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Nuts and Cardiovascular Disease Prevention

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Abstract

Purpose of Review We review recent epidemiological and clinical studies investigating the consumption of tree nuts and peanuts and cardiovascular disease (CVD) mortality as well as CVD risk factors.

Recent Findings A greater consumption of tree nuts and peanuts is associated with a reduced risk of CVD mortality, as well as lower CVD events. Furthermore, risk factors associated with the development of CVD such as dyslipidemia, impaired vascular function, and hypertension are improved with regular tree nut and peanut consumption through a range of mechanism associated with their nutrient-rich profiles. There is weak inconsistent evidence for an effect of nut consumption on inflammation. There is emerging evidence that consuming tree nuts reduces the incidence of non-alcoholic fatty liver disease (NAFLD) and promotes diversity of gut microbiota, which in turn may improve CVD outcomes.

Summary Evidence for CVD prevention is strong for some varieties of tree nuts, particularly walnuts, and length of supplementation and dose are important factors for consideration with recommendations.

Keywords Nuts; cardiovascular diseases · Cholesterol · Inflammation · Vascular stiffness · Microbiota

Introduction

Nut consumption has long been associated with beneficial health effects on metabolic risk factors such as excess adiposity. Tree nut consumption has been significantly associated with lower body mass index (BMI) and waist circumference [1] as well as reduced weight gain and risk of obesity [2]. Nut consumption has also been associated with reduced cardiovascular disease (CVD) risk factors including dyslipidemia, elevated blood pressure, and impaired vascular function.

This review will consider the nutrient profiles of nuts, the role of nuts in the context of a whole diet, and the mechanisms through which tree nuts and peanuts provide cardioprotection before focusing on evidence from the past 5 years related to CVD events and mortality. Finally, the effects of tree nuts and peanuts on lipid profiles, vascular function, blood pressure regulation, and inflammation will also be discussed. As recent reviews have provided timely updates on the beneficial effects of nuts on managing body weight [3, 4], insulin resistance [5••], and type 2 diabetes [6], these will not be included in this review.

Cardioprotective Nutrient Profiles of Nuts

Nuts are rich in unsaturated fatty acids, protein, fibres, plant sterols, minerals including potassium and magnesium, and antioxidants such as beta-carotene (vitamin A precursor), vitamins C and E, selenium, and phenolic compounds. Amongst the tree nuts and peanuts, the macronutrient profiles are similar, but they differ in the ratio of mono and polyunsaturated fatty acids, type of phenolic compounds, amounts of specific vitamins, minerals, and plant sterols present [7, 8]. For example, pistachios in comparison to other nuts, have a lower fat and caloric content per unit weight and contain the highest

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levels of unsaturated fatty acids, potassium, γ-tocopherol, phytosterols, and xanthophyll carotenoids (such as lutein) [9]. In comparison, walnuts are higher in alpha linolenic acid and almonds are rich in α-tocopherol [10, 11].

Nuts and Diet Quality

Cross-sectional studies have shown that nut consumption is associated with better nutrient profiles at a population level [12–14]. Modelling approaches have demonstrated improvements in diet quality when whole nuts are exchanged for other types of snack foods (of poor nutrient quality) [15], and the inclusion of nuts in both short [16–18] and longer term interventions [19, 20] has resulted in better quality diets overall. It should be noted that the ability of individuals to optimally incorporate nuts into their diet and avoid discretionary foods as snacks is likely to vary considerably, highlighting an important role for nutrition professionals in communicating recommendations [21]. Furthermore, it is important to recognise that the form of nuts consumed has the potential to have detrimental effects if they deliver added sugar and sodium to the diet [22].

Mechanisms of Action

Cholesterol Lowering

The nutrient composition of nuts, being rich in fibre, phytosterols, and unsaturated fat and low in saturated fat, is thought to be a key contributor to their low-density lipoprotein cholesterol (LDL-C)-lowering and high-density lipoprotein cholesterol (HDL-C)-preserving effects. Further, nuts lower serum cholesterol by reducing cholesterol absorption, inhibiting β-hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase and increasing bile acid production through stimulation of 7 α-hydroxylase [5••]. Walnut consumption in a rodent model has been associated with lower hepatic fat accumulation [23], and cholesterol efflux has been shown to increase in J774 cells cultured with serum from participants who consumed walnuts [24]. Controlled-feeding studies with almonds [25] and pistachios have also demonstrated dose-dependent improvements in ATP-binding cassette transporter A1 (ABCA1)-mediated serum cholesterol efflux capacity and global serum cholesterol efflux capacity [26]. Participants in the nut arm of the well-known PREDIMED study (which compared a lower-fat control diet with a Mediterranean diet supplemented with 30-g mixed nuts (15-g walnuts, 7.5-g almonds, and 7.5-g hazelnuts) daily or a Mediterranean diet supplemented with olive oil) experienced reductions in cholesterol ester (CE) production (CE 20:3) which was associated with reduced CVD risk. However, these changes in lipid metabolites were not associated with the risk of myocardial infarction, stroke, or cardiovascular death [27]. Interestingly, some of the variability in the lipid lowering effects of nuts in intervention studies may be due to inter-individual variability in response to phytosterols [28] and consequently intervention studies should consider individual responses in their data analyses.

Antioxidants and Polyphenolic Compounds

Oxidative stress plays a key role in both the development and progression of CVD, and antioxidant compounds in nuts have been shown to limit oxidative damage [29]. Specifically, polyphenols in nuts have antioxidant properties which can modulate nitric oxide (NO) production thereby altering vascular function. They have been shown to improve CVD risk factors through a number of mechanisms including reducing vascular inflammation, limiting LDL-C oxidation, inhibiting platelet aggregation, modulating apoptotic processes, and improving lipid profiles [10, 23, 30, 31]. Furthermore, the polyphenols in nuts are bioaccessible in the colon supporting a role for nuts in improving gut health as part of their beneficial effects [32].

