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Effects of Nut Consumption on Cardiovascular Risk Factors and Coronary Heart Diseases

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Abstract:

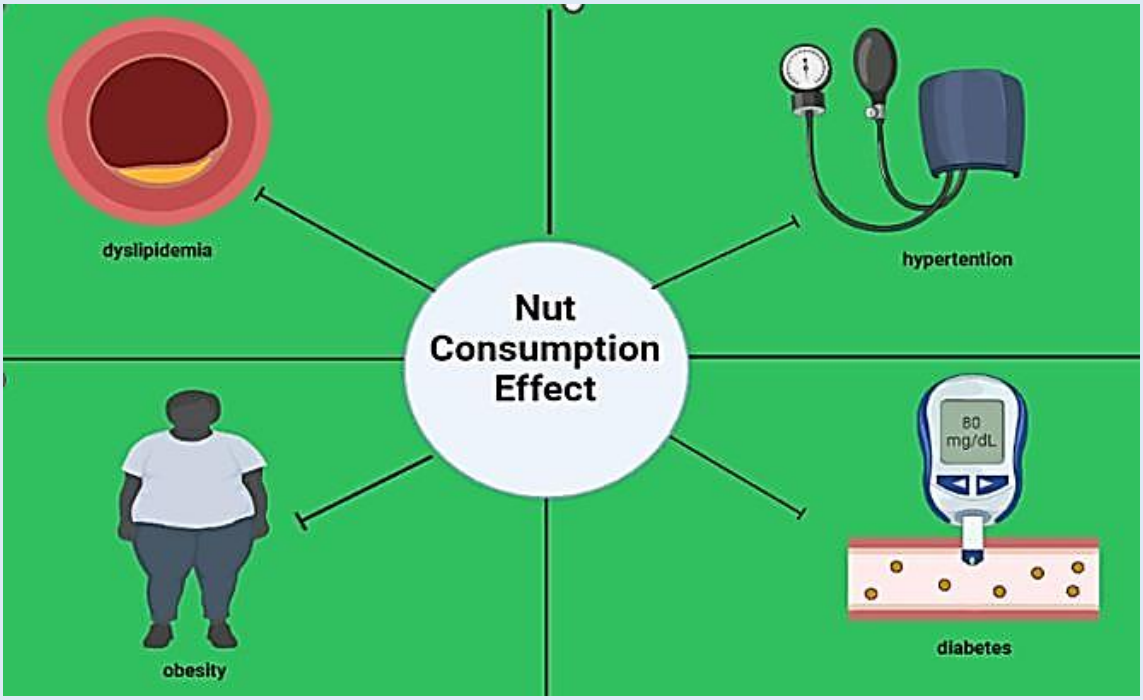
Background: Intervention and epidemiological studies have shown that nut consumption has beneficial effects on cardiovascular risk factors, such as hypertension, type 2 diabetes, body mass index, and hyperlipidemia. The aim of this review is to investigate the effects of nut consumption on cardiovascular risk factors and coronary heart diseases. In addition, we investigated possible mediating mechanisms through which nuts act with health protective effects, which could have a preventive effect on cardiovascular risk factors and coronary artery diseases.

Method: We collected accredited international investigations, whether original, review, meta-analysis that published data in Google Scholar, PubMed/Medline, Wiley Online Library, Web of Science, Science Direct, Scopus, and Research Gate databases.

Result: Some human studies and most animal and laboratory studies reported that favorable effects of nut consumption on cardiovascular risk factors and diseases are through their nutrient profile including polyphenols, unsaturated fatty acid, vitamins, phytosterols, minerals, fibers, and protein. Nut nutrient profile could act through reduction inflammation, inhibition oxidative stress, gut microbiota modification, improvement of endothelial function, modulating gene expression, miRNA, adipokines, insulin secretion, lipid and glucose metabolism, and decreasing cholesterol absorption.

Conclusion: Nuts have favorably acted on lipid profile, glucose homeostasis, vascular health, and weight control. Furthermore, human clinical trials are needed to find the exact and most effective pathways by which nuts prevent or reduce cardiovascular risk factors.

Keywords: Nut Consumption, hypertension, type 2 diabetes, body mass index, hyperlipidemia



INTRODUCTION: Nuts are considered to be a healthy food, rich in fat (50%-75%, mostly unsaturated fatty acid) and full of fiber, vitamins, minerals, protein (1), and bioactive constituents, such as phenolic antioxidants, phytosterols and low available carbohydrate content (1). The consumption of nuts has been related to several beneficial effects on health. Studies showed that nut consumption has been significantly related to the reduction of cardiovascular risk factors, such as hyperlipidemia, hypertension, T2D, and BMI (2, 3).

In this review, we have investigated mechanisms through which nuts provide protective effects against cardiovascular risk factors. Also, we studied clinical trials and meta-analyses about nut consumption's impact on cardiovascular risk factors (hyperlipidemia, blood pressure, diabetes, and BMI). Finally, we studied the effects of nuts on CHD (myocardial infarction and ischemia).

Nutrient content of nuts: Nuts, after vegetable oils, are plant foods rich in fat (43%-67%) (Table1). Nuts are considered a beneficial source of nutrients due to their low content of SFA (4%-5%) and high content of monounsaturated fatty acids (MUFAs) and polyunsaturated fatty acids (PUFAs). In fact, walnuts are also a rich source of a-linolenic acid, the plant Omega−3 (n-3) fatty acid. Lipid profile of nuts in general and walnuts (the highest content of PUFAs at 47%, 38% linoleic acid and 9% linolenic acid) in particular, play a major role in the beneficial health effects of nut consumption (4). Micronutrients are available in significant amounts in nut components, including vitamin b, antioxidant vitamins and polyphenols. These compounds have beneficial effects on the cardiovascular system, but most of them located in pellicle or out soft (1, 5). Nuts are also rich in the amino acid L-arginine, which could improve vascular function due to their important role in producing nitric oxide by endothelial cells, the major modulator of blood pressure and vascular tone (6). Nuts are also rich in phytosterol, but free of cholesterol, which aids in cholesterol reduction. Moreover, nuts are rich in minerals, including calcium, magnesium, potassium, and low in sodium, which are associated with protection against hypertension (7).

Table 1. Nutrient content of raw nuts per 100 g.

