REVIEW

Beneficial effects of walnut consumption on human health: role of micronutrients

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Purpose of review

Nuts in general and walnuts in particular are in the limelight for the association of their consumption with improved health outcomes. Walnuts have an optimal composition in bioactive nutrients and recent clinical and experimental studies have uncovered a number of beneficial effects of walnut micronutrients, working in isolation or in concert, on metabolic pathways and clinical outcomes that make this review timely and relevant.

Recent findings

Alpha-linolenic acid, a critical walnut component, is metabolized into bioactive oxylipins, has been shown to protect microglial cells from inflammation, and is associated with lower fatal myocardial infarction rates through a putative antiarrhythmic effect. Phytosterols relate to the cholesterol-lowering effect of nut consumption. Nonsodium minerals are associated with better cardiometabolic health. Walnut phytomelatonin has anticancer effects that are shared by the main walnut polyphenols and their metabolites, ellagitannins and urolithins, respectively.

Summary

This review highlights new evidence on the health-promoting properties of walnuts and their main micronutrient components. The conclusion is that walnuts are optimal healthful foods.

Keywords

alpha-linolenic acid, elagitannins, oxylipins, phytosterols, urolithins, walnuts

INTRODUCTION

In cohort studies, consumption of nuts has been consistently associated with reduced rates of coronary heart disease (CHD) and total cancer, as well as lower all-cause, cardiovascular and cancer mortality [1,2,3▪]. Of note, there is evidence of a dose–response relationship between nut consumption and reduced cardiometabolic risk. Recent meta-analyses included dose–response analyses that showed significant reductions in the relative risk of CVD and all-cause and CVD mortality for increased daily servings of total nuts [2,3▪]. A recent very large prospective study [4▪] describes findings from the prospective Nurses' Health Study (NHS) I and II and Health Professionals Follow-Up Study assessing not only total nut consumption but also separated walnut consumption in relation to CVD after follow-up for up to 32 years. Results showed a multivariable-adjusted hazard ratio of 0.71 [95% confidence interval (CI) 0.52–0.97] for CVD per each serving increase in walnuts. Randomized controlled trials (RCTs) have also uncovered a consistent cholesterol-lowering effect of nuts, but no effect on blood pressure [5]. Concerning walnuts, a recent meta-analysis of 24 RCTs of walnuts for outcomes on blood lipids uncovered a significant continuous dose–response relationship between walnut-intake and blood cholesterol reduction [6]. Nut consumption also beneficially influences oxidative stress, inflammation and vascular reactivity [1]. The optimal nutrient composition of nuts probably explains

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KEY POINTS

- Walnuts are a rich source of α-linolenic acid (ALA), phytosterols, nonsodium minerals, γ-tocopherol, melatonin and polyphenols.
- Most of these bioactives act in concert to beneficially influence metabolic and vascular physiology pathways.
- ALA, the vegetable n-3 fatty acid, may be bioactive on its own via an antiarrhythmic effect, production of anti-inflammatory oxylipins and neuroprotection.
- Phytosterols in walnuts contribute to the cholesterol-lowering effect of their consumption.
- The main polyphenols in walnuts are ellagitannins, which are metabolized to urolithins, compounds with antioxidant, anti-inflammatory, anticancer and prebiotic effects.

their salutary effects. Nuts contain sizable amounts of fat, but fatty acids are mainly unsaturated; they are also rich in fiber, protein and various bioactive micronutrients [1,7]. The nutrient composition of walnuts differs from that of all other nuts by three important aspects: they contain ≈10% of energy as alpha-linolenic acid (ALA), the main vegetable polyunsaturated n-3 fatty acid (n-3PUFA), are a rich source of phytomelatonin and possess more polyphenols than any other nut type [1,8■]. Because of their differential composition, walnuts may have specific health effects not observed with other nuts. This review focuses on the latest findings concerning health effects of walnuts and ALA and relevant micronutrients such as nonsodium minerals, phytosterols, γ-tocopherol, melatonin and polyphenols, albeit one should consider that any benefit derived from the consumption of a healthy food with a complex matrix such as walnuts is likely because of the synergy of several or all of its bioactive components acting on multiple metabolic and vascular physiology pathways, rather than to any single nutrient [9].

ALPHA-LINOLENIC ACID

Walnuts are the common food with the highest content of ALA [10], the vegetable n-3 fatty acid. The bioavailability of ALA is almost complete as, like other unsaturated fatty acids, it is nearly 100% absorbed from the diet. Once absorbed, the metabolism of ALA involves a modest conversion to its longer chain counterparts, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [11■■]. Although there is much evidence on the cardioprotective properties of dietary EPA and DHA, mostly supplied by fatty fish and fish oils [12], the role of ALA in cardiovascular health has been less explored. Recent experimental studies have begun to uncover the benefits of ALA on the arterial tree and in the brain, akin to those observed for EPA and DHA. They include neuroprotection, vasodilation of brain arteries and neuroplasticity [13]. However, results of cohort studies focusing on exposure to ALA and clinical outcomes and RCTs testing ALA-rich foods or supplements for intermediate risk factors have provided inconsistent results [11■■].