Nuts and CVD Events and Mortality

In the past 5 years, four observational studies [33–36] and nine meta-analyses of prospective studies [37, 38••, 39–41, 42•, 43–45] have examined the effects of nuts on all-cause mortality and both fatal and non-fatal CVD. Of these, eight publications reported the association between nut intake and all-cause mortality [33, 34, 36•, 40, 42•, 43–45]. All (except for one study [34]) reported lower all-cause and CVD mortality with the highest nut intake (relative risks (RR) or hazard ratio (HR) ranging from 0.71 to 0.81). The RR of deaths by ischemic heart disease (IHD) (RR = 0.76) [37] and coronary heart disease (CHD) (RR = 0.70 and 0.73) [40, 43] were also found to be lower with higher nut intake. The association between nut intake and stroke mortality was not statistically significant in two cohort studies [34, 36•]. A meta-analysis published in the same year also did not observe significant association based on two cohort studies [46]. To the contrary, two more recent meta-analyses of cohort studies reported lower RR of 0.82 [40] and 0.83 [43] between low vs. high nut intake and stroke mortality. The lower RR in these meta-analyses, which were not previously reported, may be due to greater statistical power from the greater number of studies included in the analysis. One of the two meta-analyses [40] included 18 cohort studies, which contained both cohort studies that reported no association above [34, 36•]. A number of studies further reported lower all-cause and CVD mortality with every additional serve of nuts consumed per day (28 g/day) [42•], but similar associations were not found when nut consumption was increased only by one serving per week [40].

Nuts have also been associated with lower non-fatal CVD (HR = 0.94 and RR = 0.81) [35, 38], CHD (RR = 0.76 and 0.80) [38••, 39], and IHD events (RR = 0.78) [37] with increasing nut intake, or when intake increased by 10 g or 1 serving (28.4 g). However, the association between nut intake and stroke events was not found in three out of five studies published in the last 5 years [35, 37, 43]. In the remaining two publications, the reduction of risk for stroke was modest (RR = 0.89 and 0.90 respectively) [38••, 41]. One additional review completed a dose-response analysis of nut intake and stroke events and reported a non-linear association of reduced risk with 12 g/day increments [47]. In comparison, an umbrella review by Schwingshackl et al. [48] that included systematic reviews and meta-analyses published between 1966 and April 2016 found no association between nut consumption and reduced risk of stroke events. Finally, no association was found between nut intake and heart failure [39].

Overall, studies published in the past 5 years were consistent with previous studies that nut intake is linked to lower cardiovascular events and deaths, and that this association was the strongest when intake was in 1 serving/day increments. The association between nut consumption and stroke events remains weak.

Changes in Risk Factors for CVD with Nut Consumption

Hyperlipidemia

A comprehensive review in 2015 concluded that there is consistent evidence for reductions in total cholesterol, LDL-C, apolipoprotein B (ApoB), and triglycerides following tree nut consumption [49]. Studies published since have reported similar findings [50] and a more recently published umbrella review by Schwingshackl et al. [48] provided very similar conclusions. It should be noted that whilst these meta-analyses have reported improvements in lipid profiles overall, not all interventions with nuts have found significant reductions in total and LDL-C. These differences are likely influenced by population type, dose consumed, length of supplementation, and starting lipid levels. In addition, a potential limitation is that some studies only consider compliance/adherence to supplementation through self-report, and low compliance would cause underestimation of effects in their analyses [49].

Changes in HLD-C are less consistent, with meta-analyses concluding no overall improvement in HDL-C with nut consumption [48, 49]. It is important to acknowledge that effects on HDL-C may be population dependent and influenced by total energy intake. Jamshed et al. [51] found that incorporating low doses of two different varieties of almonds (10 g per day soaked overnight with skins removed and consumed in the morning on an empty stomach) into the diet of patients with coronary artery disease for 12 weeks was effective at increasing HDL-C (+ 21–22%) compared with baseline levels and was 13–15% higher than the control group. A 12-week study in Asian Indians with type 2 diabetes reported that supplementation with 30-g cashew nuts resulted in a significant increase in HDL-C compared with participants in the nut-free group [52]. When walnuts were included in an energy-restricted diet for 1 year, HDL-C increased significantly more compared to an energy-matched higher carbohydrate or higher fat diet despite no difference in the amount of weight lost between groups [53]. In this same study, the walnut-enriched energy-restricted diet also significantly reduced total and LDL-C (203 to 194 mg/dL and 121 to 112 mg/dL, $P < 0.05$ respectively) [54]. However, unexpectedly when almonds were included as part of a hypocaloric diet, whilst both groups saw improvements in several lipid measures, greater increases in HDL-C were observed in the nut-free group [54, 55]. Some studies have shown that during active weight loss, HDL-C decreases, but after weight loss is maintained, HDL-C increases. It could be that subjects on the almond diet were still losing weight [56, 57].

When considering the effects of nuts on lipids, it is important to consider the nutrient composition of comparator foods, how this contributes to overall energy and macronutrient intake, and importantly, whether this differs compared to the intervention diet [25, 58]. Accordingly, strategies to include nuts in the diet, whether by replacing other foods, adding them on top of a background diet or incorporating them into an energy-restricted diet, should also be considered. The contribution of walnuts to the macronutrient profile of the diet may be especially important, as by maintaining a higher total and unsaturated fat content, they may prevent reductions in HDL-C that can occur with energy restriction [53].

Management of hyperlipidaemia should be a holistic approach that incorporates improvements in diet and physical activity and medication when appropriate [59]. One study has considered whether the inclusion of nuts to the diet of people taking statins is able to provide an additional cholesterol lowering benefit. The STALL study demonstrated that when 100 g of almonds was added to the diets of people on a consistent statin dose for 4 weeks, there was a reduction in non-HDL-C (− 4.9% vs + 3.5%, $P = 0.02$) but no changes in total or HDL-C when compared with participants on a nut-free diet [60••]. This is an area where more studies are needed to consider different doses of both nuts and statins as well as length of supplementation.

Impaired Vascular Function

To better understand associations between nut consumption and cardiovascular risk reduction, numerous intervention studies have evaluated whether the inclusion of nuts improves

vascular health and function. Nuts, including their skins, also contain antioxidant vitamins and bioactive polyphenols, and many types are high in the amino acid L-arginine. L-Arginine is the precursor of nitric oxide, a potent vasodilator responsible for regulating vascular tone and blood pressure [61]. Furthermore, the nutrient profile of nuts, which are a source of magnesium, potassium, and calcium may promote blood pressure lowering benefits.