	Almond	Walnut	Hazelnut	Macadamia	Pecan	Pistachio	Brazil Nut	Cashew Nut	Peanut	Pine Nut	Chestnut
Energy (kcal)	579	654	628	718	691	560	659	553	567	673	213
Carbohydrate (g)	21.55	13.71	16.7	13.82	13.86	27.17	11.74	30.19	16	13.08	45.54
Protein (g)	21.15	15.23	14.95	7.91	9.17	20.16	14.32	18.22	26	13.69	2.42
Lysine (g)	0.568	0.424	0.42	0.018	0.287	1.138	0.49	0.928	0.926	0.54	0.143
Arginine (g)	2.465	2.278	2.211	1.402	1.177	2.134	2.14	2.123	3.085	2.413	0.173
Total fat (g)	49.93	65.21	60.75	75.77	71.97	45.32	67.1	43.85	49	68.37	2.26
Saturated fat (g)	3.8	6.126	4.464	12.061	6.18	5.907	16.134	7.783	7	4.89	0.425
MUFA (g)	31.55	8.933	45.652	58.877	40.801	23.257	23.879	23.797	24	18.76	0.78
PUFA (g)	12.329	47.174	7.92	1.502	21.614	14.38	24.399	7.845	16	34.07	0.894
Total Fiber (g)	12.5	6.7	9.7	8.6	9.6	10.6	7.5	3	8.5	3.7	8.1
Folate (µg)	44	98	113	11	22	51	22	25	240	34	62
Calcium (mg)	269	98	114	85	70	105	160	37	92	16	27
Magnesium (mg)	270	158	163	130	121	121	376	292	168	251	32
Sodium (mg)	1	2	0	5	0	1	3	12	18	2	3
Potassium (mg)	733	441	680	368	410	1025	659	660	705	597	518
Copper (mg)	1.031	1586	1725	0.756	1.2	1.3	1.743	2195	1.144	1.324	0.447
Iron (mg)	3.71	2.91	4.7	3.69	2.53	3.92	2.43	6.68	4.58	5.53	1.01
Zinc (mg)	3.12	3.09	2.45	1.3	4.53	2.2	4.06	5.78	3.27	6.45	0.52
Selenium (µg)	4.1	4.9	2.4	3.6	3.8	7	1917	19.9	7.2	0.7	NA
α-tocopherol (mg)	25.63	0.7	15.03	0.54	1.4	2.86	5.65	0	8.33	9.33	NA
β-tocopherol (mg)	0.23	0.15	0.33	0	0.39	0	0.01	0.03	NA	0	NA
γ-tocopherol (mg)	0.07	20.83	0	0	24.44	20.41	9.56	5.31	NA	11.15	NA
δ-tocopherol (mg)	0.07	1.89	0	0	0.47	0.8	0.63	0.36	NA	0	NA

	Almond	Walnut	Hazelnut	Macadamia	Pecan	Pistachio	Brazil Nut	Cashew Nut	Peanut	Pine Nut	Chestnut
Total phytosterol (mg)	~198	~110.2	~122	~116	~158.7	~214	~123.8	~151	NA	236.1	22
Stigmasterol	4	0	1	0	3	5	6	0	0	-	
Campesterol	5	5	7	8	6	10	2	9	20	-	
B-sitosterol	130	87	102	108	117	198	64	113	132	-	
δ 5-avenasterol	21	7.3	2.6	-	14.3	-	19.7 (δ avenasterol + B sitostanol)	14	40.1	-	
B-sitostanol	4	-	3.9	-	-	-	-	5.9	-		
Campestanol	2	2.3	3	-	2.8	-	-	2	3.9	-	
Others	32	8.6	2.5	-	15.6	-	31.8	13	34.2	-	
Total polyphenol (mg) #	287	1576	687	126	1284	867	224	232.9	NA	NA	NA
Total polyphenol (mg) $	212.9 ± 12.3	1580.5 ± 58	314.8 ± 47.3	497.8 ± 52.6	1463.9 ± 32.3	571.8 ± 12.5	169.2 ± 14.6	316.4 ± 7.0	645.9 ± 47	152.9 ± 14.1	NA
Flavonoids (mg) $	93.5 ± 10.8	744.8 ± 93.3	113.7 ± 30.2	137.9 ± 9.9	704.7 ± 29.5	143.3 ± 18.7	107.8 ± 6.0	63.7 ± 2.1	189.8 ± 13.1	45.0 ± 5.4	NA
Ellagitannins (mg) ‡	ND	823 ± 59	ND	ND	301 ± 7	ND	ND	ND	ND	NA	149 ± 3
Proanthocyanidins (mg) #	176	60	491	NA	477	226	NA	2	NA	NA	0
Carotenoids (µg)	2	NA	106	NA	55	332	0	NA	NA	NA	NA
Lutein + zeaxanthin (µg)	1	9	92	0	17	2903	0	22	0	9	NA

Sources: US Department of Agriculture Nutrient Data Base. https://ndb.nal.usda.gov/ndb/search/list,(15)

Mechanisms of action: Bioactive components, amino acids, unsaturated fats and fibers are thought to be involved in reducing the effects of nut consumption on lipid profile, blood pressure, blood sugar and BMI (1, 2, 8) (Figure 1).

