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Nuts and CVD☆

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Abstract

Nuts are nutrient-dense foods with complex matrices rich in unsaturated fatty acids and other bioactive compounds, such as L-arginine, fibre, healthful minerals, vitamin E, phytosterols and polyphenols. By virtue of their unique composition, nuts are likely to beneficially affect cardiovascular health. Epidemiological studies have associated nut consumption with a reduced incidence of CHD in both sexes and of diabetes in women, but not in men. Feeding trials have clearly demonstrated that consumption of all kinds of nuts has a cholesterol-lowering effect, even in the context of healthy diets. There is increasing evidence that nut consumption has a beneficial effect on oxidative stress, inflammation and vascular reactivity. Blood pressure, visceral adiposity and the metabolic syndrome also appear to be positively influenced by nut consumption. Contrary to expectations, epidemiological studies and clinical trials suggest that regular nut consumption is not associated with undue weight gain. Recently, the PREvención con DIeta MEDiterránea randomised clinical trial of long-term nutrition intervention in subjects at high cardiovascular risk provided first-class evidence that regular nut consumption is associated with a 50 % reduction in incident diabetes and, more importantly, a 30 % reduction in CVD. Of note, incident stroke was reduced by nearly 50 % in participants allocated to a Mediterranean diet enriched with a daily serving of mixed nuts (15 g walnuts, 7·5 g almonds and 7·5 g hazelnuts). Thus, it is clear that frequent nut consumption has a beneficial effect on CVD risk that is likely to be mediated by salutary effects on intermediate risk factors.

Key words: Nuts: Mediterranean diet: CVD: Cholesterol: Body weight

By definition, tree nuts are dry fruits with one seed in which the ovary wall becomes hard at maturity. Common edible tree nuts include almonds, Brazil nuts, cashews, hazelnuts, macadamia nuts, pecans, pine nuts, pistachios and walnuts, but the consumer definition also includes peanuts, which are botanically legumes but have a nutrient profile similar to that of tree nuts and are thus identified as part of the nuts food group[1]. For the purpose of this review, the term 'nuts' comprises all common tree nuts (with the exception of chestnuts, which are starchy and contain little fat compared with other tree nuts) plus peanuts.

Extensive research on nuts and health outcomes has been conducted since the publication in the early 1990s of the results of two landmark studies: the Adventist Health Study, which related frequent nut consumption to a lower risk of CHD[2] and the randomised clinical trial (RCT) of Sabaté *et al.*[3] showing that walnut intake reduced serum cholesterol levels, as had also been shown for almonds[4].

Together with cereal grains and legumes, nuts have been regular constituents of human diet since pre-agricultural times[5]. Whole grains, legumes and nuts are high-energy, nutrient-dense seeds. In the outer layer and the germ, all

Abbreviations: NHS, Nurses' Health Study; PREDIMED, PREvención con DIeta MEDiterránea; RCT, randomised clinical trial.

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seeds are made of complex matrices, rich in minerals, vitamins and bioactive phytochemicals that serve the purpose of protecting the plant's DNA from oxidative stress, thus facilitating the perpetuation of the species, while the endosperm stores a complete mixture of macronutrients destined to sustain the future seedling. Most seed components are bioavailable after consumption by humans and many of them synergise in the body to beneficially affect metabolic and vascular physiology pathways leading to protection from CVD and diabetes[6].

The scientific evidence behind the proposal of seeds in general and nuts in particular as heart-healthy foods stems from both epidemiological observations and RCT. As recently reviewed[7,8], large observational studies have shown that the frequency of nut consumption relates inversely to incident CHD and diabetes, while numerous short-term feeding trials comparing nut-enriched diets with control diets have demonstrated beneficial effects on blood lipids and other intermediate markers of cardiovascular risk. The accruing evidence on the beneficial cardiovascular effects of nuts has prompted the inclusion of this food group in many guidelines for healthful eating. Thus, in the summer of 2003, the US Food and Drug Administration issued a health claim for nuts and nut-containing products because of the link of nut consumption with a reduced risk of heart disease[9]. Also, nuts were included in the American Heart Association report setting goals for health promotion and disease reduction for 2020[10] and in both the recent Canadian Cardiovascular Society Guidelines[11] and the newest American Heart Association/American College of Cardiology guideline on lifestyle management to reduce cardiovascular risk[12]; furthermore, nuts are integral part of plant-based dietary patterns recommended to the general population for health[13] and are an important component and part of the definition of the Mediterranean diet[14]. Here, we summarise present knowledge on the expanding topic of nut consumption and CVD.