The most consistently used technique for assessing vascular reactivity in nut studies is flow-mediated dilatation (FMD), which measures the ability of the brachial artery to dilate in response to increased blood flow following temporary occlusion of the vessel. FMD of the brachial artery is closely associated with coronary endothelial function and impaired FMD increases risk for future cardiovascular events [62].

Meta-analyses of nut intervention studies, with and without soy nuts (whilst these are a legume some reviews have included them), report beneficial effects on vascular reactivity [63, 64•, 65]. These analyses included predominantly randomised controlled trials (range: 8 to 13 studies) supplementing single and mixed nuts for periods of 4 to 24 weeks. Daily nut consumption significantly improved FMD (range: + 0.41 to 1.03%). Furthermore, sub-analysis by nut type showed significant independent increases in FMD with walnut supplementation (range: + 0.39 to 1.08%) [63, 64•, 65]. The same benefits were not seen for other nut types. In addition, a meta-analysis of four randomised, controlled-feeding studies, showed that pistachios (32–128 g/d for 4–12 weeks) did not improve endothelial reactivity assessed via FMD (WMD: + 0.28%; 95%CI: − 0.58, 1.13; $P = 0.525$) [66]. A recent acute study reported that peanuts (85 g) preserved endothelial function (FMD) in overweight and obese men when consumed as part of a high-fat meal [67].

Other techniques for assessing vascular reactivity include peripheral artery tonometry (PAT), which calculates a reactive hyperemia index (RHI) from endothelium-mediated changes in the digital pulse waveform in response to occlusion of brachial blood flow [68]. PAT also provides an estimate of vascular stiffness, termed augmentation index (AI), based on the shape of the projected waveforms during rest. In a randomised, crossover, controlled-feeding study, men and women with well-controlled type II diabetes consumed a low-fat control diet or a moderate-fat diet containing pistachios (20% of total energy; 59–128 g/day) for 4 weeks each [69, 70]. Vascular function was assessed at baseline (after a 2-week run in on a Western diet), and at the end of each 4-week feeding period via PAT, FMD, and impedance cardiography, the latter providing a measure of total peripheral resistance (TPR). At the end of 4 weeks, there were no significant differences in FMD, RHI, or AI between the control diet and the pistachio-supplemented diet. However, the pistachio diet significantly reduced TPR compared to the control diet (− 3.7 ± 2.9%, $P = 0.004$). In a study by Huguenin et al. [71], microvascular reactivity was not improved following 3 months of Brazil nut supplementation (13 g/day) in patients with hypertension and dyslipidemia.

Recent studies assessing changes in arterial stiffness suggest that the inclusion of pistachios [72], but not almonds [73] may be beneficial. In a parallel trial, subjects with mild dyslipidemia were randomised to one of two groups, a lifestyle modification group involving increased physical activity and a low-fat diet (consistent with American Heart Association therapeutic lifestyle change diet) or lifestyle modification plus 40 g/day pistachios for 12 weeks [72]. At 12 weeks, participants in the pistachio group had beneficial changes in several vascular stiffness parameters, with a significant reduction in left brachial-ankle pulse wave velocity; this was significantly less than the control group (lifestyle modification alone). Comparatively, Chen et al. [73] reported no improvement in carotid-femoral or carotid-radial pulse wave velocity or PAT following supplementation with 85 g/day of almonds for 6 weeks in patients with coronary artery disease.

A study by Barbour and colleagues [74] was the first to evaluate whether daily peanut consumption improved cerebrovascular reactivity. In this parallel study, older, overweight adults consumed their habitual diet with or without peanuts for 12 weeks; males consumed 84 g/day and females 56 g/day of peanuts, comprising ~ 15% of total daily energy. At baseline and 12 weeks, cerebrovascular reactivity was assessed using Transcranial Doppler (TCD), which provides a non-invasive measure of cerebral blood flow velocity in response to a stimulus, in this instance carbogen gas inhalation (5% CO_2/95% O_2). Peanut consumption improved CVR in the left (+ 5%) and right (+ 7%) middle cerebral artery. Whilst there was no change in large artery elasticity, small artery elasticity improved by 10% after peanut consumption. Choudhury et al. [75] reported that almond supplementation (50 g/day for 4 weeks) significantly improved hyperaemic reactive blood flow following vessel occlusion in men.

Taken together, these studies suggest that nuts, in particular walnuts, may improve vascular health, specifically vascular reactivity of peripheral arteries as assessed via FMD. There is emerging evidence that peanuts may improve cerebrovascular reactivity, which may have potential for enhancing cognitive function due to improved blood flow; however, more studies are needed to confirm these effects in peanuts and other nut types. Similarly, there is less conclusive evidence for improvements in arterial stiffness, although the studies described here suggest that benefits may be confined to populations without established cardiovascular disease.

Elevated Blood Pressure

Two recent meta-analyses of intervention trials, both published in 2015, have evaluated the effect of nut consumption on blood pressure, with conflicting results [49, 76]. Data from

randomised controlled trials of tree nuts and legumes (soy nuts and peanuts) ($n = 21$) were analysed using a random effects model by Mohammadifard et al. [76]; all-type nut consumption significantly lowered SBP in participants without type 2 diabetes [mean difference (MD): − 1.29; 95% CI: − 2.35, − 0.22; $P = 0.02$]. Furthermore, sub-analyses by nut type showed that pistachios reduced SBP and DBP in all participants, including those with diabetes (SBP, MD: − 1.82; 95% CI: − 2.97, − 0.67; $P = 0.002$; DBP, MD: − 0.80; 95% CI: − 1.43, − 0.17; $P = 0.01$) and mixed nuts lowered DBP (MD: − 1.19; 95% CI: − 2.35, − 0.03; $P = 0.04$) [73]. Comparatively, Del Gobbo et al. [49] synthesised data from controlled trials of tree nuts only (all trials, $n = 21$; RCTs, $n = 17$). They reported no BP-lowering effect for tree nuts (total or individual nut type) [48]. In their analysis, the effect of size and variance for each trial was standardised to a 1-oz daily serving (28.4 g) of nuts and analysed using a fixed-effects model. Given these methodological differences, it is difficult to conclude with certainty the antihypertensive effect of nuts from these meta-analyses.