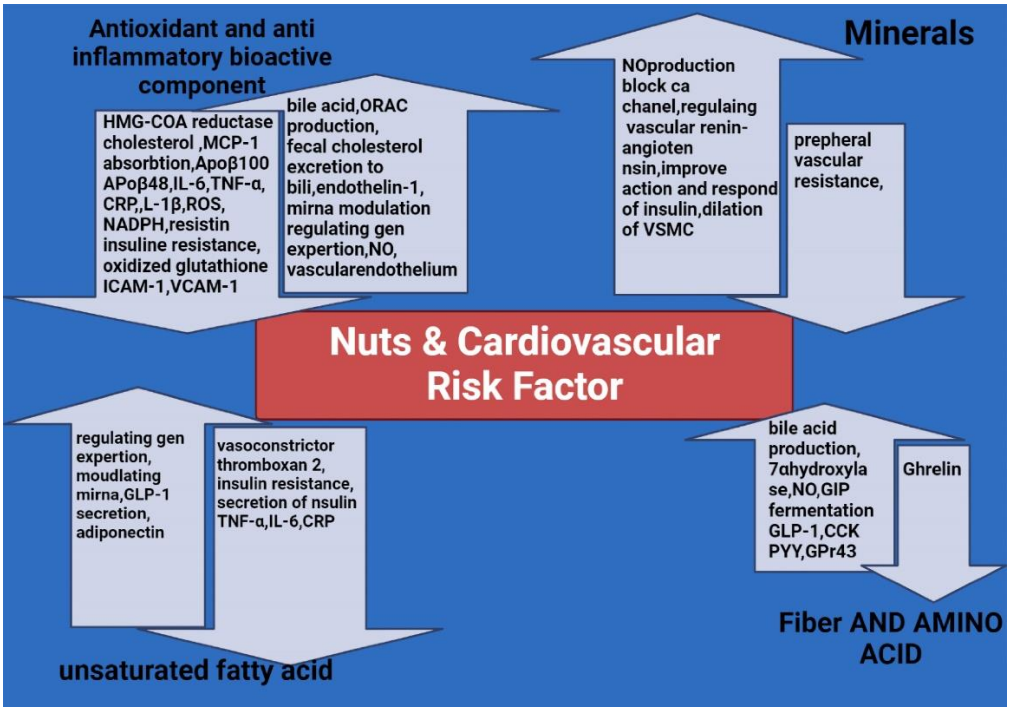


Figure 1. Nut contents and their effects on mechanisms in cardiovascular risk factors contribute to the prevention of CVD. In the figure, arrows are placed mechanisms for which pathways were changed in the body after individual nutrient administration. Upward arrows represent upregulation of pathways, while downward arrows represent pathways of downregulation.

Lipid profile lowering:

Antioxidant and anti-inflammatory bioactive components: Phytosterols reduce serum cholesterol in five pathways:

1. Phytosterols increase bile acid production and inhibit β-hydroxy β-methulglutaryl-CoA (HMG-CoA) reductase through stimulation of 7 α-hydroxylase (9).

2. Phytosterols intake significantly increased total fecal cholesterol excretion at moderate and high doses (458 mg/day, 2059 mg/day) (10).

3. Phytosterols compete against biliary and dietary cholesterol absorption in the intestinal lumen by Niemann-Pick C1-Like 1 (NPC1L1) protein, which is required for intestinal cholesterol and phytosterols absorption (11).

4. Phytosterols inhibit the absorption of cholesterol in the intestinal lumen and releasing them from hepatocytes into bile by the heterodimer of ATP-binding cassette (ABC) transporters, G5 (ABCG5) andG8 (ABCG8) (12).

5. Phytosterols decrease apo B100 in Human hepatocellular carcinoma (HepG2), which led to a 30% reduction in the VLDL ratio. (13). Furthermore, phytosterols reduced cholesterol ester (CE) concentrations in (HepG2) cells, apoB48 in human colon adenocarcinoma cell line (Caco2), and ApoB100 in HepG2 that could lead to a reduction of lipid production in cells (10).

The Lysine to arginine ratio: Animal studies have shown

that a low ratio of lysine to arginine activates 7α-hydroxylase, which causes an increase in bile acid and thus reduces hepatic cholesterol. This could cause a decrease in LDL-C. (14).

Unsaturated fatty acids: A few studies on Caco-2 cells showed the expression of cholesterol transporter NPC1L1 reduced by PUFAs (15). Furthermore, studies showed PUFAs supplementation regulated some genes related to lipid metabolism. They act in conjunction with some transcription mediators, including the liver X receptor (LXR), the nuclear receptors peroxisome proliferator-activated receptor (PPAR), hepatocyte nuclear factor-(HNF)-4, sterol-regulatory element-binding protein (SREBP), and Nuclear Factor kappa-light-chain-enhancer of activated B cells (NFκB) (16). Ortega investigated effects of unsaturated fat consumption on small non-coding RNAs (miRNAs) and found some unsaturated fat consumption modulated significantly miR-106a and miR-130b, which were associated with increasing circulation adiponectin and decreasing LDL.

Fibers: Insoluble fibers in nuts increase fermentation by gut bacteria, which provide a source of short-chain fatty acids. Short-chain fatty acids decrease cholesterol synthesis in the liver and these effects may lead to a decrease in blood cholesterol from the fibers in the nuts (17).

Modulating blood pressure: Researchers have reported that diets containing mixed nuts have protective effects against hypertension. Polyphenols and minerals, such as calcium, potassium, amino acids, and antioxidants could reduce blood pressure (3).

Minerals and Unsaturated fatty acids: Magnesium intake decreases blood pressure by increasing the production of nitric oxide, prostacyclin and blocking calcium channels (5). Potassium intake could decrease blood pressure by decreasing peripheral vascular resistance, regulating the activity of the renin-angiotensin system, dilatation of vascular smooth muscle, reducing angiotensin effects, and reducing extracellular fluid volume (18). Calcium intake suppresses parathyroid hormone (19). Both PUFA and MUFA could regulate BP by decreasing thromboxane 2, which is a vasoconstrictor (20).

Amino acid arginine: Arginine and polyphenols could accelerate the function of the circulatory system via the increase of the first intermediate of endothelial dilation by different pathways. Arginine is the substrate for nitric oxide synthase enzyme (NOS). Some studies showed arginine supplements could improve endothelial cells (21).

Antioxidant and anti-inflammatory bioactive components: Polyphenols, tocopherols, phytosterols, ALA and selenium have anti-inflammatory and antioxidant effects in nuts. Inflammation and oxidation through increasing CRP, IL-6 TNF-α, IL-1β, and oxidative stress (↑NADPH, ↑ROS) induce vascular endothelium dysfunction, which leads to hypertension, so nut consumption could decrease inflammatory cytokines and oxidation by their bioactive compounds and improve blood pressure by enhancing vascular endothelium (22). Resistin is a hormone secreted from adipose tissue that correlated with some inflammatory cytokines and inflammation pathways. Zhang investigated 14 case-control studies containing 718 patients with hypertension and 645 controls found a direct relationship between resistin concentrations and hypertension (Zhang et al., 2017). Human intervention evaluating the effect of nut consumption on serum levels of resistin reported significant alterations in serum levels of resistin by the consumption of nuts in participants (23).

Polyphenols induce nitric oxide (NO) production by increasing [Ca2+] and phosphorylation of eNOS by the PI3-kinase/Akt pathway, which leads to fast and stable activation of nitric oxide synthase and production of EDHF. In addition, experimental studies reported that polyphenols also increase endothelial prostacyclin and suppress the formation of endothelin 1. All these mechanisms could explain the vasodilatory and vasoprotective effects of arginine and polyphenols which leads to blood pressure regulation (24).