Nutrient content of nuts

Nutrient-dense nuts are one of the natural plant foods rich in fat after vegetable oils, with a total fat content ranging from 46 % in cashews and pistachios to 76 % in macadamia nuts (Table 1). The fatty acid composition of nuts is beneficial because the SFA content is low (range 4–16 %) and nearly one-half of the total fat content is made up of unsaturated fat, mostly MUFA, although sizeable proportions of PUFA, predominantly linoleic acid, are present in Brazil nuts, pine nuts and walnuts[15]. Of note, walnuts are also a rich source of α-linolenic acid, the plant *n*-3 fatty acid[15]. As discussed below, the particular lipid profile of nuts in general and walnuts in particular is likely to be an important contributor to the beneficial health effects of frequent nut consumption.

Nuts are also rich sources of other bioactive macronutrients with potential health benefits[1]. Thus, nuts are a good source of protein (approximately 25 % of energy) and often have a high content of the amino acid L-arginine, which is the substrate for endothelium-derived NO synthesis, a main regulator of vascular tone and blood pressure[16]. This might explain the positive effects of nut intake on vascular reactivity, as discussed below. Nuts are also a good source of dietary fibre, which ranges from 4 to 11 g/100 g[17] (Table 1). Among nut constituents, there are significant amounts of essential micronutrients that are associated with an improved health status when consumed at doses beyond those necessary to prevent deficiency states. They include sizeable amounts of the B vitamin folate and antioxidant vitamins (e.g. tocopherols) and polyphenols[18]. It is important to know that most of the antioxidants in nuts are located in the pellicle or outer soft shell, as shown for almonds[19], which means that significant quantities are lost when nuts are peeled or roasted. These facts should be considered when giving advice on nut consumption in healthful diets. Walnuts are an exception because they are usually consumed as the raw, unpeeled product; moreover, walnuts have the highest polyphenol content of all nuts[18].

Nuts are free of cholesterol, but their fatty fraction contains sizeable amounts of phytosterols[20], which are likely to contribute to their cholesterol-lowering effect (see below). Also, nuts have an optimal nutritional density regarding beneficial minerals such as Ca, Mg and K[6,20]. As in the case of most vegetables, the Na content of nuts is very low (Table 1). A high intake of Ca, Mg and K, together with a low Na intake, is associated with protection against hypertension,

Table 1. Average composition of nuts in macro- and micronutrients and selected phytochemicals (per 100 g)*

Nuts	Energy (kJ)	Protein (g)	Fibre (g)	Fat (g)	SFA (g)	MUFA (g)	PUFA (g)	LA (g)	ALA (g)	PS (mg)	Na (mg)	K (mg)	Ca (mg)	Total polyphenols (mg)
Almonds	2418	21·3	8·8	50·6	3·9	32·2	12·2	12·2	0·00	120	1	728	248	287
Brazil nuts	2743	14·3	8·5	66·4	15·1	24·5	20·6	20·5	0·05	NR	3	659	160	244
Cashews	2314	18·2	5·9	46·4	9·2	27·3	7·8	7·7	0·15	158	12	660	37	233
Hazelnuts	2629	15·0	10·4	60·8	4·5	45·7	7·9	7·8	0·09	96	0	680	114	687
Macadamia nuts	3004	7·9	6·0	75·8	12·1	58·9	1·5	1·3	0·21	116	5	368	85	126
Peanuts	2220	25·8	8·5	49·2	6·8	24·4	15·6	15·6	0·00	220	18	705	92	396
Pecans	2889	9·2	8·4	72·0	6·2	40·8	21·6	20·6	1·00	102	0	410	70	1816
Pine nuts	2816	13·7	3·7	68·4	4·9	18·8	34·1	33·2	0·16	141	2	597	16	58
Pistachios	2332	20·6	9·0	44·4	5·4	23·3	13·5	13·2	0·25	214	1	1025	107	1420
Walnuts	2738	15·2	6·4	65·2	6·1	8·9	47·2	38·1	9·08	72	2	441	98	1558

LA, linoleic acid; ALA, α-linolenic acid; PS, plant sterols; NR, not reported.