Alpha-linolenic acid-derived oxylipins

Oxylipins are PUFA metabolites obtained by the action of cyclooxygenase, lipoxygenase and cytochrome P450 epoxygenase. As oxylipins play a role in cardiovascular disease (CVD) and aging, there is an emerging interest on dietary strategies to improve their status [14■]. Holt *et al.* [15] treated hypercholesterolemic women with walnuts (5 or 40 g/day) for 4 weeks and reported that those receiving 40 g/day improved microvascular function in relation to changes in plasma epoxides, particularly arachidonic-acid-derived 14 (15)-epoxyeicosatrienoic acid. Similarly, a raise in circulating ALA-derived oxylipins was observed in 19 healthy men with low intake of marine n-3PUFA who consumed 14 g/day of ALA from linseed oil for 12 weeks [16]. The notion that dietary ALA modifies the oxylipin profile beyond mere changes of its own derivatives was also observed in a study with rats fed diets enriched with either ALA, EPA or DHA [17].

Experimental and clinical studies indicate that marine n-3PUFA promote the formation of anti-inflammatory and vasodilatory oxylipins, but ALA-derived oxylipins have been little studied. In this regard, challenge with ALA of THP-1-derived M1-like macrophages induced a reduction in lipopolysaccharide (LPS)-induced cytokine production [18]. Of note, in an interesting study conducted in *Caenorhabditis elegans*, concomitant exposure to ALA and its derived oxylipin 9S-hydroperoxy-10E,12Z,15Z-octadecatrienoic acid induced an increase in the worm's lifespan [19■].

Among different nuts tested for effects on vascular reactivity in RCTs, only walnuts have been shown to improve endothelial function, as indicated in a recent meta-analysis [20]. This beneficial effect could be ascribed to ALA itself and/or derived oxylipins, but polyphenols, magnesium and L-arginine in walnuts probably play a role.

Alpha-linolenic acid in brain function

As DHA is an integral compound of the membrane phospholipids of neural tissues, there has been interest in exploring whether intake of DHA or its parent foods protects against neurological diseases. The role of ALA on brain function has been little studied, although the picture is beginning to change. In an in-vitro study, primary cultures of embryonic E14 mice neural stem cells were challenged with different doses of linoleic acid and ALA [21]. Authors found that ALA had the highest potential to induce differentiation of neural stem cells toward astrocytes and oligodendrocytes, in parallel to changes in the expression of *Notch-1*, *Hes-1* and *Ki-67* genes.

Activation of microglia mediates chronic inflammation-associated brain aging, injury and neurodegeneration. Fisher *et al.* [22] investigated the cellular mechanisms underlying walnuts' protective effects on brain microglial-associated inflammation. To this purpose, they fed walnuts or control diets to aged rats and collected serum, which contained ALA and other walnut-derived bioactives. Added to the medium used to pretreat BV-2 microglial cells subjected to LPS-induced injury, serum from walnut-fed animals protected microglial cells from LPS-induced inflammation. In line with this finding, Lee *et al.* [23] recently reported that addition of ALA to the cell culture medium attenuated the over-production of nitric oxide, release of pro-inflammatory cytokines and generation of reactive oxygen species in C6 glial cells treated with a neurotoxin, translating into increased cell viability.

Finally, the potential of ALA to prevent the anxiety disorder ensuing traumatic brain injury was tested in a rat model of mild controlled cortical impact, whereby administration of ALA by subcutaneous injection resulted in a significant reduction in contusion volume and protected against anxiety-like behavior [24].

Dietary alpha-linolenic acid and chronic disease: updated epidemiology

In contrast with the vast information collected for marine n-3PUFA, epidemiologic data on dietary ALA in relation to prevalent diseases has been scarce and contradictory [11■■]. In this respect, a global consortium of 19 cohort studies constituting 45 637 unique individuals and 7973 cases of CHD with data on blood or tissue biomarkers of intake of seafood-derived n-3PUFA and ALA reported a similarly reduced risk of fatal (but not nonfatal) coronary events per 1-SD increases in all biomarkers, the relative risk for ALA being of 0.91 (CI 0.84–0.98) [25■■]. Such beneficial effect against cardiac death suggests an antiarrhythmic effect of ALA similar to that of marine n-3PUFA.