Modulating blood sugar: Phytosterols, unsaturated fat, minerals and fiber are thought to involve in the effects of nuts consumption on reducing blood sugar (25, 26).

Antioxidant and anti-inflammatory bioactive components: The clinical correlation between the pathophysiology of diabetes and inflammation is known. Studies showed activation of at least two main inflammation pathways including, JunN-terminal kinases (JNK) and the transcription factor of NF-kB lead to an increase in pro-inflammatory markers (hs-CRP, TNFβ, IL-1β, IL-6, etc) that are related to progression T2D (27, 28); (29).

Clinical trials studies showed useful effects of nut consumption on inflammatory markers such as IL-1β, which has a significant role in the development of T2D by increasing activated pathways in islets of Langerhans and leads to beta-cell dysfunction (30). Interventional studies showed walnut and pistachio consumption (6 and 4 weeks repeatedly) significantly reduced IL-6, which is a marker for the development of T2D by inducing apoptosis in pancreatic islets (23, 31).

Obesity increases the production of TNF-alpha by different cells, which leads to islet inflammation and insulin resistance in patients. In inflammatory conditions, this factor causes the death of pancreatic islets cells and increases insulin resistance (32). Zhao and Arpon reported that the consumption of walnuts (6 weeks) (25) and mixed nuts (5 years) (26) could improve serum levels of TNF-alpha. MicroRNA (miR156c and miR159a) exerts an anti-inflammatory effect by targeting the TNF-α receptor in mammalian adipose tissue. Studies in mice have shown that these molecules are associated with a decrease in the inflammatory signaling pathway of TNF-α, due to reducing inflammatory cytokines in adipocytes and visceral fat stores under various pro-inflammatory conditions. Nuts also contain microRNAs (miR156c and miR159a) that reduce inflammation by the reduction of TNF-α inflammatory signaling pathway (33).

The exact mechanism of CRP action in diabetes is still unclear, but it is related to insulin resistance, increasing (HbA1c) and blood glucose. Rajaram, Gulati and Zhang reported almond and mixed nuts consumption improves serum levels of CRP in three kinds of subjects (diabetic, healthy, and obese people) (34-36).

Resistin, a hormone secreted from adipose tissue, is related to reduce glucose regulation and insulin resistance. Resistin causes the progression of T2D through inflammation pathways that are related to increasing biomarkers such as CRP, TNF-a, IL-6, and insulin resistance through AMPK- independent and -dependent mechanisms in HepG2 cells (37). A diet rich in pistachios (57 g/day) for 4 months significantly decreased gene expression in lymphocytes, compared to the control group (23). Nut consumption also has a favorable effect on health due to their antioxidant properties. Antioxidant properties could modulate blood sugar by reducing inflammatory pathways that lead to β-cell dysfunction (38).

MiRNA modulation by polyphenols appears to be another possible intermediate mechanism of modulating blood sugar due to nut consumption. Polyphenols by modulating miRNA expression contributed to the control of inflammations and oxidation (such as mir122, 125b and 155), which leads to the control of diabetes (39).

Fiber: Soluble fibers improve glycemic control in diabetic patients by increasing insulin sensitivity and decreasing hyperinsulinemia (40). Fibers reduce the speed of digestion; Thus, intestinal fermentation bacteria produce short-chain fatty acids which are involved in reducing glucose uptake by the liver and increasing secretion of GLP-1(41). Gastric inhibitory polypeptide (GIP) and GLP-1 maintains normal glucose levels by stimulating the secretion of insulin and improving the proliferation of β-cells (41).

Minerals: Magnesium improves the action and response of insulin, which leads to an improvement in glycemic control (42). Magnesium is also a co-factor for many metabolic reactions included in carbohydrate metabolisms. Therefore, a magnesium deficiency can lead to the development of diabetes by interfering with carbohydrate metabolisms. (43).

Unsaturated fat: Studies have reported that unsaturated fats in nuts reduce the risk of developing T2D via reduction of IR (44). It is hypothesized that insulin sensitivity has been increased via facilitated movement of glucose receptors from within the membrane to the membrane surface by unsaturated fats (45). In addition, unsaturated fats increase the secretion of insulin from beta cells by stimulating Glucagon-like peptide-1 (GLP-1) secretion and inhibiting the expression of lipogenic genes, thus improving glucose homeostasis. (44). Interventional and experimental studies found that unsaturated fat in diets or in cell culture reduced levels of IL-6, IL-1, TNF-α and hs-CRP, elevated levels of these pro-inflammatory markers lead to progression of T2DM (46).

Unsaturated fats modulate some small non-coding RNAs (miRNAs), which post-transcriptionally and negatively regulate gene expression. It was recently reported that a PUFA-enriched diet and some nut supplementation modulated specific miRNAs like miR-375 and MiR-192, which improves insulin and glucose metabolism (47, 48). MUFAs and PUFAs enriched in diet change plasma miR-125a-5p, which (49) was related to changes in adiponectin (anorexigenic peptide) and plasma fasting TG. Adiponectin causes glucose uptake in acid oxidation, skeletal muscle, stimulates fatty and adipose tissue, improves insulin sensitivity, increases energy expenditure, and reduces glucose output by the liver through activation AMPK signaling (47).

BMI: The effect of nut consumption on BMI depends on diet because nuts are a high-fat and high-calorie nutrient. A few mechanisms may be involved in reducing BMI by nut consumption. However, it should be noted that nuts in a healthy and controlled diet (in terms of energy intake) could have beneficial effects and otherwise increase BMI (50, 51).

Fiber, protein, and unsaturated fat: Some studies showed that nut consumption could influence the appetite of participants. The mechanism of the effect of reducing appetite after nut consumption has been considered in three pathways: 1- nuts are rich in protein and fiber, which makes participants feel full longer. 2- Protein and unsaturated fat in nuts cause the release of gut satiety hormones including, peptide YY (PYY), cholecystokinin (CCK), GLP-1, and suppressed secretion of Ghrelin (hunger hormone) (52).

Numerous studies reported that fiber fermentation by fermentation bacteria in intestine active G-protein-coupled receptors 43 (Gpr43), which suppress fat accumulation in adipose tissues and insulin signaling, which can influence BMI (53).