Several controlled intervention studies have since evaluated the effect of nuts on blood pressure when included as part of an isocaloric (habitual) or hypocaloric (weight loss) diet. Amongst the isocaloric studies, both peanuts ($n = 1$) [74] and a variety of tree nuts have been evaluated including almonds ($n = 3$) [51, 73, 75], pistachios ($n = 1$) [69], pecans ($n = 1$) [77], and cashews ($n = 2$) [52, 78] ranging in doses from 10 to 128 g/day for 4 to 12 weeks. Resting SBP or DBP was significantly reduced in two of the seven studies only [52, 75]. SBP reduced by 4–6% in healthy and 'at-risk' (two or more CVD risk factors) men, whereas DBP reduced by 6–12% in healthy men only following supplementation with 50 g almond/day for 4 weeks [75]. Similar reductions in SBP (~ 4%) were observed in diabetic individuals consuming a standard diabetic diet supplemented with 30 g/day cashews for 12 weeks [52]. Sauder et al. [69] reported a significant reduction in systolic ambulatory BP (− 3.5 ± 2.2 mmHg) but not resting BP following a 4-week isocaloric diet supplemented with pistachios at 20% total energy (59 to 128 g/d) compared to an energy matched control diet.

Four studies have evaluated whether almonds (50 g/day, 15% total energy) [55, 79] or walnuts (30–42 g/day) [54, 80] incorporated into energy-restricted diets can improve BP compared to advice alone and/or energy restriction without nuts. These studies have yielded mixed results; at this stage, it is unclear whether the inclusion of nuts provides significant additional benefits for BP lowering beyond that achieved by weight loss alone.

Inflammation

The evidence of whether nuts can alter inflammatory biomarkers is mixed. Cross-sectional data from 5013 participants in the Nurses' Health Study and Health Professionals' Follow-Up Study found that greater intake of nuts (tree nuts and peanuts) was associated with lower amounts of the inflammatory biomarkers C reactive protein (CRP) and interleukin-6 (IL-6) but no association with tumour necrosis factor alpha (TNF-α) receptor 2 [81]. Data from PREDIMED indicate that following the 1-year intervention, changes in urinary polyphenol metabolites were associated with decreased inflammatory biomarkers (plasma concentrations of intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion protein (VCAM-1), IL-6, TNF-α, and MCP-1). These positive effects were observed in participants randomised to the Mediterranean diet (both the nut group and the olive oil group) but not the lower-fat control diet [82].

Despite these promising findings, evidence from shorter term RCTs focused on individual nuts are not supportive of nuts reducing inflammatory mediators. No significant changes in CRP were observed following 12 weeks of consuming high-oleic peanuts in healthy, overweight adults [83]. These findings were consistent with other studies of tree nuts included in two recent systematic reviews of RCTs that demonstrated that nut consumption was associated with small, non-significant reductions in inflammatory biomarkers (CRP, adiponectin, TNF-α, IL-6, interleukin-10 (IL-10), VCAM-1, ICAM-1) [64•, 84]. The majority of studies published since have also failed to demonstrate significant improvements in inflammatory biomarkers following nut consumption [77, 85–87], although a crossover study with Korean adults reported improvements in IL-10 and a tendency for reductions in ICAM-1, IL-1β, and IL-6 following 4 weeks of snacking on 56 g almonds/day compared with cookies [88]. These discrepancies are likely to be due to the dose, length of supplementation, and populations included in the studies.

Emerging Evidence for Nuts and CVD

Non-alcoholic Fatty Liver Disease

Non-alcoholic fatty liver disease (NAFLD) is associated with increased risk of CVD. Dietary strategies are recommended as part of the management approach along with weight loss. Nuts [86] and other foods commonly found in the Mediterranean diet are also encouraged [89, 90]. Cross-sectional data on 348 Korean adults found that low nut consumption in men was associated with increased odds of NAFLD (OR 3.66) [91]. Data from the PREDIMED study showed that inclusion of nuts into a Mediterranean diet was associated with a lower fatty liver index compared with a low-fat control diet suggesting slower progression of NAFLD [92••]. Future studies

Table 1 Mechanisms by which nuts improve components of cardiovascular, metabolic and gut health

Component	Proposed mechanisms
Cholesterol metabolism	• Reduced cholesterol absorption
	• Inhibition of HMG-CoA reductase
	• Increased bile acid production
	• Stimulation of 7 α-hydroxylase
	• Increased cholesterol efflux
	• Reduced cholesterol ester production
Vascular function and blood pressure	• Modulation of nitric oxide production
	• Reduced vascular inflammation
	• Reduced LDL oxidation
	• Inhibition of platelet aggregation
	• Reduced oxidative stress
Inflammation	• Reduced production of pro-inflammatory cytokines
Fatty liver	• Increased fatty acid β-oxidation
	• Reduced oxidative stress and inflammation
	• Reduced fibrogenesis
Gut microbiome	• Altered gut microbiota profile

should continue to explore dose effects and whether benefits are associated with all nuts.

Gut Microbiota

The association between atherosclerosis and gut microbiota has been attracting increased attention with studies demonstrating that gut microbes are involved in the metabolism of proatherogenic compounds [93]. Gut dysbiosis is associated with intestinal inflammation and reduced integrity of the gut barrier, which in turn increases circulating levels of bacterial structural components and microbial metabolites that may facilitate the development of CVD [94]. Nuts contain components such as polyphenols and polysaccharides, that are non-digestible to humans and act as prebiotics which provide substrates for gut microbiota and aid with restoring balance [95]. Studies with walnuts [96, 97], almonds [98••], and pistachios [99] have shown that consumption over 3–16 weeks improves probiotic and butyric acid-producing species. Further analyses are needed to understand how these changes relate to changes in lipid metabolism and CVD risk.