* Sources: US Department of Agriculture Nutrient Data Base. http://ndb.nal.usda.gov/ndb/foods/list (accessed 24 March 2014); National Institute for Health and Welfare, N.U. Fineli. Finnish Food Composition Database. http://www.fineli.fi (accessed 24 March 2014); and Phenol-Explorer 3.0. Data base on polyphenol content in foods. http://www.phenol-explorer.eu (accessed 24 March 2014).

insulin resistance and overall cardiovascular risk[21], besides bone demineralisation.

In summary, the macronutrient, micronutrient and phytochemical components of nuts have been documented to contribute to a reduced risk of CHD and related metabolic disturbances. This might explain why nut consumption is associated with reduced cardiovascular risk in both observational studies and RCT, as discussed below.

Nut consumption and cardiovascular health

Nut consumption has been the subject of much epidemiological and clinical research. Prospective studies have examined clinical cardiovascular end points, i.e. CHD, stroke, type 2 diabetes, hypertension and the metabolic syndrome, while RCT have generally explored intermediate biomarkers of CVD risk[7,8]. An exception is the PREvención con DIeta MEDiterránea (PREDIMED) trial of primary cardiovascular prevention, which included nut supplementation in one study arm and had hard cardiovascular end points as the main outcome[22]. The scientific evidence acquired from these studies is summarised below.

Epidemiological studies

Four large prospective studies conducted in the USA examining associations of dietary components with health outcomes reported a beneficial effect of nut consumption on fatal and non-fatal CHD after follow-up ranging from 6 to 18 years[2,23–25]. These studies were reviewed in 2006 by Kelly & Sabaté[26], who estimated an 8·3 % reduction in CHD risk for each weekly serving of nuts. Protection against CHD mortality with increasing nut consumption was also observed in the PREDIMED study population when assessing the cohort as a longitudinal study[27]. A recent report of two large cohorts of women from the Nurses' Health Study (NHS) and men from the Health Professionals Follow-up Study with follow-up of 30 and 24 years, respectively, again showed reduced CHD mortality for both sexes with increasing nut consumption[28] (Fig. 1). Remarkably, nut consumption was also associated with a reduction in all-cause and cancer mortality in these two reports[27,28]. An additional report from the NHS concerning women with type 2 diabetes further evaluated the relationship between nut consumption and CVD (including CHD and stroke) and observed a multivariable adjusted 54 % lower risk of CVD[29]. Although considering nuts and fruits together, findings from the prospective Greek European Prospective Investigation into Cancer and Nutrition cohort also suggest a protective effect of higher consumption against CHD, with 23 and 34 % risk reductions for men and women, respectively[30]. A dose–response relationship between nut consumption and reduced CHD mortality was observed in all studies. Consistent findings in all prospective studies strongly suggest a causal association between nut consumption and reduced CHD rates.

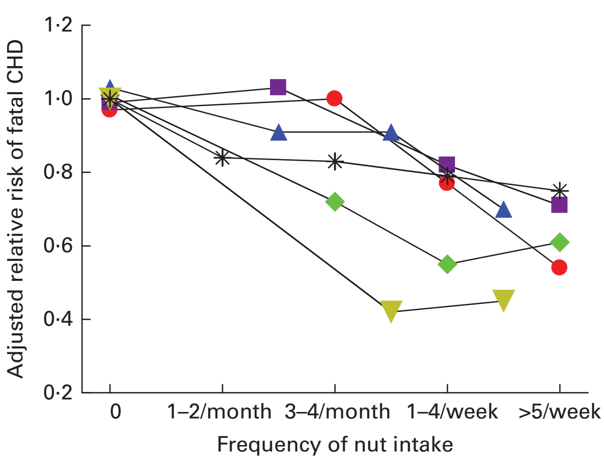

Fig. 1. Incidence of fatal CHD by frequency of nut intake. Shown are the results of six large prospective studies where nut consumption was the exposure of interest and the outcome was death from CHD. –●–, Adventist Health Study, 1992; –◆–, Nurses' Health Study, 1998; –▲–, Physicians' Health Study, 2002; –■–, Iowa Women's Health Study, 2006; –▼–, PREvención con DIeta MEDiterránea, 2013; –✳–, Nurses' Health Study and Health Professionals Follow-up Study, 2013. A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn

The findings of prospective studies are less consistent regarding nut consumption and stroke risk. Thus, a non-significant decreased risk of fatal stroke with increasing nut consumption was reported for postmenopausal women participating in the Iowa Women's Health Study[31]; no association between frequency of nut consumption and stroke risk was observed in men from the Physicians' Health Study[32], and an additional report of the large NHS and Health Professionals Follow-up Study cohorts showed that regular nut consumption related to a weak but significant lower risk of stroke in women, but not in men[33].