Effect of nut consumption and cardiovascular risk factors (clinical trial study):

Effect of nuts consumption on lipid profile: Hyperlipidemia is one of

the most important and common underlying cardiovascular diseases (54). It was proven that elevated serum LDL cholesterol levels are directly related to the development of atherosclerosis and coronary artery disease (55). Nutrition has a significant effect on lipid levels. The first study on the beneficial effect of nuts consumption performed in a group of normolipidemic young men (56). Following this study, many clinical trials studies were done to investigate the effect of different nuts on lipid profiles (57, 58).

A human intervention to investigate the effect of the daily use of 60 g/day almond for four weeks in hyperlipidemic men and found TC (p=0.01), LDL (p<0.001), apo-B100 (p=0.009) effectively reduced, but no significant difference was observed in HDL (59).

Peanuts and almond consumption on lipid profile in subjects with T2DM didn't significantly improve the TC, HDL-C, LDL-C and triglycerides in the two interventional groups, compared to the baseline by the third month (60). Baru almond oil consumption (500 mg per day) for 3 months by hemodialysis patients had no significant effects on lipid profile (61). While one study showed whole almonds (WA) (66 ± 5 g per day) or almond oil (AO) (35 ± 2 g per day) consumption for six weeks by healthy men and women significantly improved TC (4%), LDL (6%) and TG concentration (14%) compared with baseline. HDL cholesterol (WA 1.21 ± 0.06, AO1.24 ±0.06) was significantly higher than baseline after each of the treatment periods (62). Moreover, Zibaeenezhad investigated the effect of almond oil consumption on patients with hyperlipidemia (63). The case group received 10 ml of Persian almond oil, two times per day for 1 month. They reported that the TC and LDL levels significantly decreased in the case group (P = 0.009, p < 0.001 respectively), but the triglyceride and HDL didn't change significantly with almond oil consumption.

A comprehensive narrative review, including 14 systemic reviews, meta-analyses of RCTs on almonds and some other nuts and 64 RCTs, reported almonds consistently improved blood lipid profiles, including LDL-C, VLDL-C, TC, non-HDL-C, LDL-C, and small Apo-B particles (64). A meta-analysis investigated 15 RCTs of the almond consumption on cardiovascular disease with 534 subjects and for 4 to 16 weeks. They showed that almond intervention significantly decreased total cholesterol (−10.69 mg/dL;), LDL cholesterol (−5.83 mg/dL;) and HDL cholesterol (−1.26 mg/dL), but without heterogeneity (P = 0.29), apoB (−6.67 mg/dL) TG changes were not 't significant, but with significant heterogeneity (P < 0.01) (65). Moreover, a separate analysis of 18 intervention studies (period time 8 weeks 18 months) reported that almond consumption (20 to 113 g/d) significantly reduced LDL-C, TC and TAG (−0.124 mmol/l, −0.153 mmol/l, and −0.067 mmol/l respectively), and HDL-C was not affected (66).

Walnuts are one of the nuts that were investigated for their beneficial effect on lipid profile. The study demonstrated that walnut intake (20 gr/day) for 8 weeks in hyperlipidemic patients significantly increased HDL by 9% and TG decreased levels by 17.1% from the baseline, but there was no significant change in LDL (67). Walnut oil consumption significantly decreased lipid profile in hyperlipidemic type 2 diabetic patients. In the 3-month consumption of Persian walnut oil capsules (1.25 cc) for 15 times, Tc(P<.001), TG P = 0.021), and LDL (P<.001) significantly decreased, compared to the control group without any change in the participant's previous diet. They showed that Persian walnut oil consumption significantly increased HDL-c, but there was no change in the control group (68). Due to the allergenicity of walnut kernels for some people, walnut oil was used in their study.

A meta-analysis of only walnut intervention studies (26 RCT with a total of 1059 participants) found a significant reduction in TC (WMD=−5.51mg/dL), LDL cholesterol (WMD= −4.69mg/dL), Apolipoprotein B (WMD=−3.74), and apolipoprotein concentrations (WMD = −2.91) in case group. (69).

A RCTs study, that has not been included in meta-analyses (64, 65, 69), investigated walnut consumption effects on lipid profile and found that the HDL-C (46.6±10.8) and TC/HDL-C (4.2±1.1) significantly improved from baseline (70). Two recent meta-analyses studies published in 2020 and 2021 investigated cashew nut and almonds on lipid profile (71, 72). Morvaridzadeh found no significant change in TC, TG, HDL, and LDL (71). Moreover, another meta-analysis reported a significant reduction in TG (WMD =−6.68 mg dL), TC (WMD = −4.92 mg dL), and LDL (−5.65 mg dL) however it did not significantly change HDL levels (72).

Some experimental studies reported Amygdalus scoparia kernel consumption has efficient effects on health. A clinical trial study investigated the effects of the Amygdalus scoparia kernel on the lipid profile in hyperlipidemic patients. Results showed that in the intervention group, which received the ASK oil(10cc/day) for 60 days, TG levels significantly decreased (24.80 ± 51.70), and it didn't have a significant effect on TC, LDL, and HDL cholesterol levels (73). Human interventions evaluated the effect of nut consumption on lipid profile and are shown in Table 2.

Effect of nuts on blood pressure: Hypertension is one of many serious public health problems that affect almost 25% of adult people in the world and is responsible for the most preventable death (74, 75). Several dietary factors affect blood pressure and researchers showed that some diets, like DASH and vegetarian diets could reduce blood pressure. Nuts are one of the nutrients that many clinical studies investigated the consumption of that on blood pressure (76-78).

Mazidi investigated 20 intervention studies and found no significant change on diastolic blood pressure (DBP) and systolic blood pressure (SBP) (79). Mohammadifard studied 21 RCTs and showed a significant change in SBP by the consumption nuts in participants without T2DM (P = 0.16), but in T2DM participants they found no significant effect on SBP (p = 0.02) (80). Mejia analyzed 20 RCTs about the effect of tree nuts on blood pressure and showed no significant change in their blood pressure in the case and control groups at the end of the studies (81). Gobbo reported no significant effect of tree nut consumption on blood pressure between case and control group after examining 21 trials (82).

