fully accounted for by regression) likely remains, given complex correlations between aspects of diet and lifestyle. Indeed, individuals with greater nut intake in this study were more likely to be male, older, less often smokers, and more physically active with a higher quality diet. Certainly, these findings suggest that—at an individual level—individuals who report greater nut consumption may be qualitatively different (and potentially different at the metabolic, genetic, or epigenetic level) in ways that may not necessarily be related to nut consumption alone.

For this and other reasons, recent work by other groups has raised concerns over the methodology, validity, and impact of nutritional epidemiology research[12, 13]. Certainly, valid concerns exist over the complexity of quantifying the nutritional exposure (specifically the inter-relatedness of micronutrient structure of certain foods, as noted above), residual confounding, and modification of its effect on outcomes by complex social-ecological factors not necessarily measured in available observational studies[13]. However, it is also impossible to overstate the fundamental impact that nutritional epidemiology has had on improvements in cardiometabolic health, with specific examples of *trans* fat and sugar-sweetened beverage consumption[12]. Careful examination of serial measures of diet combined with causal analytic methods, leveraging metabolic-epigenetic effects of diet exposure (e.g., metabolomic, proteomic, and transcriptomic responses to a diet) are necessary to fully understand the relationship between diet and heart disease and to optimize diet composition. Application of these molecular techniques in personalized “N of 1” studies

has been successfully performed[14], and integrating molecular measures with studies of acute and chronic dietary exposures in a controlled setting may clarify the functional biology of diet and inform dose of a given food and its specific impact on mechanisms central to health. Studies utilizing genomic data across race, sex, and obesity status will also be critical to understanding how diet may influence outcomes.

In this context, the results of Liu and colleagues suggest that nut intake may be one aspect of a salutatory diet profile that may afford protection against CVD among the growing group of individuals with T2D. In an era of "big data," results from large cohort epidemiology are important inputs to construction of prospective, controlled studies of dietary exposures (that leverage social-ecological factors, standard metabolic exposures, and emerging molecular markers of health) that may move us closer to understanding what constitutes "optimal" nutrition.

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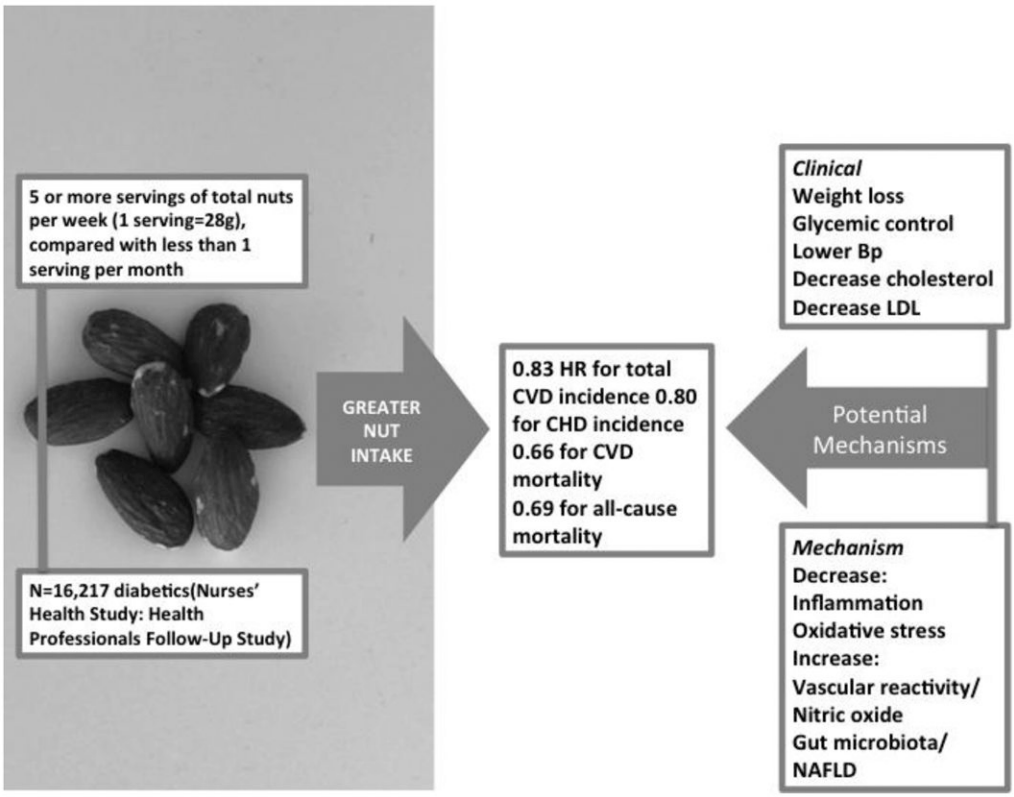

Figure:
Summary of study by Liu et al. with potential mechanisms for systemic benefit of tree nuts.