Conclusion

The association between nut consumption and better CVD health is seen across a wide range of populations, with varying dose and types of nuts. The cardioprotective mechanisms include cholesterol lowering, reduced inflammation, improved vascular health, and potentially microbiota and NAFLD (Table 1). A recent review looking at cardioprotective foods ranked nuts and seeds highly as foods that should be included in diets to prevent ischemic heart disease [100]. Dose-response data support lower risk for coronary heart disease with higher nut consumption up to about 10–15 g/day [39] and association with reductions in all-cause mortality up to 15–20 g/day [44]. Whilst non-linear associations exist for nut intake and reduce risk of CHD incidence, Micha et al. concluded that five servings/week, each of about 1 oz. (~ 28 g), is the optimal mean population intake based on ischemic heart disease prevention [100].

Whilst the effects associated with inclusion of a single food such as nuts into the diet may be beneficial for dyslipidemia, the magnitude of effect is likely to be smaller than changes associated with a whole of dietary pattern change [101]. Observational data indicate that nut eaters generally have healthier dietary patterns compared with people who never or rarely consume nuts, and this equates to better nutrient profiles and diet quality [12, 35]. Taken together, this suggests that nuts have significant independent CV benefits, and when incorporated as part of an overall healthy diet, these benefits are magnified.

Compliance with Ethical Standards

Conflict of Interest Dr. Coates reports grants from the Peanut Company of Australia, the Almond Board of California, the Almond Board of Australia, and the International Nut and Dried Fruit Council, outside the submitted work. Dr. Tan reports grants from Almond Board of California, outside the submitted work. Dr. Hill reports grants from Almond Board of California, the Almond Board of Australia, and the International Nut and Dried Fruit Council, outside the submitted work.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. O'Neil CE, Fulgoni VL, 3rd, Nicklas TA: Tree nut consumption is associated with better adiposity measures and cardiovascular and metabolic syndrome health risk factors in U.S. adults: NHANES 2005–2010. Nutr J 2015, 14:64.
2. Freisling H, Noh H, Slimani N, Chajès V, May AM, Peeters PH, et al. Nut intake and 5-year changes in body weight and obesity risk in adults: results from the EPIC-PANACEA study. Eur J Nutr. 2017;
3. Jackson CL, Hu FB: Long-term associations of nut consumption with body weight and obesity. Am J Clin Nutr 2014, 100 Suppl 1: 408s–411s.
4. Tan SY, Dhillon J, Mattes RD: A review of the effects of nuts on appetite, food intake, metabolism, and body weight. Am J Clin Nutr 2014, 100 Suppl 1:412s–422s.
5. •• Kim Y, Keogh JB, Clifton PM. Benefits of nut consumption on insulin resistance and cardiovascular risk factors: multiple potential mechanisms of actions. Nutrients. 2017;9(11) **Recent and comprehensive review of the mechanisms by which nuts reduce risk for CVD and type 2 diabetes.**
6. Hernandez-Alonso P, Camacho-Barcia L, Bullo M, Salas-Salvado J: Nuts and dried fruits: an update of their beneficial effects on type 2 diabetes. Nutrients 2017, 9(7).
7. Ros E. Nuts and CVD. Br J Nutr. 2015;113(Suppl 2):S111–20.
8. USDA National Nutrient Database for Standard Reference; Release 28, Version Current: September 2015; /nea/bhnrc/ndl.
9. Terzo S, Baldassano S, Caldara GF, Ferrantelli V, Lo Dico G, Mulè F, et al. Health benefits of pistachios consumption. Nat Prod Res. 2017:1–12.
10. Rusu ME, Gheldiu AM, Mocan A, Vlase L, Popa DS. Anti-aging potential of tree nuts with a focus on the phytochemical composition, molecular mechanisms and thermal stability of major bioactive compounds. Food Funct. 2018;9(5):2554–75.
11. Stuetz W, Schlormann W, Glei M. B-vitamins, carotenoids and alpha-/gamma-tocopherol in raw and roasted nuts. Food Chem. 2017;221:222–7.
12. Brown RC, Tey SL, Gray AR, Chisholm A, Smith C, Fleming E, et al. Nut consumption is associated with better nutrient intakes: results from the 2008/09 New Zealand Adult Nutrition Survey. Br J Nutr. 2016;115(1):105–12.