Most prospective studies have assessed effects of total nuts on CVD risk. Confirming prior findings, the recent report of Guasch-Ferré *et al.* [4■] of a large prospective study shows that participants consuming nuts at least five times per week had 14% lower risk of CVD and 20% lower risk of CHD, but not lower risk of stroke, compared with those with the lowest nut consumption. Interestingly, total nut consumption was more strongly associated with reduced rates of fatal CHD (−31%), but not nonfatal myocardial infarction (−3%), pointing again to an antiarrhythmic effect of nuts, the best candidate being ALA. In that study, walnut consumption was more strongly related to a lower risk of CVD than total nuts, and was also associated with a lower risk of stroke, suggesting an additional effect of walnuts [13]. In addition to its antiarrhythmic potential, ALA may exert beneficial cardiovascular effects by way of cholesterol-lowering, antithrombotic and anti-inflammatory action, and vasculoprotection via improved endothelial function and reduced atherosclerosis [26].

PHYTOSTEROLS

Like all plant foods, nuts are cholesterol-free but contain chemically related phytosterols, nonnutritive molecules that play a structural role in plant membranes similar to that of cholesterol in animal membranes. These compounds are also believed to have antioxidant properties. Phytosterols are more hydrophobic than cholesterol, a reason why they displace cholesterol from intestinal micelles, thereby interfering with cholesterol absorption, which leads to a reduction of low-density lipoprotein (LDL)-cholesterol [27■■]. The phytosterols content of nuts in general (from 95 to 279 mg/100 g) and walnuts in particular (113 mg/100 g) [5] place them among the whole foods richest in these molecules. Phytosterols, together with unsaturated fatty acids and fiber, justify in part the cholesterol-lowering properties of nuts. Indeed, a pooled analysis of 61 nut RCTs with outcomes on lipid changes reported that the total phytosterol dose from nuts correlated inversely to LDL-cholesterol reduction ($r = -0.60$) [28].

MINERALS

Like many plant foods, nuts contain little sodium but are rich in potassium, magnesium and calcium [7]. These three minerals are involved in many aspects of cellular metabolism and other biological processes, including insulin sensitivity, blood pressure regulation and vascular reactivity. Obviously, no cohort studies have related the specific mineral content of walnuts to health outcomes, but much evidence on the beneficial role of non-sodium minerals as contributed by the overall diet is available and the latest findings are briefly reviewed here.

Whereas high-sodium (salt) intake is associated with hypertension, CVD and all-cause mortality, nonsodium minerals generally have the opposite effect [9]. The low-sodium and high-potassium content of nuts (2 mg/100 g and 441 mg/100 g, respectively, in walnuts) is one of the most beneficial of all common vegetable foods. As detailed in a recent comprehensive review [29], raising dietary K^+ blunts the effects of high dietary Na^+, indicating that modest sodium restriction with increasing potassium intake is a good general strategy to control blood pressure, prevent stroke and reduce CVD mortality.

Concerning dietary magnesium, the latest meta-analysis with data from 40 cohort studies concludes that increasing intake is associated with a reduced risk of stroke, heart failure, diabetes and all-cause mortality, but not CHD or total CVD [30]. These findings are confirmed by a recent comprehensive review on the topic [31], which lists walnuts among the plant foods with highest magnesium content (158 mg/100 g) and concludes that high dietary magnesium intake relates to a lower risk of major cardiovascular risk factors (mainly metabolic syndrome, diabetes and hypertension) and is associated with improved endothelial function.

Nuts are among the foods with the highest calcium content (walnuts contain 98 mg/100 g) [7]. A 2015 meta-analysis found no relationship between dietary calcium and risk of CVD mortality [32] and a recent study from a large prospective cohort reported that dietary calcium was unrelated to all-cause mortality [33]. However, a recent meta-analysis of nine intervention studies lasting from 1 to 7 years demonstrates the potential of dietary calcium with vitamin D in the prevention of total fractures, particularly hip fractures [34]. A combined diet score of potassium, magnesium and calcium was associated with reduced stroke risk in the NHS I and II cohorts [35], suggesting synergy among these minerals in influencing disease risk.

VITAMIN E (γ-TOCOPHEROL)

The term 'vitamin E' comprises four tocopherols (α-tocopherol, β-tocopherol, γ-tocopherol and δ-tocopherol), but only RRR-α-tocopherol satisfies the criteria of being a vitamin. As long as intestinal function is preserved, tocopherols are bioavailable because, being small fatty molecules, they are absorbed along with dietary fat in the intestine and enter the circulation via chylomicron particles [36]. Walnuts are an excellent source of γ-tocopherol, supplying 21 mg/100 g [37], and there is evidence that the liver hydroxylation and oxidation products of this form of vitamin E are potent free radical scavengers and reduce pro-inflammatory eicosanoids and the inflammatory response, actions that are not shared by α-tocopherol. For these reasons, γ-tocopherol and not α-tocopherol is believed to be the cardioprotective form of vitamin E [36]. A similar effect of γ-tocopherol over α-tocopherol has been observed in relation to cancer, both in experimental and epidemiological studies [38].