The association between nut consumption and type 2 diabetes risk has also been investigated in prospective studies. Findings from the large NHS cohort suggested that nut and peanut butter consumption was associated with a reduced incidence of diabetes in women[34]. No such relationship was observed in postmenopausal women participating in the Iowa Women's Health Study[35]. A subsequent report from a Chinese cohort of nearly 64 000 women also showed that nut consumption protected from diabetes risk[36]. These findings, however, were not confirmed in male participants in the Physicians' Health Study[37]. A more recent report from a large cohort of women combining data from NHS and NHS II after follow-up of 10 years showed that consumption of walnuts, but not other nuts, was associated with reduced rates of incident diabetes[38]. Finally, a cross-sectional assessment of the PREDIMED cohort of older persons at high cardiovascular risk showed a reduced prevalence of diabetes with increasing nut consumption[39]. In this study, a lower prevalence of the metabolic syndrome, a high-cardiovascular risk cluster of risk factors related to insulin resistance, was also observed in frequent nut eaters[39]. Similarly, nut consumption is related to lower incident metabolic syndrome in the prospective Seguimiento Universidad de Navarra cohort of Spanish university graduates[40] and in a large cross-sectional report from the US National Health and Nutrition Examination Survey for 2001–4[41].

Four prospective studies have evaluated the frequency of nut consumption in relation to incident hypertension[42–45]. In the young biracial cohort of the Coronary Artery Risk Development in Young Adults study, subjects in the upper category of nut consumption had a 15 % decreased risk of hypertension compared with the lowest category after 15 years of follow-up[42]. In the large Physicians' Health Study men cohort[43], the risk of hypertension was reduced by 18 % in participants who consumed nuts daily compared with non-consumers, although the benefit was restricted to participants who were not overweight or obese at baseline. Another report from the Seguimiento Universidad de Navarra cohort found a non-significant 23 % lower risk of incident hypertension for the highest *v.* lowest nut consumption category after 4·3 years of follow-up[44]. Moreover, a recent report from the Atherosclerosis Risk in Communities study in middle-aged adults showed a 13 % lower risk of incident hypertension in the top quintile of nut consumption compared with the bottom quintile after follow-up for 9 years[45]. The US National Health and Nutrition Examination Survey 2001–4 cross-sectional study also reported lower prevalent hypertension for nut consumers compared with non-consumers[41].

As reviewed[7,8], prospective studies have also reported an association between increasing nut consumption and reduced circulating levels of inflammatory biomarkers.

In summary, the results of several prospective studies strongly suggest that regular consumption of nuts is beneficial for CHD risk. The risk of stroke in relation to nut consumption has been less investigated compared with CHD risk, and data support a weak protective effect in women, but not in men. Confirmation of a protective role on stroke as well as diabetes risk must await further studies. Data from epidemiological studies also suggest a protective effect of nut consumption on the metabolic syndrome and hypertension, one of its components. Finally, there is also suggestive epidemiological evidence that frequent nut consumption is associated with reduced systemic inflammation.

Randomised clinical trials with outcomes on intermediate biomarkers

RCT to investigate the effects on cardiovascular risk factors and an attempt to understand the underlying mechanisms for protection from CHD followed the first observational studies. Most RCT have compared diets supplemented with nuts with control diets for outcomes on blood lipid changes in individuals with normal or moderately elevated blood cholesterol levels. Some studies have also evaluated the effects of nuts on glycaemic control in patients with type 2 diabetes. Other studies have focused on the relevant question of whether unrestricted nut intake influences body weight. Further RCT have assessed the effects of nut diets on intermediate risk markers, such as blood pressure, insulin sensitivity, endothelial function and inflammatory status. Almonds and walnuts have been the most studied nuts, followed by pistachios. The long-term PREDIMED trial has targeted both the effects of nut consumption on intermediate cardiometabolic markers and clinical outcomes, such as the metabolic syndrome, diabetes and cardiovascular events, among others. Given the relevance of PREDIMED for the issue of nuts and cardiovascular health, its results will be dealt within a separate section.