13. Griel AE, Eissenstat B, Juturu V, Hsieh G, Kris-Etherton PM. Improved diet quality with peanut consumption. J Am Coll Nutr. 2004;23(6):660–8.
14. O'Neil CE, Nicklas TA, Fulgoni VL. Tree nut consumption is associated with better nutrient adequacy and diet quality in adults: National Health and Nutrition Examination Survey 2005-2010. Nutrients. 2015;7(1):595–607.
15. Rehm CD, Drewnowski A. Replacing American snacks with tree nuts increases consumption of key nutrients among US children and adults: results of an NHANES modeling study. Nutr J. 2017;16(1):17.
16. Barbour JA, Stojanovski E, Moran LJ, Howe PRC, Coates AM. The addition of peanuts to habitual diets is associated with lower consumption of savory non-core snacks by men and sweet non-core snacks by women. Nutr Res. 2017;41:65–72.
17. Burns AM, Zitt MA, Rowe CC, Langkamp-Henken B, Mai V, Nieves C Jr, et al. Diet quality improves for parents and children when almonds are incorporated into their daily diet: a randomized, crossover study. Nutr Res. 2016;36(1):80–9.
18. Pearson KR, Tey SL, Gray AR, Chisholm A, Brown RC. Energy compensation and nutrient displacement following regular consumption of hazelnuts and other energy-dense snack foods in non-obese individuals. Eur J Nutr. 2017;56(3):1255–67.
19. Bitok E, Jaceldo-Siegl K, Rajaram S, Serra-Mir M, Roth I, Feitas-Simoes T, et al. Favourable nutrient intake and displacement with long-term walnut supplementation among elderly: results of a randomised trial. Br J Nutr. 2017;118(3):201–9.
20. Neale EP, Tapsell LC, Martin A, Batterham MJ, Wibisono C, Probst YC. Impact of providing walnut samples in a lifestyle intervention for weight loss: a secondary analysis of the HealthTrack trial. Food Nutr Res. 2017;61(1):1344522.
21. Kranz S, Hill AM, Fleming JA, Hartman TJ, West SG, Kris-Etherton PM. Nutrient displacement associated with walnut supplementation in men. J Hum Nutr Diet. 2014;27(Suppl 2):247–54.
22. Sterling SR, Bertrand B, Judd S, Baskin ML. Nut intake among overweight and obese African-American women in the rural south. Am J Health Behav. 2016;40(5):585–93.
23. Choi Y, Abdelmegeed MA, Song BJ. Preventive effects of dietary walnuts on high-fat-induced hepatic fat accumulation, oxidative stress and apoptosis in mice. J Nutr Biochem. 2016;38:70–80.
24. Berryman CE, Grieger JA, West SG, Chen CYO, Blumberg JB, Rothblat GH, et al. Acute consumption of walnuts and walnut components differentially affect postprandial lipemia, endothelial function, oxidative stress, and cholesterol efflux in humans with mild hypercholesterolemia. J Nutr. 2013;143(6):788–94.
25. Berryman CE, Fleming JA, Kris-Etherton PM. Inclusion of almonds in a cholesterol-lowering diet improves plasma HDL subspecies and cholesterol efflux to serum in normal-weight individuals with elevated LDL cholesterol. J Nutr. 2017;147(8):1517–23.
26. Holligan SD, West SG, Gebauer SK, Kay CD, Kris-Etherton PM. A moderate-fat diet containing pistachios improves emerging markers of cardiometabolic syndrome in healthy adults with elevated LDL levels. Br J Nutr. 2014;112(5):744–52.
27. Toledo E, Wang DD, Ruiz-Canela M, Clish CB, Razquin C, Zheng Y, et al. Plasma lipidomic profiles and cardiovascular events in a randomized intervention trial with the Mediterranean diet. Am J Clin Nutr. 2017;106(4):973–83.
28. Fumeron F, Bard JM, Lecerf JM. Interindividual variability in the cholesterol-lowering effect of supplementation with plant sterols or stanols. Nutr Rev. 2017;75(2):134–45.
29. Calcabrini C, De Bellis R, Mancini U, Cucchiarini L, Stocchi V, Potenza L. Protective effect of Juglans regia L. walnut extract against oxidative DNA damage. Plant Foods Hum Nutr. 2017;72(2):192–7.
30. Gormaz JG, Valls N, Sotomayor C, Turner T, Rodrigo R. Potential role of polyphenols in the prevention of cardiovascular diseases: molecular bases. Curr Med Chem. 2016;23(2):115–28.
31. Huguenin GV, Oliveira GM, Moreira AS, et al. Improvement of antioxidant status after Brazil nut intake in hypertensive and dyslipidemic subjects. Nutr J. 2015;14:54.
32. Rocchetti G, Chiodelli G, Giuberti G, Lucini L. Bioaccessibility of phenolic compounds following in vitro large intestine fermentation of nuts for human consumption. Food Chem. 2018;245:633–40.
33. Eslamparast T, Sharafkhah M, Poustchi H, Hashemian M, Dawsey SM, Freedman ND, et al. Nut consumption and total and cause-