MELATONIN

At night, the mammalian pineal gland synthetizes melatonin, a hormone with experimental evidence of pleiotropic effects, such as antioxidant, anti-inflammatory, antiobesity and anticancer activities, and neuroprotection, that is best known for its sleep-regulatory role. Many plants contain sizable amounts of bioavailable melatonin [39▪]. Walnuts are one of the main food sources of phytomelatonin, with an average content of 350 ng/100 g, and this together with ALA and antioxidants was believed to underlie the beneficial effect on mood observed in a small 6-week trial of walnut supplementation in healthy young men [40]. There is evidence that melatonin from walnuts is absorbed, as shown by a roughly four-fold rise in serum melatonin levels in an experiment with rats fed exclusively walnuts [41]. A sound experimental study comparing diets with walnut flour (containing 7.5 ng/g melatonin), synthetic melatonin and control in a murine model of breast cancer provides new insight into the anti-tumorigenic and immunomodulatory actions of walnut phytomelatonin [42]. Concerning the primary function of melatonin, evidence is lacking to support the claim that walnuts improve sleep quality, an interesting topic for future research.

POLYPHENOLS

Among common foods, walnuts are one of the most important sources of total polyphenols, with a reported content of up to 2500 mg/100 g [8▪,43▪▪]. The most abundant are ellagitannins, mainly pedunculagin [43▪▪]. Indeed, walnuts are the richest plant source of ellagitannins (~1600 mg/100 g) [44▪]. Upon hydrolysis, ellagitannins release ellagic acid, which is further metabolized by intestinal bacteria to urolithins, in a process influenced by individual differences in gut microbiota [45▪▪,46]. Urolithins are much better absorbed than ellagitannins, reach the bloodstream and target many organs and tissues. Ellagitannins and urolithins disclose many biological activities, such as antioxidant, anti-inflammatory, anticancer and prebiotic effects, suggesting a range of beneficial effects on human health [43▪▪]. However, the mechanisms of action supporting such benefits are still under debate. A recent meta-analysis reported a reduction of adiposity, LDL-cholesterol and glucose following consumption of ellagitannin-rich foods, particularly walnuts [44▪].

The most widely investigated effects of ellagic acid and urolithins concern inhibition of cancer-cell proliferation. Research *in vitro* and in animal models has shown that phenolic walnut extracts induce a dose-dependent inhibition of the growth of colon, breast, and prostate cancer cells [43▪▪,47,48]. Modulation of cell signaling, cell cycle arrest and key cellular processes such as mitogen-activated protein kinases signaling appear to underlie the antitumor activity of walnut extracts [43▪▪]. A recent study in a mice model of obesity showed that a diet containing 6.7% walnuts protected against intestinal tumorigenesis and growth, along with preservation of intestinal stem cell function [49]. For the particular case of colon cancer, other likely contributors to the chemopreventive effect of walnuts are changes of the gut microbiome. Both in animal experiments [48,50] and RCTs [51▪,52], walnut feeding promoted bacterial diversity and enriched the microbiota with probiotic-type bacteria, including *Lactobacillus* spp. and *Roseburia* spp., and increased the abundance of butyrate-producing *Firmicutes* whereas reducing *Bacteriodetes*. Walnut consumption was also associated with