There were two recent meta-analysis studies published in 2020 and 2021. Jalali analyzed 3 RCTs to evaluate the effect of cashew nuts consumption on blood pressure and they showed a significant decline in SBP (P-value = 0.01) in the group receiving cashew nut, compared to the controls (83). A recent meta-analysis evaluated 31 RCTs by Jayedi and the results showed that SBP and DBP by 0.50 and 0.23 mmHg could significantly decrease after 20 g/d enhancement in nut intake (84). Nut consumption had a significant effect on SBP in diabetic patients (MD: -1.31). The decrease in DBP was dependent on the dose of nuts consumption, with the greatest reduction at 80 g/d.

A clinical trial that wasn't included in the meta-analysis (79-84) investigated the effects of nut snacks consumption on blood pressure (85). Mixed tree nut consumption for 12 weeks showed a significant reduction in DBP ($p<0.05$), compared to pretzel consumption. They observed no significant changes in SBP (85). Human interventions assessing the effects of nut consumption on blood pressure are shown in Table 3.

Table 2. Summary of clinical trials and meta-analysis of RCTs examining the effect of nut consumption on lipid profile

Reference	Subjects Study	Design/Period	Nut Type	Diet Intervention	Results
Beman-Ali Jalali-Khanabadi et al./ 2009(101)	Men with Mild Hyperlipidemia	Clinical trial/4 weeks	almond	30 healthy male volunteers(60gr/d)	↓ TC (mmol/L) (6.61± 0.68) to (5.99±1.03) p= 0.01,↔ TG,↔ HDLc,↓ LDLc (mmol/L) (4.38±0.70 to 3.76±0.66) p <0.001,↔ Lipoprotein,↔ apo-A1,↓ apo-B100 (1.26±0.305 to 1.11±0.246) p= 0.009
Yun-Ying Hou et al./2018(102)	type 2 diabetes mellitus	A Randomized Controlled Trial/ third month	Peanuts and almonds	60 g/day peanuts for men and 50 g/day for women in the Peanut group [n=17], and 55 g/day almonds for men and 45 g/day for women in the Almond group[n=15], for third month	↔BMI,↔ Total cholesterol, ↔LDL-C,↔ HDL-C,↔ Triglycerides
Raquel M. Schincaglia et al./2020(103)	hemodialysis patients	randomized, double-blind, placebo-controlled clinical trial/12 weeks	baru almond oil (Dipteryx alata Vog.)	Hemodialysis patients were supplemented with 5 g of baru oil (BG, n = 17) or 5 g of mineral oil (placebo, BP, n = 12).	↔BMI, ↔ TC,↔ TG ,↔ HDL-c, ↔ LDL-c ↔ VLDL, ↔ nHDL-c, ↔ CT:HDL-c ratio,↔ LDL-c:HDL-c ratio,↔ nHDL-c/HDL-c
Hyson DA al./2002(104)	normolipemic men and women	randomized crossover trial design/6weeks	Almonds and Almond Oil	24 normolipemic men and women randomly assigned to either a wholealmond (WA) or almond oil (66 ± 5 g per day) (AO) diet)(35 ± 2 g per day) for 6 wk,	↓ Tc(4%,p=<0.05),↓ LDL (6%, p=<0.05) cholesterol no differences between the WA and AO diet periods,↓ TG (14%, (WA 1.21 ± 0.06* AO1.24 ±0.06,p=<0.05),↔ VLDL,↑ HDL(WA 1.21 ± 0.06* AO1.24 ±0.06),↔ Apolipoprotein A-1,↔ Apolipoprotein B
Mohammad Javad Zibaeenezhada et al./2019(105)	patients with hyperlipidemia	A Randomized Controlled Trial/4weeks	Almond oil	Ninety-seven patients were divided into the intervention (n=49) and control (n=48) groups. The intervention group received 10 ml of almond oil two times daily for 30 days	↓ Total cholesterol −16.12 ± 26.16 p= 0.009,↔ TG, ↓LDL −20.88 ± 18.41 p= <0.001, ↑HDL 6.01 ± 5.78 p= <0.001↔ Systolic Blood Pressure,↔ Diastolic Blood Pressure
Mark L. Dreher et al./2021(106)	Not exactly mentioned	A Comprehensive Review of 64 RCTs and 14 systemic reviews and/or meta-analyses of RCTs	almonds and some other nuts	RCTS with consumed at >42.5 g/day or for >6 weeks.	↓TC,↓ LDL-C, ↓non-HDL-C, ↓VLDL-C,↓ Apo-B, and ↓small LDL-C
Michelle A Lee-Bravatti et al./2019(107)	among adults (≥18 y of age) who were either healthy or had risk factors for CVD (e.g., dyslipidemic, diabetic, or hypertensive) at baseline.	Meta-analysis of 15 RCTs	Almond	total of 534 subjects, The study durations included in the meta-analysis ranged between 4 and 16 wk, dose of almond intake ranged between 25 and 100 g/d.	↓ TC −10.69 mg/dL; 95% CI: −16.75, −4.63 mg/dL, I^2 =67%, P<0.01) ↓LDL(:−5.83mg/dL; 95% CI:−9.91,−1.75mg/dL, I2 = 61%, P < 0.01), ↓HDL (−1.26 mg/dL; 95% CI: −2.47, −0.05 mg/dL), ↓ apoB −6.67 mg/dL; 95% CI: −12.63, −0.72 mg/dL, I^2 = 50%,P = 0.09), ↔ TG
Kathy Musa-Veloso et al./2016(108)	among adults (≥18 y of age) who were either healthy or had risk factors for CVD (e.g., dyslipidemic, diabetic, or hypertensive) at baseline	meta-analysis of 18 randomised controlled trials	Almond	total of 837 subjects, The study durations included in the meta-analysis ranged between 4wk to 18month, dose of almond intake ranged between 20and 113g/d.	↓TC −0·153 mmol/l (P < 0·001),↓LDL-C −0·124 mmol/l (P = 0·001), ↓TAG −0·067 mmol/l (P = 0·042),↔ HDL-C