specific mortality: results from the Golestan Cohort Study. Int J Epidemiol. 2017;46(1):75–85.
34. Gopinath B, Flood VM, Burlutksy G, Mitchell P. Consumption of nuts and risk of total and cause-specific mortality over 15 years. Nutr Metab Cardiovasc Dis. 2015;25(12):1125–31.
35. Guasch-Ferre M, Liu X, Malik VS, et al. Nut consumption and risk of cardiovascular disease. J Am Coll Cardiol. 2017;70(20): 2519–32.
36.• Hshieh TT, Petrone AB, Gaziano JM, Djousse L. Nut consumption and risk of mortality in the Physicians' Health Study. Am J Clin Nutr. 2015;101(2):407–12. **This paper suggests that nut intake of 1–3 servings/month is not likely to provide protection against CVD mortality when compared to at least 2–4 servings/week.**
37. Afshin A, Micha R, Khatibzadeh S, Mozaffarian D. Consumption of nuts and legumes and risk of incident ischemic heart disease, stroke, and diabetes: a systematic review and meta-analysis. Am J Clin Nutr. 2014;100(1):278–88.
38.•• 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(1):207. **This meta-analysis conducted separate analyses for tree and ground nuts. Peanuts was reported to show slightly lower relative risks for CVD events than tree nuts.**
39. Bechthold A, Boeing H, Schwedhelm C, Hoffmann G, Knüppel S, Iqbal K, et al. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. Crit Rev Food Sci Nutr. 2017:1–20.
40. Chen GC, Zhang R, Martinez-Gonzalez MA, et al. Nut consumption in relation to all-cause and cause-specific mortality: a meta-analysis 18 prospective studies. Food Funct. 2017;8(11):3893–905.
41. Deng C, Lu Q, Gong B, Li L, Chang L, Fu L, et al. Stroke and food groups: an overview of systematic reviews and meta-analyses. Public Health Nutr. 2018;21(4):766–76.
42.• Grosso G, Yang J, Marventano S, Micek A, Galvano F, Kales SN. Nut consumption on all-cause, cardiovascular, and cancer mortality risk: a systematic review and meta-analysis of epidemiologic studies. Am J Clin Nutr. 2015;101(4):783–93. **This study examined the dose-response relationship between nut consumption and all-cause and CVD mortality.**
43. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. Br J Nutr. 2016;115(2):212–25.
44. Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi AM, Knüppel S, Iqbal K, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr. 2017;105(6):1462–73.
45. van den Brandt PA, Schouten LJ. Relationship of tree nut, peanut and peanut butter intake with total and cause-specific mortality: a cohort study and meta-analysis. Int J Epidemiol. 2015;44(3): 1038–49.
46. Zhang Z, Xu G, Wei Y, Zhu W, Liu X. Nut consumption and risk of stroke. Eur J Epidemiol. 2015;30(3):189–96.
47. Shao C, Tang H, Zhao W, He J. Nut intake and stroke risk: a dose-response meta-analysis of prospective cohort studies. Sci Rep. 2016;6:30394.
48. Schwingshackl L, Hoffmann G, Missbach B, Stelmach-Mardas M, Boeing H. An umbrella review of nuts intake and risk of cardiovascular disease. Curr Pharm Des. 2017;23(7):1016–27.
49. Del Gobbo LC, Falk MC, Feldman R, Lewis K, Mozaffarian D. 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(6): 1347–56.
50. Mah E, Schulz JA, Kaden VN, Lawless AL, Rotor J, Mantilla LB, et al. Cashew consumption reduces total and LDL cholesterol: a randomized, crossover, controlled-feeding trial. Am J Clin Nutr. 2017;105(5):1070–8.
51. Jamshed H, Sultan FA, Iqbal R, Gilani AH. Dietary almonds increase serum HDL cholesterol in coronary artery disease patients in a randomized controlled trial. J Nutr. 2015;145(10):2287–92.
52. Mohan V, Gayathri R, Jaacks LM, Lakshmipriya N, Anjana RM, Spiegelman D, et al. Cashew nut consumption increases HDL cholesterol and reduces systolic blood pressure in Asian Indians with type 2 diabetes: a 12-week randomized controlled trial. J Nutr. 2018;148(1):63–9.
53. Le T, Flatt SW, Natarajan L, et al. Effects of diet composition and insulin resistance status on plasma lipid levels in a weight loss intervention in women. J Am Heart Assoc. 2016:5(1).
54. Rock CL, Flatt SW, Barkai HS, Pakiz B, Heath DD. Walnut consumption in a weight reduction intervention: effects on body weight, biological measures, blood pressure and satiety. Nutr J. 2017;16(1):76.
55. Abazarfard Z, Salehi M, Keshavarzi S. The effect of almonds on anthropometric measurements and lipid profile in overweight and obese females in a weight reduction program: a randomized controlled clinical trial. J Res Med Sci. 2014;19(5):457–64.
56. Dattilo AM, Kris-Etherton PM. Effects of weight reduction on blood lipids and lipoproteins: a meta-analysis. Am J Clin Nutr. 1992;56(2):320–8.
57. Rolland C, Broom I. The effects of very-low-calorie diets on HDL: a review. Cholesterol. 2011;2011:306278.
58. Jenkins DJA, Kendall CWC, Lamarche B, Banach MS, Srichaikul K, Vidgen E, et al. Nuts as a replacement for carbohydrates in the diabetic diet: a reanalysis of a randomised controlled trial. Diabetologia. 2018;61:1734–47.
59. Fischer S, Schatz U, Julius U. Practical recommendations for the management of hyperlipidemia. Atheroscler Suppl. 2015;18:194–8.
60.•• Ruisinger JF, Gibson CA, Backes JM, et al. Statins and almonds to lower lipoproteins (the STALL study). J Clin Lipidol. 2015;9(1): 58–64. **This paper demonstrates that almonds can provide additional cholesterol-lowering benefits to statin therapy.**
61. Moncada S, Higgs A. The L-arginine-nitric oxide pathway. N Engl J Med. 1993;329(27):2002–12.
62. Inaba Y, Chen JA, Bergmann SR. Prediction of future cardiovascular outcomes by flow-mediated vasodilatation of brachial artery: a meta-analysis. Int J Cardiovasc Imaging. 2010;26(6):631–40.
63. Huang Y, Zheng S, Wang T, Yang X, Luo Q, Li H. Effect of oral nut supplementation on endothelium-dependent vasodilation - a meta-analysis. Vasa. 2018:1–5.
64.• Neale EP, Tapsell LC, Guan V, Batterham MJ. The effect of nut consumption on markers of inflammation and endothelial function: a systematic review and meta-analysis of randomised controlled trials. BMJ Open. 2017;7(11):e016863. **An important meta-analysis evaluating the effects of nuts on endothelial function and biochemical markers of vascular health (inflammation).**
65. 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. 2017;
66. Fogacci F, Cicero AFG, Derosa G, Rizzo M, Veronesi M, Borghi C. Effect of pistachio on brachial artery diameter and flow-mediated dilatation: a systematic review and meta-analysis of randomized, controlled-feeding clinical studies. Crit Rev Food Sci Nutr. 2017:1–8.
67. Liu X, Hill AM, West SG, Gabauer RM, McCrea CE, Fleming JA, et al. Acute peanut consumption alters postprandial lipids and