Since the first RCT by Sabaté *et al.*[3] examining the lipid effects of nuts showed that a walnut diet reduced blood cholesterol levels in healthy individuals, the effects of nut consumption on blood lipids and lipoproteins have been investigated in many studies. A pooled analysis of twenty-five RCT conducted in seven countries examining nut-enriched diets *v.* control diets during periods of 3–8 weeks for outcomes on blood lipids clearly demonstrated that nuts had a cholesterol-lowering effect that was related to both dose and baseline cholesterol level, stratified by sex and across all age groups, and independent of the type of nut tested[46]. Specifically, daily consumption of 67 g (2·4 oz) of nuts was associated with mean reduction of 10·9 mg/dl (5·1 %) in total cholesterol, 10·2 mg/dl (7·4 %) in LDL-cholesterol and 0·22 (8·3 %) in LDL:HDL ratios ($P<0·001$, all). Nuts had no significant effect on HDL-cholesterol or TAG, except in participants with serum TAG >150 mg/dl, in whom a significant mean 10·2 mg/dl reduction was observed. A separate meta-analysis of thirteen RCT examined the effect of walnut-enriched diets on blood lipid levels[47]. Compared with control diets, diets enriched with walnuts in amounts ranging from 30 to 108 g/d (10–24 % of energy) were associated with weighed mean reductions of total cholesterol and LDL-cholesterol of 10·3 and 9·2 mg/dl ($P<0·001$, both), respectively, which are similar to those described in the pooled analysis for different nut types[46]. RCT testing the lipid effects of nuts have usually been short term, but efficacy is maintained in the long term. Thus, inclusion of walnuts (12 % of energy) to the usual diet of free-living individuals to whom no dietary advice was given during a 6-month period reduced total cholesterol by 5 mg/dl ($P=0·02$) and TAG by 8 mg/dl ($P=0·03$), with a nearly significant decrease of 3·5 mg/dl in LDL cholesterol ($P=0·06$)[48]. Also, a walnut diet against a control diet for up to 1 year in obese patients with type 2 diabetes showed maintained, albeit small, LDL-cholesterol reductions and HDL-cholesterol increases with the walnut diet[49].

Acute studies using test meals with a high glycaemic index with or without nuts have shown reduced postprandial glucose responses with nut meals, suggesting that nuts may be useful in controlling diabetes[50]. Improved glycaemic control has been recently reported in patients with type 2 diabetes fed diets enriched with 2 oz mixed nuts[51] or almonds[52] *v.* control diets for 12 weeks. It may seem counterintuitive to recommend energy-dense nuts to diabetic patients for the fear of gaining weight. Indeed, there is a widespread perception that all fatty foods provide excess energy and promote obesity, which has had a negative effect on the image of nuts. However, there is no epidemiological or RCT evidence that their frequent consumption promotes weight gain; on the contrary, reports from large prospective cohorts show inverse associations between the frequency of nut consumption and BMI or weight gain over time after adjustment for confounders[2,23,53–55]. Similar findings regarding

BMI together with reduced waist circumference have been shown for increasing nut consumption in cross-sectional studies[41,56,57] and in the PREDIMED cohort considered as a longitudinal study[39]. Finally, a recent meta-analysis of RCT that tested nut diets *v.* control diets showed small non-significant associations of nut intake with reduced adiposity measures[58], as had been previously described for walnut trials[47]. Mechanistically, the lack of weight gain after consuming nuts is largely due to their prominent satiating effect, which results in food compensation accounting for up to 75 % of the energy they provide[59]. An additional factor contributing to offset energy acquisition after eating nuts is fat malabsorption, documented as increased faecal fat excretion, which is due in part to incomplete digestion of their matrices because the fat of nuts is enclosed within cell membranes, which are not readily available to digestive enzymes even after thorough mastication[60]. In conclusion, a substantial body of evidence permits to allay fear of undue weight gain when eating these high-fat foods.