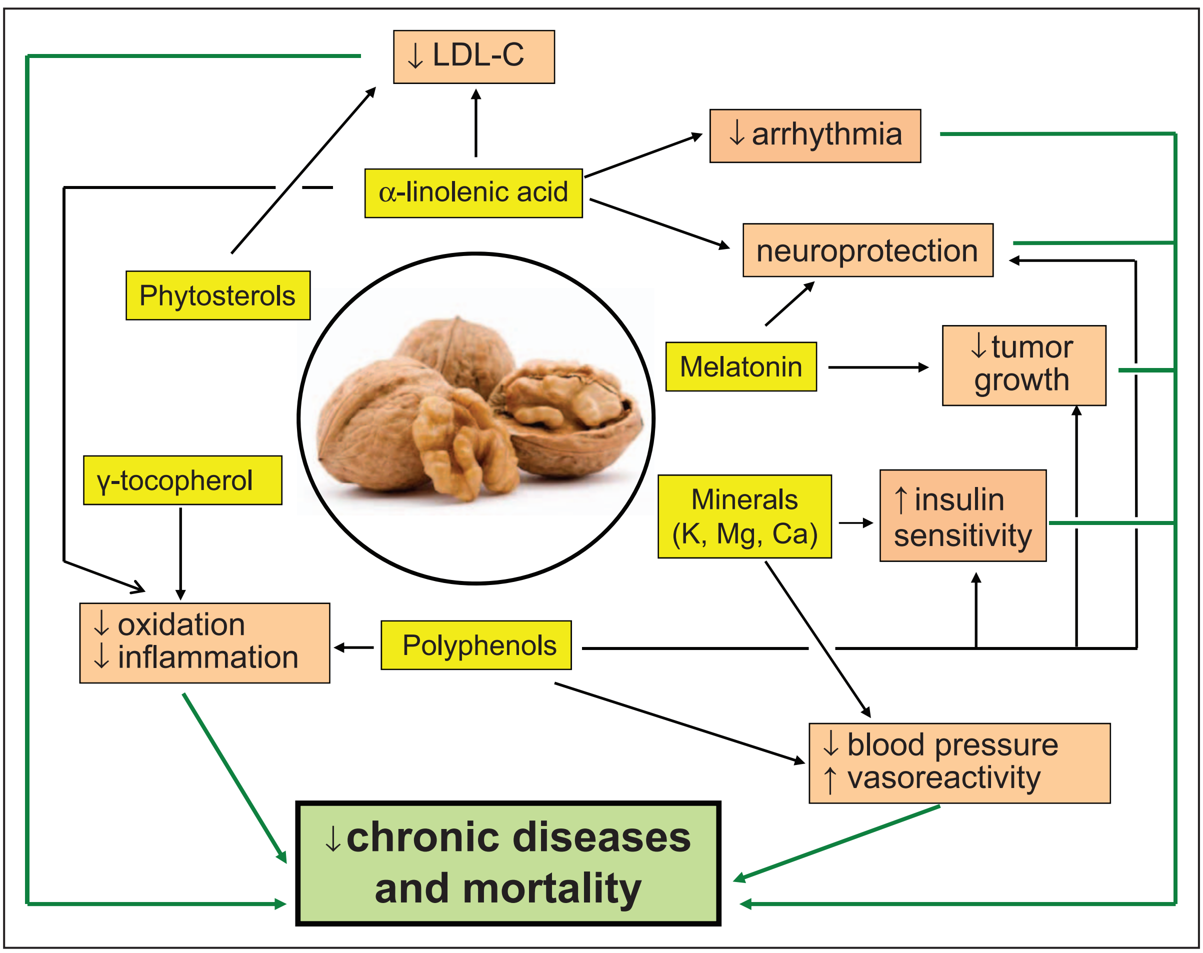

FIGURE 1. The consumption of walnuts improves overall health because of their unique composition in bioactive nutrients and phytochemicals and a complex synergy among them for effects on diverse metabolic pathways. ALA and the main micronutrients of walnuts are represented together with their principal biological targets (long arrow connections). The net effects demonstrated in experimental and/or clinical studies on outcome variables relevant to cardiovascular, brain and overall health for each relevant walnut nutrient and for consumption of whole walnuts are shown. The overall result would be reduced incidence of and/or mortality from chronic noncommunicable diseases such as CVD, cancer and neurodegenerative disorders, as suggested in observational cohort studies examining clinical associations of exposure to nuts, in general, or walnuts, in particular. ALA, alpha-linolenic acid; Ca, calcium; CVD, cardiovascular disease; K, potassium; Mg, magnesium.

reduced fecal concentrations of toxic secondary bile acids deoxycholate and lithocholate [51▪]. Such beneficial effects on the intestinal microbiota can likely be ascribed to nondigestible material from walnuts, mainly ellagitannins and fiber polysaccharides.

CONCLUSION

All nuts are rich sources of bioactive nutrients, but walnuts have a distinct composition (high ALA, melatonin and polyphenol content). Recent findings from clinical studies suggest that ALA metabolism gives rise to vasodilatory and anti-inflammatory oxylipins, which might underlie the beneficial effect of walnut consumption on endothelial function. Incipient experimental research also suggests that ALA is neuroprotective, although polyphenols from walnuts probably synergize for beneficial effects on brain function. Recent epidemiological observations have related the blood or tissue content of ALA as biomarker of intake to protection from fatal CHD to the same degree as that afforded by EPA and DHA, pointing to a similar antiarrhythmic effect of both vegetable and marine n-3PUFA. Given that dose–response relationships exist between walnut consumption and both reduced CVD rates and blood cholesterol reduction, dose appears to be a relevant factor when recommending walnuts to improve cardiometabolic risk. Phytosterols in nuts are responsible in part for their cholesterol-lowering effect, as indicated by a recent meta-analysis of nut-feeding trials. Nonsodium minerals such as potassium and magnesium, shared by all nuts, have beneficial effects on cardiometabolic risk, as confirmed by recent reviews. Walnuts are rich in γ-tocopherol, a form of vitamin E that has anti-inflammatory and anticancer properties in addition to being a potent antioxidant. Evidence is emerging on antitumorigenic actions of walnut phytomelatonin, but its sleep-promoting effects have not been tested in humans. Finally, recent experimental evidence suggests that the main polyphenols in walnuts, ellagitannins and their metabolites (urolithins), have beneficial effects against oxidation, inflammation, and tumor growth and also positively influence the intestinal microbiota. As shown in part in Fig. 1, most bioactive walnut micronutrients synergize to affect multiple metabolic pathways leading to protection from chronic noncommunicable diseases. For simplicity, the scheme cannot include all the described effects of particular molecules. Given their highly bioactive micronutrient content, walnuts may be considered as natural health capsules that can be incorporated into the usual diet to promote overall health.