MJ Zibaeenezhad et al./2017(110)	hyperlipidemic type 2 diabetic patients	randomized, double-blind, placebo-controlled trial/3month	walnut oil	100 hyperlipidemic type 2 diabetic patients aged 35–75 years were assigned to receive 15 cc Persian walnut oil or placebo every day for 90 days	↓ TC (TD) = − 30.04, P<.001),↓ (TG) level (TD = − 15.04, P = 0.021),↓ (LDL) level (TD = − 30.44, P<.001),↓TC/HDL (TD = 2.28, P = 0.06),↑ HDL (TD = 2.28, P = 0.06)
M. J. Zibaeenezhad et al./2005(109)	Hyperlipidemic Patients	In a randomized case-control/8weeks	walnut	52 volunteers were divided into 2 groups: Group A consumed walnuts, 20 grams per day for 8 weeks and the control group (group B) consumed no walnuts	↓ TG (17.1%, p= 0.0195),↑ HDL (9%, p= 0.030),↔ LDL,↔ TC
Marta Guasch-Ferré et al./2018(111)	1059 among adults (≥18 y of age) who were either healthy or had risk factors for CVD (e.g., dyslipidemic, diabetic, or hypertensive) at baseline	Meta-analysis of 26 clinical trials/4wkto1 year	walnut	1059 participants. The intervention periods of the trials ranged from 4 wk to 1 year, with a mean duration of 8 wk. The amount of walnuts ranged from 15 to 108 g/d (daily mean)	↓TC (WMD=−−5.51mg/dL, P<0.001), ↓LDL cholesterol concentrations (WMD= −4.69mg/dL; P = 0.03), ↓ApolipoproteinB (WMD=−3.74, P = 0.008) and ↓apolipoprotein(WMD = −2.91, P = 0.057),↔HDL,↔BMI
Alyssa M. Tindall et al./2019(116)	Men and women with overweight and obesity (body mass index [BMI; kg/m2], 25–40), aged 30 to 65 years, who had LDL-C between the 50th and 90th percentiles (128–177 mg/dL for men and 121–172 mg/dL for women) and/or elevated brachial BP (120–159/80–99 mm Hg for bSBP/bDBP)	randomized,crossover, controlled-feeding trial/6weeks	walnut	participants consumed 3 isocaloric weight-maintenance diets for 6 weeks each: a walnut diet delivered as a snack (57–99 g/d	↑HDL-C(142.8±33.4,p=0.001)↓ TC:HDL-C(4.2±1.1,p=0.004),↔ BMI,↔ TC,↔ HDL-C,↔ LDL-C,↔ TG
Mojgan Morvaridzadeh et al./2020(113)	healthy or, diabetic, at baseline	Meta-Analysis of 3 randomized clinical trials/8wkto12wk	Cashew Nut	531 participants, with 8wk to 12wk duration. The amount of walnuts ranged from 28 to 64 g/d (daily mean)	↔TC, ↔TG, ↔LDL, ↔HDL
Omid Asbaghi et al./2021	health (healthy/unhealthy) and obesity status (normal/overweight/obese)	Meta-Analysis of 3 randomized clinical trials/>3wk	Almond	1154 paticipantsinvestigated almond intake as a stand-alone, trial duration (<6/ ≥ 6 weeks) almond dose (≥45/< 45 g d−1)	↓TG (WMD =−6.68mg dL, p = 0.008),↓TC (WMD = −4.92 mg dL, p = 0.001p < 0.001), ↓LDL(−5.65 mg dL) ,↔HDL
Mohammad Javad Zibaeenezhad et al./2017(115)	patients with dyslipidemia	a randomized, openlabel controlled clinical trial/60 days	Amygdalus scoparia kernel oil	Men and women aged 20 to 70 years with dyslipidemia Amygdalus scoparia kernel oil intake 10 cc per day orally for 60 days	↓TG(24.80 ± 51.70 vs 3.13 ± 44.80, p = 0.03),↔LDL,↔TC,↔HDL

Table 3. Summary of clinical trials and meta-analysis of RCTs examining the effect of nut consumption on blood pressure.

Reference	Subjects Study	Design/Period	Nut Type	Diet Intervention	Results
Mohammad Javad Zibaee Nezhad et al./2016(92)	Diabetes Mellitus Type 2	randomized control clinical trial/three months	Walnut Oil	100 patients with DM type 2. experiment group (n = 50), walnut oil (15 g/day for three months) was added to their diet, while the control group (n = 50) did not undergo any interventions	↓HbA1c level 7.86% ± 21.97 (P = 0.005), ↓FBS level decreased by 8.24% ± 16.77 (P = 0.001)
David J. A. Jenkins et al... /2018(90)	type 2 diabetes	a reanalysis of a randomized controlled trial/ 3 months	mixed nuts	parallel design to one of three diets for 3 months: (1) 'full-dose nut diet' (n = 40): a diet with 2.0 MJ (477 kcal) per 8.4 MJ (2000 kcal) energy provided as mixed nuts (75 g/day); (2) 'full-dose muffin diet' (n = 39): a diet with 1.97 MJ (471 kcal) per 8.4 MJ (2000 kcal) energy provided as three whole-wheat muffins (188 g/day	↓HbA1c −2.0 mmol/mol (95% CI −3.8, −0.3 mmol/mol),
Arti Muley et al... /2020(93)	type 2 diabetes	a systematic review of Fifteen trials / three month or earlier to 12 months	Tree nuts	667 patients with DM type 2, tree nuts investigated Separately and combine duration of intervention was three month or earlier to 12 months	↓FBS (MD -0.26 mmol/L), ↓HbA1c(-0.11%)in tree nuts combined group, ↓FBS(MD of -0.45, 0.16, and-0.90mmol/L, respectively)in walnuts ,almonds, and hazelnut group,↓HbA1c-0.17% in walnut group
Alyssa M Tindall et al./2019(75)	prediabetes or type 2 diabetes	meta-analysis of 40 randomized controlled trials/1 to 12 months	Almonds, cashews, pecans, pistachios, walnuts, nut oil	Median duration of 3 months (range: 1–12 months), and the dose of nuts tested varied from 20 to 113 g/d (median: 52 g/d).	↓ HOMA-IR (WMD: −0.23; 95% CI: −0.40, −0.06; I2 = 51.7%), ↓ fasting insulin (WMD: −0.40 µIU/mL; 95% CI: −0.73, −0.07 µIU/mL; I2 = 49.4%) in tree nuts or peanuts group, ↔FBS, ↔HbA1c
Ling Yang et al./2020(94)	Non-healthy or healthy; with or without medical diagnosis of disease	systematic review and meta-analysis of 14 randomized clinical trials/ 5 weeks to	Walnut	823 participants non-healthy or healthy dose of walnut varied between 60 g/week to 15−57 g/day and duration of intervention 5 weeks to 12 months	↑leptin (weighted mean difference (WMD): 2.502 g/mL; 95 % CI:2.147–2.856, p < 0.001), diponectin (WMD: 0.440 ng/mL; 95 % CI: 0.323 to 0.557, p < 0.001), ↔HbA1c, ↔FBS