The unique composition of nuts in bioactive nutrients and phytochemicals suggests that their consumption can beneficially affect cardiometabolic markers other than blood lipids and glycaemic control. A few studies have examined the effects of nuts on oxidative stress, inflammation and vascular reactivity, as reviewed[7,8,61,62]. A growing body of evidence from small RCT indicates that nuts, particularly walnuts, have beneficial effects on endothelial function, as ascertained by flow-mediated dilatation studies in the brachial artery[63–66], reduced circulating levels of endothelial activation molecules[67] or inhibition of pro-inflammatory cytokine production by blood mononuclear cells[68]. While an effect of nut diets on resting blood pressure has been difficult to detect in clinical studies, testing haemodynamic responses to stress has uncovered a beneficial effect of walnuts[66] and pistachios[69] on blood pressure and total peripheral resistance, suggesting a novel mechanism for the cardioprotective effects of nuts. Improved vascular reactivity in studies with walnuts may be ascribed to their richness in L-arginine, PUFA, particularly α-linolenic acid, and polyphenols[62].

Nuts being a rich source of antioxidants, it is not surprising that their consumption has been related to improved oxidative status[70]. This has been reported for MUFA-rich nuts, such as almonds, both acutely[71] and after 1 month feeding[72], pistachios[73] and hazelnuts[74], but not for PUFA-rich nuts such as walnuts, albeit no deleterious effects on oxidation have been described[47,70]. Studies on nut-feeding have documented reduced circulating concentrations of inflammatory cytokines but no consistent changes of C-reactive protein[47,61]. A novel mechanism by which walnut consumption may reduce cardiovascular risk has recently been reported: increased cholesterol efflux from cholesterol-laden macrophages exposed to human serum collected after a walnut meal[75]. Cholesterol efflux from macrophages is an important step in the anti-atherogenic reverse cholesterol transport pathway. This is a provocative finding that needs to be confirmed in further studies; it suggests that nut (walnut) consumption improves the functionality of HDL, the main lipoprotein particles involved in reverse cholesterol transport. In this sense, another recent report of a PREDIMED substudy showed that the Mediterranean diet enriched with mixed nuts shifted both LDL and HDL subfractions to a less atherogenic pattern, also suggesting improved cholesterol transport capacity after nut diets[76]. In summary, the emerging picture is that nut consumption has positive effects on cardiovascular risk factors well beyond established cholesterol lowering without incurring increases in adiposity.

Cardiovascular effects of nuts in the PREvención con DIeta MEDiterránea trial

The PREDIMED study is a large, parallel group, multi-centre, 5-year RCT of nutrition intervention conducted in Spain. Eligible participants were men, 55–80 years of age, and women, 60–80 years of age, at high risk but no CVD at enrolment. Participants were randomised to three diet groups, two Mediterranean diets, supplemented with either extra-virgin olive oil or mixed nuts, or control diet (advice on a low-fat diet). They received quarterly individual and group educational sessions and, depending on group assignment, free provision of extra-virgin olive oil (one litre/week), mixed Mediterranean nuts (30 g/d: 15 g walnuts, 7·5 g almonds and 7·5 g hazelnuts) or small non-food gifts. Of note, the diets were non-energy restricted and increased physical activity was not promoted; thus, the full effect of dietary intervention alone could be ascertained. The primary end point was an aggregate of major cardiovascular events (myocardial infarction, stroke and cardiovascular death).

Since its inception in October 2003, the results of the trial have provided much evidence on the beneficial health effects of Mediterranean diets enriched with both supplemental foods, culminating with the findings concerning the primary end point[22]. The efficacy of the PREDIMED nutritional intervention has generally been similar for both the extra-virgin olive oil and nut-supplemented Mediterranean diets in comparison with the control diet. The main results regarding the Mediterranean diet enriched with mixed nuts are summarised below.

In a study involving the first 772 participants completing intervention for 3 months[77], results showed that, compared with the control diet, the two Mediterranean diets resulted in significant reductions of both systolic and diastolic blood pressure and total and LDL-cholesterol; increased HDL-cholesterol; decreased fasting glucose levels in diabetic participants and increased insulin sensitivity in those without diabetes; and reduction in circulating levels of inflammatory cytokines. Both intervention diets were also associated with reduced oxidised LDL levels[78]. The nut-enriched diet reduced fasting TAG levels as well[77]. While results on lipids, glycaemic control and oxidation and inflammation biomarkers were confirmatory of previous data, the blood pressure-lowering effect of the nut-enriched diet was novel. Of note, reduced blood pressure by both PREDIMED Mediterranean diets after intervention for 1 year has recently been confirmed in a 24 h ambulatory blood pressure monitoring substudy[79].