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Conflicts of interest

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REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

1. Ros E. Nuts and CVD. Br J Nutr 2015; 113(Suppl 2):S111–S120.
2. Mayhew AJ, de Souza RJ, Meyre D, *et al.* A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. Br J Nutr 2016; 115:212–225.
3. ▪ Aune D, Keum N, Giovannucci E, *et al.* Nut consumption and risk of cardiovascular disease, total cancer, all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective studies. BMC Med 2016; 14:207.

   Relevant meta-analysis of epidemiologic studies relating dietary exposure to nuts to various health outcomes.
4. ▪ Guasch-Ferré M, Liu X, Malik VS, *et al.* Nut consumption and risk of cardiovascular disease in three large prospective cohorts. J Am Coll Cardiol 2017; 70:2519–2532.

   Largest prospective study relating exposure to nuts in the diet to cardiovascular outcomes. Unlike other studies of this kind, this report separates the effect of walnuts from that of other nut types.
5. Del Gobbo LC, Falk MC, Feldman R, *et al.* Effects of tree nuts on blood lipids, apolipoproteins, and blood pressure: systematic review, meta-analysis, and dose-response of 61 controlled intervention trials. Am J Clin Nutr 2015; 102:1347–1356.
6. Guasch-Ferré M, Li J, Hu FB, *et al.* Effects of walnut consumption on blood lipids and other cardiovascular risk factors: an updated meta-analysis and systematic review of controlled trials. Am J Clin Nutr 2018; 108:174–187.
7. Segura R, Javierre C, Lizarraga MA, Ros E. Other relevant components of nuts: phytosterols, folate and minerals. Br J Nutr 2006; 96(Suppl 2):S36–44.
8. ▪ Hayes D, Angove MJ, Tucci J, Dennis C. Walnuts (Juglans regia) chemical composition and research in human health. Crit Rev Food Sci Nutr 2016; 56:1231–1241.

   Comprehensive review of walnut components in relation to health effects focusing on fatty acids and polyphenols.
9. Ros E, Hu FB. Consumption of plant seeds and cardiovascular health: epidemiological and clinical trial evidence. Circulation 2013; 128:553–565.
10. Kris-Etherton PM, Taylor DS, Yu-Poth S, *et al.* Polyunsaturated fatty acids in the food chain in the United States. Am J Clin Nutr 2000; 71(1 Suppl):179S-S188.
11. ▪▪ Baker EJ, Miles EA, Burdge GC, *et al.* Metabolism and functional effects of plant-derived omega-3 fatty acids in humans. Prog Lipid Res 2016; 64:30–56.

    Thorough review of plant-derived omega-3 fatty acids focused on human studies concerning the metabolic fate of ALA, interconversion to longer chain derivatives, epidemiologic associations and effects on cardiovascular diseases and risk factors.
12. Rimm EB, Appel LJ, Chiuve SE, *et al.*, American Heart Association Nutrition Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Epidemiology and Prevention; Council on Cardiovascular Disease in the Young; Council on Cardiovascular and Stroke Nursing; and Council on Clinical Cardiology. Seafood long-chain n-3 polyunsaturated fatty acids and cardiovascular disease: a science advisory from the American Heart Association. Circulation 2018; 138:e35–e47.