vascular responses in healthy overweight or obese men. J Nutr. 2017;147(5):835–40.
68. Axtell AL, Gomari FA, Cooke JP: Assessing endothelial vasodilator function with the Endo-PAT 2000. J Vis Exp 2010(44).
69. Sauder KA, McCrea CE, Ulbrecht JS, Kris-Etherton PM, West SG. Pistachio nut consumption modifies systemic hemodynamics, increases heart rate variability, and reduces ambulatory blood pressure in well-controlled type 2 diabetes: a randomized trial. Hypertension. 2014;3:e000873.
70. Sauder KA, McCrea CE, Ulbrecht JS, Kris-Etherton PM, West SG. Effects of pistachios on the lipid/lipoprotein profile, glycemic control, inflammation, and endothelial function in type 2 diabetes: a randomized trial. Metabolism. 2015;64(11):1521–9.
71. Huguenin GV, Moreira AS, Siant'Pierre TD, et al. Effects of dietary supplementation with Brazil nuts on microvascular endothelial function in hypertensive and dyslipidemic patients: a randomized crossover placebo-controlled trial. Microcirculation. 2015;22(8):687–99.
72. Kasliwal RR, Bansal M, Mehrotra R, Yeptho KP, Trehan N. Effect of pistachio nut consumption on endothelial function and arterial stiffness. Nutrition. 2015;31(5):678–85.
73. Chen CY, Holbrook M, Duess MA, et al. Effect of almond consumption on vascular function in patients with coronary artery disease: a randomized, controlled, cross-over trial. Nutr J. 2015;14:61.
74. Barbour JA, Howe PR, Buckley JD, Bryan J, Coates AM. Cerebrovascular and cognitive benefits of high-oleic peanut consumption in healthy overweight middle-aged adults. Nutr Neurosci. 2016:1–8.
75. Choudhury K, Clark J, Griffiths HR. An almond-enriched diet increases plasma alpha-tocopherol and improves vascular function but does not affect oxidative stress markers or lipid levels. Free Radic Res. 2014;48(5):599–606.
76. Mohammadifard N, Salehi-Abargouei A, Salas-Salvado J, Guasch-Ferre M, Humphries K, Sarrafzadegan N. The effect of tree nut, peanut, and soy nut consumption on blood pressure: a systematic review and meta-analysis of randomized controlled clinical trials. Am J Clin Nutr. 2015;101(5):966–82.
77. McKay DL, Eliasziw M, Chen CYO, Blumberg JB: A pecan-rich diet improves cardiometabolic risk factors in overweight and obese adults: a randomized controlled trial. Nutrients 2018, 10(3).
78. Tey SL, Robinson T, Gray AR, Chisholm AW, Brown RC. Do dry roasting, lightly salting nuts affect their cardioprotective properties and acceptability? Eur J Nutr. 2017;56(3):1025–36.
79. Dhillon J, Tan SY, Mattes RD. Almond consumption during energy restriction lowers truncal fat and blood pressure in compliant overweight or obese adults. J Nutr. 2016;146(12):2513–9.
80. Ndanuko RN, Tapsell LC, Charlton KE, Neale EP, Batterham MJ. Effect of individualised dietary advice for weight loss supplemented with walnuts on blood pressure: the HealthTrack study. Eur J Clin Nutr. 2018;72:894–903.
81. Yu Z, Malik VS, Keum N, Hu FB, Giovannucci EL, Stampfer MJ, et al. Associations between nut consumption and inflammatory biomarkers. Am J Clin Nutr. 2016;104(3):722–8.
82. Medina-Remon A, Casas R, Tressserra-Rimbau A, et al. Polyphenol intake from a Mediterranean diet decreases inflammatory biomarkers related to atherosclerosis: a substudy of the PREDIMED trial. Br J Clin Pharmacol. 2017;83(1):114–28.
83. Barbour JA, Howe PR, Buckley JD, Bryan J, Coates AM. Effect of 12 weeks high oleic peanut consumption on cardio-metabolic risk factors and body composition. Nutrients. 2015;7(9):7381–98.
84. Mazidi M, Rezaie P, Ferns GA, Gao HK. Impact of different types of tree nut, peanut, and soy nut consumption on serum C-reactive protein (CRP): a systematic review and meta-analysis of randomized controlled clinical trials. Medicine (Baltimore). 2016;95(44): e5165.
85. Chen CM, Liu JF, Li SC, Huang CL, Hsirh AT, Weng SF, et al. Almonds ameliorate glycemic control in Chinese patients with better controlled type 2 diabetes: a randomized, crossover, controlled feeding trial. Nutr Metab (Lond). 2017;14:51.
86. Gulati S, Misra A, Pandey RM. Effect of almond supplementation on glycemia and cardiovascular risk factors in Asian Indians in North India with type 2 diabetes mellitus: a 24-week study. Metab Syndr Relat Disord. 2017;15(2):98–105.
87. Liu Y, Hwang HJ, Ryu H, Lee YS, Kim HS, Park H. The effects of daily intake timing of almond on the body composition and blood lipid profile of healthy adults. Nutr Res Pract. 2017;11(6):479–86.
88. Jung H, Chen CO, Blumberg JB, Kwak HK. The effect of almonds on vitamin E status and cardiovascular risk factors in Korean adults: a randomized clinical trial. Eur J Nutr. 2017;
89. George ES, Forsyth A, Itsiopoulos C, Nicoll AJ, Ryan M, Sood S, et al. Practical dietary recommendations for the prevention and management of nonalcoholic fatty liver disease in adults. Adv Nutr. 2018;9(1):30–40.
90. Zelber-Sagi S, Salomone F, Mlynarsky L. The Mediterranean dietary pattern as the diet of choice for non-alcoholic fatty liver disease: evidence and plausible mechanisms. Liver Int. 2017;37(7):936–49.
91. Han JM, Jo AN, Lee SM, Bae HS, Jun DW, Cho YK, et al. Associations between intakes of individual nutrients or whole food groups and non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol. 2014;29(6):1265–72.
92.•• Cueto-Galan R, Baron FJ, Valdivielso P, et al. Changes in fatty liver index after consuming a Mediterranean diet: 6-year follow-up of the PREDIMED-Malaga trial. Med Clin (Barc). 2017;148(10): 435–43. **Incorporating nuts into a Mediterranean diet was associated with a lower fatty liver index.**
93. Yamashita T, Kasahara K, Emoto T, Matsumoto T, Mizoguchi T, Kitano N, et al. Intestinal immunity and gut microbiota as therapeutic targets for preventing atherosclerotic cardiovascular diseases. Circ J. 2015;79(9):1882–90.
94. Ahmadmehrabi S, Tang WHW. Gut microbiome and its role in cardiovascular diseases. Curr Opin Cardiol. 2017;32(6):761–6.
95. Lamuel-Raventos RM, Onge MS. Prebiotic nut compounds and human microbiota. Crit Rev Food Sci Nutr. 2017;57(14):3154–63.
96. 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(2).
97. Holscher HD, Guetterman HM, Swanson KS, An R, Matthan NR, Lichtenstein AH, 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(6):861–7.
98.•• Holscher HD, Taylor AM, Swanson KS, Novotny JA, Baer DJ. Almond consumption and processing affects the composition of the gastrointestinal microbiota of healthy adult men and women: a randomized controlled trial. Nutrients. 2018;10(2) **A RCT demonstrating that incorporating almonds promotes diversity of gut microbiota, which in turn may improve CVD outcomes.**
99. Hernandez-Alonso P, Canueto D, Giardina S, et al. Effect of pistachio consumption on the modulation of urinary gut microbiota-related metabolites in prediabetic subjects. J Nutr Biochem. 2017;45:48–53.
100. Micha R, Shulkin ML, Penalvo JL, et al. Etiologic effects and optimal intakes of foods and nutrients for risk of cardiovascular diseases and diabetes: systematic reviews and meta-analyses from the Nutrition and Chronic Diseases Expert Group (NutriCoDE). PLoS One. 2017;12(4):e0175149.
101. Anagnostis P, Paschou SA, Goulis DG, Athyros VG, Karagiannis A. Dietary management of dyslipidaemias. Dietary management of dyslipidaemias. Is there any evidence for cardiovascular benefit? Maturitas. 2018;108:45–52.