Another substudy investigated both 3-month changes in circulating inflammatory biomarkers and the expression

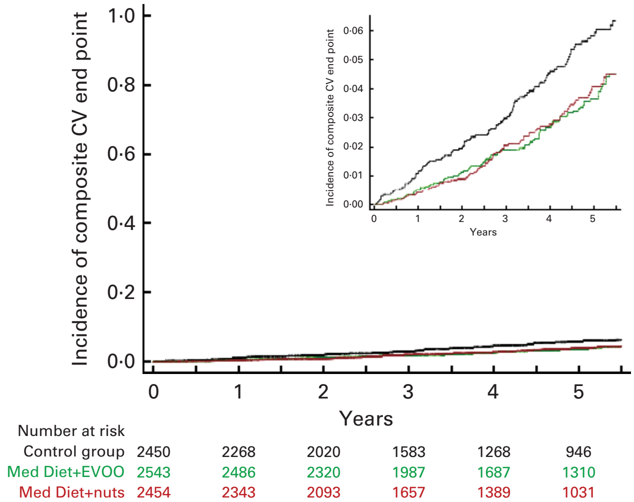

Fig. 2. Incidence of CVD by intervention group in the PREvención con DIeta MEDiterránea study. Med Diet with extra-virgin olive oil (EVOO): hazard ratios (HR) 0·70 (95 % CI 0·53, 0·91), $P=0·009$; Med Diet with nuts: HR 0·70 (95 % CI 0·53, 0·94), $P=0·016$. Med Diet, Mediterranean diet. Estruch *et al.*[22] copyright© (2013) Massachusetts Medical Society. Reprinted with permission. A colour version of this figure can be found online at http://www.journals.cambridge.org/bjn

of ligands for inflammatory molecules in circulating monocytes after the intervention[80]. The findings indicate reductions in both circulating inflammatory mediators and, importantly, reduced monocyte expression of pro-inflammatory ligands after the two Mediterranean diets, thus beginning to unravel the molecular bases for their anti-inflammatory effects. Concurring with these findings, a recent 2-year vascular imaging study in a PREDIMED subcohort detected an anti-atherosclerotic effect of the Mediterranean diets *v.* the control diet, namely delayed progression of carotid intima-media thickness and plaque, which was more pronounced with the nut-supplemented diet[81].

The effects of the interventions on the metabolic syndrome status and incident diabetes were secondary end points of the PREDIMED study. In the first 1224 trial participants completing intervention for 1 year, the nut-enriched Mediterranean diet was associated with a 14 % reduction in the prevalence of the metabolic syndrome, which was mainly due to reduced visceral adiposity[82]. Because there were no weight changes, this suggests fat redistribution away from the abdominal compartment. In one of the eleven PREDIMED recruiting centres, annual oral glucose tolerance tests were performed in non-diabetic participants to accurately detect incident diabetes. Results in 418 subjects followed for a mean of 4 years showed that both Mediterranean diets protected against development of diabetes, and the reduction of incident diabetes in the nuts arm was 52 % compared with the control diet[83]. Again, this beneficial effect took place in the absence of weight loss or increased energy expenditure in physical activity. More recently, the results on diabetes incidence for the full PREDIMED cohort have become available and this time the nut-enriched diet only showed a non-significant 18 % reduction[84].

Table 2. Effects of nut consumption on CVD and risk factors. Summary of scientific evidence

Diseases/factors	Effect	Level of evidence	References
Epidemiological studies			
CHD	Decrease	++	2, 23–30
Stroke	No change	+	32, 33
Hypertension	Decrease	+	41–45
Metabolic syndrome	Decrease	+	39–41
Diabetes	No change/decrease	+/−	34–38
Inflammatory markers	Decrease	+	6, 7
Body weight	No change/decrease	++	2, 23, 39, 41, 53–57
Randomised clinical trials			
Blood lipid profile			
Total cholesterol	Decrease*	++	46–49, 77
LDL-cholesterol	Decrease*	++	46–49, 77
HDL-cholesterol	No change/increase*	+	46, 47, 49, 77
TAG	Decrease*	+	46, 47, 77
Insulin sensitivity	Increase*	+	50, 77
Blood pressure	Decrease*	+	66, 69, 77, 79
Oxidation	Decrease*	+/−†	47, 70–75, 78
Inflammation	Decrease*	+	67, 68, 77
Vascular reactivity	Increase	+	63–66
Body weight	No change*	++	47, 58, 82
Visceral adiposity	Decrease*	+	58, 76, 82
Metabolic syndrome	Decrease*	+	50, 82
Type 2 diabetes	Decrease‡	+	83, 84
CVD	Decrease‡	+	22
Stroke	Decrease‡	+	22
Peripheral artery disease	Decrease‡	+	85