13. Blondeau N, Lipsky RH, Bourourou M, *et al.* Alpha-linolenic acid: an omega-3 fatty acid with neuroprotective properties-ready for use in the stroke clinic? Biomed Res Int 2015; 2015:519830.
14. Caligiuri SPB, Parikh M, Stamenkovic A, *et al.* Dietary modulation of oxylipins
▪ in cardiovascular disease and aging. Am J Physiol Heart Circ Physiol 2017; 313:H903–H918.
Comprehensive review of a current hot topic.
15. Holt RR, Yim SJ, Shearer GC, *et al.* Effects of short-term walnut consumption on human microvascular function and its relationship to plasma epoxide content. J Nutr Biochem 2015; 26:1458–1466.
16. Greupner T, Kutzner L, Nolte F, *et al.* Effects of a 12-week high-α-linolenic acid intervention on EPA and DHA concentrations in red blood cells and plasma oxylipin pattern in subjects with a low EPA and DHA status. Food Funct 2018; 9:1587–1600.
17. Mendonça AM, Cayer LGJ, Pauls SD, *et al.* Distinct effects of dietary ALA, EPA and DHA on rat adipose oxylipins vary by depot location and sex. Prostaglandins Leukot Essent Fatty Acids 2018; 129:13–24.
18. Pauls SD, Rodway LA, Winter T, *et al.* Anti-inflammatory effects of α-linolenic acid in M1-like macrophages are associated with enhanced production of oxylipins from α-linolenic and linoleic acid. J Nutr Biochem 2018; 57: 121–129.
19. Qi W, Gutierrez GE, Gao X, *et al.* The ω-3 fatty acid α-linolenic acid extends
▪ Caenorhabditis elegans lifespan via NHR-49/PPARα and oxidation to oxylipins. Aging Cell 2017; 16:1125–1135.
Article uncovering novel presumed antiaging mechanisms of ALA.
20. Xiao Y, Huang W, Peng C, *et al.* Effect of nut consumption on vascular endothelial function: a systematic review and meta-analysis of randomized controlled trials. Clin Nutr 2018; 37:831–839.
21. Hejr H, Ghareghani M, Zibara K, *et al.* The ratio of 1/3 linoleic acid to alpha-linolenic acid is optimal for oligodendrogenesis of embryonic neural stem cells. Neurosci Lett 2017; 651:216–225.
22. Fisher DR, Poulose SM, Bielinski DF, Shukitt-Hale B. Serum metabolites from walnut-fed aged rats attenuate stress-induced neurotoxicity in BV-2 microglial cells. Nutr Neurosci 2017; 20:103–109.
23. Lee AY, Lee MH, Lee S, Cho EJ. Neuroprotective effect of alpha-linolenic acid against Aβ-mediated inflammatory responses in C6 glial cell. J Agric Food Chem 2018; 66:4853–4861.
24. Figueiredo TH, Harbert CL, Pidoplichko V, *et al.* Alpha-linolenic acid treatment reduces the contusion and prevents the development of anxiety-like behavior induced by a mild traumatic brain injury in rats. Mol Neurobiol 2018; 55:187–200.
25. Del Gobbo LC, Imamura F, Aslibekyan S, *et al.,* Cohorts for Heart and Aging
▪▪ Research in Genomic Epidemiology (CHARGE) Fatty Acids and Outcomes Research Consortium (FORCe). ω-3 Polyunsaturated fatty acid biomarkers and coronary heart disease: pooling project of 19 cohort studies. JAMA Intern Med 2016; 176:1155–1166.
Seminal report of pooled data from 19 epidemiological studies conducted in 16 countries dealing with blood or tissue biomarkers of omega-3 intake in relation to incident coronary heart disease. Results show a similar association of higher levels of biomarkers of marine omega-3 and ALA with a lower incidence of fatal coronary heart disease, suggesting an antiarrhythmic effect for all omega-3 fatty acids irrespective of marine or plant origin.
26. Rajaram S. Health benefits of plant-derived α-linolenic acid. Am J Clin Nutr 2014; 100(Suppl 1):S443–S448.
27. Moreau RA, Nyström L, Whitaker BD, *et al.* Phytosterols and their derivatives:
▪▪ Structural diversity, distribution, metabolism, analysis, and health-promoting uses. Prog Lipid Res 2018; 70:35–61.
Thorough updated review on phytosterols, covering all aspects of these fascinating molecules, as defined in the title, a must for anyone interested in the topic. The high phytosterol content of nuts is underlined.
28. Del Gobbo LC, Falk MC, Feldman R, *et al.* Are phytosterols responsible for the low-density lipoprotein-lowering effects of tree nuts? A systematic review and meta-analysis. J Am Coll Cardiol 2015; 65:2765–2767.
29. McDonough AA, Veiras LC, Guevara CA, Ralph DL. Cardiovascular benefits associated with higher dietary K^+ vs. lower dietary Na^+: evidence from population and mechanistic studies. Am J Physiol Endocrinol Metab 2017; 312:E348–E356.
30. Fang X, Wang K, Han D, *et al.* Dietary magnesium intake and the risk of cardiovascular disease, type 2 diabetes, and all-cause mortality: a dose-response meta-analysis of prospective cohort studies. BMC Med 2016; 14:210.
31. Rosique-Esteban N, Guasch-Ferré M, Hernández-Alonso P, Salas-Salvadó J. Dietary magnesium and cardiovascular disease: a review with emphasis in epidemiological studies. Nutrients 2018; 10: pii: E168.
32. Asemi Z, Saneei P, Sabihi SS, *et al.* Total, dietary, and supplemental calcium intake and mortality from all-causes, cardiovascular disease, and cancer: a meta-analysis of observational studies. Nutr Metab Cardiovasc Dis 2015; 25:623–634.