++, evidence from several studies; +, limited evidence from few studies; +/−, equivocal evidence; PREDIMED, PREvención con DIeta MEDiterránea.

* Evidence collected in the PREDIMED trial, among others.

† Oxidation improved with nuts rich in MUFA (i.e. almonds, pistachios and hazelnuts) and unchanged with nuts rich in PUFA (i.e. walnuts).

‡ Evidence collected only in the PREDIMED trial.

Recently, the results of the PREDIMED trial on the primary end point have been reported, showing for the first time a reduction of incident CVD after long-term consumption of the two Mediterranean diets[22]. After a median follow-up of 4·8 years in 7447 participants, those assigned the two Mediterranean diets showed a 30 % reduction in CVD events (myocardial infarction, stroke or cardiovascular death) compared with the control diet. As seen in Fig. 2, the curves of the two Mediterranean diet groups and the control group diverged soon after the beginning of the study. Such an early (and sustained) reduction in cardiovascular events fits with the improvement of intermediate markers of CVD detected after follow-up for only 3 months[77,78,80]. The nut diet was also associated with a significant 49 % reduction in stroke risk[22]. The two intervention diets were associated with non-significant reductions in myocardial infarction and no effect could be discerned on total mortality, although one must keep in mind that the trial was not powered for these outcomes. Of note, the interventions were intended to improve the overall dietary pattern, but the major between-group differences in food intake were for the supplemental items. Thus, nuts were probably responsible for most of the observed benefit in the corresponding Mediterranean diet group. A protective effect of both intervention diets on peripheral arterial disease, another cardiovascular outcome, has also been reported recently[85].

The beneficial effects shown in various PREDIMED reports for the Mediterranean diet with nuts on intermediate biomarkers of cardiovascular risk include blood pressure, the lipid profile, insulin resistance, lipoprotein oxidation and systemic inflammation. This diet was also associated with reduction in visceral adiposity, metabolic syndrome and diabetes, as well as delayed atherosclerosis progression. Taken together, these multivariate effects provide a mechanistic explanation for the observed protection of the nut-supplemented diet against CVD. The results of the PREDIMED trial show the full potential of nuts and other healthy foods such as extra-virgin olive oil to improve cardiovascular health.

Conclusion

Nuts are high-energy, nutrient-dense seeds rich in beneficial macronutrients, micronutrients and bioactive phytochemicals. The unique composition of nuts appears to be of paramount importance for their health effects. There is truly consistent evidence from epidemiological and clinical studies of the salutary effects in the consumption of individual nut components and whole nuts on the risk for CVD, as well as on diabetes and major and emerging cardiovascular risk factors, as summarised in Table 2. An increasing body of scientific evidence indicates that including nuts in a healthy dietary pattern affords protection against cardiometabolic disorders beyond that attributable to the other components of a healthy diet. Importantly, contrary to popular belief due to the high energy content of nuts, their consumption does not induce undue weight gain, or is even associated with reduced adiposity, which is attributable in part to satiation and subsequent lesser intake of alternate high-energy foods. Nut components such as unsaturated fatty acids, L-arginine, beneficial minerals, phenolic compounds and phytosterols target multiple cardiovascular risk factors and metabolic pathways, which explain why nuts so strongly reduce cardiovascular risk. The PREDIMED trial has provided first-level evidence that long-term adherence to a healthful diet enriched with one daily serving of mixed nuts reduces the incidence of type 2 diabetes and CVD, particularly stroke. Ongoing research in the context of this landmark trial will eventually indicate whether the salutary effects of nuts extend to prevention of other prevalent chronic diseases, including cancer and neurodegenerative disorders.

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