33. Yang B, Campbell PT, Gapstur SM, *et al.* Calcium intake and mortality from all causes, cancer, and cardiovascular disease: the Cancer Prevention Study II Nutrition Cohort. Am J Clin Nutr 2016; 103:886–894.
34. Weaver CM, Alexander DD, Boushey CJ, *et al.* Calcium plus vitamin D supplementation and risk of fractures: an updated meta-analysis from the National Osteoporosis Foundation. Osteoporos Int 2016; 27:367–376.
35. Adebamowo SN, Spiegelman D, Willett WC, Rexrode KM. Association between intakes of magnesium, potassium, and calcium and risk of stroke: 2 cohorts of US women and updated meta-analyses. Am J Clin Nutr 2015; 101:1269–1277.
36. Mathur P, Ding Z, Saldeen T, Mehta JL. Tocopherols in the prevention and treatment of atherosclerosis and related cardiovascular disease. Clin Cardiol 2015; 38:570–576.
37. Abdallah IB, Tlili N, Martinez-Force E, *et al.* Content of carotenoids, tocopherols, sterols, triterpenic and aliphatic alcohols, and volatile compounds in six walnuts (Juglans regia L.) varieties. Food Chem 2015; 173:972–978.
38. Das Gupta S, Suh N. Tocopherols in cancer: an update. Mol Nutr Food Res 2016; 60:1354–1363.
39. Meng X, Li Y, Li S, *et al.* Dietary sources and bioactivities of melatonin.
▪ Nutrients 2017; 9:E367.
Comprehensive review of dietary sources, bioactivity and mechanisms of action of melatonin.
40. Pribis P. Effects of walnut consumption on mood in young adults – a randomized controlled trial. Nutrients 2016; 8:668.
41. Reiter RJ, Manchester LC, Tan DX. Melatonin in walnuts: influence on levels of melatonin and total antioxidant capacity of blood. Nutrition 2005; 21:920–924.
42. Garcia CP, Lamarque AL, Comba A, *et al.* Synergistic antitumor effects of melatonin and PUFAs from walnuts in a murine mammary adenocarcinoma model. Nutrition 2015; 31:570–577.
43. Sánchez-González C, Ciudad CJ, Noé V, Izquierdo-Pulido M. Health benefits
▪▪ of walnut polyphenols: an exploration beyond their lipid profile. Crit Rev Food Sci Nutr 2017; 57:3373–3383.
Updated review summarizing the health benefits of walnut polyphenols and the possible molecular mechanisms involved. The role of elagitannins and derived urolithins against disease initiation and progression, including cancer, cardiovascular and neurodegenerative diseases is reviewed in depth.
44. García-Conesa MT, Chambers K, Combet E, *et al.* Meta-analysis of the effects
▪ of foods and derived products containing ellagitannins and anthocyanins on cardiometabolic biomarkers: analysis of factors influencing variability of the individual responses. Int J Mol Sci 2018; 19:E694.
Updated meta-analysis of randomized controlled trial testing ellagitannin-containing and anthocyanin-containing foods, including walnuts, for cardiometabolic effects.
45. Tomás-Barberán FA, González-Sarrías A, García-Villalba R, *et al.* Urolithins,
▪▪ the rescue of 'old' metabolites to understand a 'new' concept: metabotypes as nexus among phenolic metabolism, microbiota dysbiosis, and host health status. Mol Nutr Food Res 2017; 61:.
Thorough review of the role and potential of urolithins in human health and a perspective of the research approach needed to demonstrate these health effects. This article fills in a critical part of the urolithin jigsaw puzzle.
46. Selma MV, González-Sarrías A, Salas-Salvadó J, *et al.* The gut microbiota metabolism of pomegranate or walnut ellagitannins yields tow urolithin-metabotypes that correlate with cardiometabolic risk biomarkers: comparision between normoweight, overweight-obesity and metabolic syndrome. Clin Nutr 2018; 37:897–905.
47. Koh SJ, Choi YI, Kim Y, *et al.* Walnut phenolic extract inhibits nuclear factor kappaB signaling in intestinal epithelial cells, and ameliorates experimental colitis and colitis-associated colon cancer in mice. Eur J Nutr 2018. [Epub ahead of print]
48. Nakanishi M, Chen Y, Qendro V, *et al.* Effects of walnut consumption on colon carcinogenesis and microbial community structure. Cancer Prev Res (Phila) 2016; 9:692–703.
49. Guan F, Tabrizian T, Novaj A, *et al.* Dietary walnuts protect against obesity-driven intestinal stem cell decline and tumorigenesis. Front Nutr 2018; 5:37.
50. Byerley LO, Samuelson D, Blanchard E, *et al.* Changes in the gut microbial communities following addition of walnuts to the diet. J Nutr Biochem 2017; 48:94–102.
51. Holscher HD, Guetterman HM, Swanson KS, *et al.* Walnut consumption
▪ alters the gastrointestinal microbiota, microbially derived secondary bile acids, and health markers in healthy adults: a randomized controlled trial. J Nutr 2018; 148:861–867.
First clinical study investigating the effects of walnuts on intestinal microbiota. Walnut consumption was associated with increases in potentially beneficial butyrate-producing bacteria in the Firmicutes phylum and reduction of pro-inflammatory fecal secondary bile acids.
52. Bamberger C, Rossmeier A, Lechner K, *et al.* A walnut-enriched diet affects gut microbiome in healthy Caucasian subjects: a randomized, controlled trial. Nutrients 2018; 10:; pii: E244.