Reference	Subjects Study	Design/Period	Nut Type	Diet Intervention	Results
		12 months			
Elizabeth P Neale et al./2020(95)	Healthy, Metabolic syndrome, type 2 diabetes	a systematic review and meta-analysis of 16 RCT/four days, to one year	Walnut	1620 823 participants non-healthy or healthy dose of walnut varied between 30 grams to 56 grams per day and duration of intervention four days, to one year	↔FBS, ↔HbA1c, ↔ HOMA-IR, ↔fasting insulin
Jane Bowen et al./2019(96)	obese adults with elevated fasting blood glucose	randomized controlled trial/ 8 weeks	Almond	76 adults randomly assigned to daily consumption of either almond 56 g/day (n=37) or 72 gr/ day snakes(n=39)	↔Plasma glucose, ↔ Serum insulin, ↔↔HbA1c, ↔CRP, ↔ IL-6, ↔ TNFa
Mengxiao et.al Ren/2020(53)	Type 2 Diabetes	randomized controlled trial/ 3 months	Almond	Forty-five participants with T2DM, including 22 in the almond-based 56 g/day (a-LCD) group and 23 in the low-fat diet (LFD) group for 3 months	↓ HbA1c ($p < 0.01$) in a-LCD group, ↑ GLP-1 concentration in a-LCD group (.017)
Khadijeh et al. Rabiei/2018(97)	type 2 diabetic	double-blind, placebo controlled clinical trial/ 7 weeks	hydroalcoholic extract of walnut	20 received hydroalcoholic extract of walnut and 20 received placebo for 7 weeks	↓ postprandial glucose ($P = 0.030$), ↓ HbA1c ($P = 0.028$), ↔ blood glucose, ↔ HOMA-IR
Natasha Godwin et al. /2019(91)	Healthy, Obese, and Overweight	Two-Arm Randomized Controlled Trial/	Mixed Nuts	Subjects were instructed to consume the snack of 42 g of mixed nuts or 69 g of Snyder's mini unsalted pretzels along with 16 oz of water within 5 min. Blood was collected 1 h after consumption of the snacks. Samples were centrifuged at 1200 g for 10 min at 4C to separate serum, which was stored at -80C for later use. Two 24-h recalls were filled out for the 2 days leading up to the testing period.	↑ glucose ($P < .001$), ↑ insulin ($P < .001$) in pretzels, ↔ glucose, ↔ insulin in nuts group

Effect of nuts on blood sugar (type 2 diabetes): Currently, type 2 diabetes is one of the most chronic metabolic diseases. According to the International Diabetes Organization, it was reported that almost 425 million people had T2DM in 2017 and this figure will rise to 629 million by 2045. (86). Nutrition has a direct effect on the prevention, incidence, and control of this disease. Nuts are one of the nutrients that are highly studied to investigate their effects on managing metabolic diseases. Research has proposed that nut consumption improve insulin resistance and blood sugar (87, 88).

Walnut oil consumption improved (FBS) and HbA1c in diabetic patients. Results showed that the consumption of walnut oil (15 g/day for three months) in type 2 diabetic patients had a favorable effect on HbA1c level (P = 0.005) and FBS (P = 0.001) (89).

A randomized controlled clinical trial in diabetic patients reported that the consumption of mixed nuts (75g/day) significantly reduced HbA1c (−2.0 mmol/mol) (87). A systematic review of 15 RCT with a total sample size of 667 investigated effects of tree nuts on glycemic outcomes in diabetic patients. They found all tree nuts combined consumption significantly lowered in both FBS and HbA1c (MD= -0.26 mmol/L and -0.11% respectively) at 90 days or earlier follow-up. The analysis indicated that walnuts, almonds, and hazelnuts consumption reduced (MD of -0.45, -0.16, and -0.90 mmol/L, respectively) in FBS, and -0.17% in HbA1c following ingestion of walnuts at 90 days or earlier follow-up (90). A meta-analysis of 40 RCTs investigated the effects of nut consumption on markers of glycemic control. They showed peanut consumption or whole tree nuts had a beneficial effect on HOMA-IR (WMD: −0.23 µIU/mL) and fasting insulin (WMD: −0.40 µIU/mL). They found no significant effect of nut consumption on FBS or HbA1c (91).

Meta-analyses of walnut intervention studies found no significant effects on glycemic biomarkers (92, 93) but significantly increased leptin ($p < 0.001$) and adiponectin levels ($p < 0.001$) (92).

In three randomized, cross-over controlled studies (52, 94, 95) that were not included in the meta-analyses (91-93), Bowen reported that almond consumption had no significant effects on metabolism action in obese adults with elevated FBS (94), but Ren reported that an almond-based low carbohydrate diet (56 g/day for 90 days) significantly improved HbA1c and GLP-1 concentration (52). Walnut oil capsules (100mg 2 times in a day) for 56 days had no significant effect on FBS level and HOMA-IR score in diabetic patients (95).

A study investigated the acute effects of similar caloric values (253 kcal) of pretzels or snacks of mixed nuts consumption on insulin reaction, glucose, appetite hormones and subjective appetite ratings in obese and overweight adults. They reported the pretzels group showed higher subjective satiety ($P < .001$). Insulin and glucose didn't elevate in the mixed nut group but were found in the pretzels group 60 min post snack consumption ($P < .001$). Mixed nut consumption significantly decreases ghrelin and leptin ($P < .05$) (88). Human interventions assessing the effect of nut consumption on blood sugar are shown in Table 4.

Table 4. Summary of clinical trials and meta-analysis of RCTs examining the effect of nut consumption on blood sugar

Reference	Subjects Study	Design/Period	Nut Type	Diet Intervention	Results
Mohammad Javad Zibaee Nezhad et al./2016(92)	Diabetes Mellitus Type 2	randomized control clinical trial/three months	Walnut Oil	100 patients with DM type 2. experiment group (n = 50), walnut oil (15 g/day for three months) was added to their diet, while the control group (n = 50) did not undergo any interventions	↓HbA1c level 7.86% ± 21.97 (P = 0.005), ↓FBS level decreased by 8.24% ± 16.77 (P = 0.001)
David J. A. Jenkins et al... /2018(90)	type 2 diabetes	a reanalysis of a randomized controlled trial/ 3 months	mixed nuts	parallel design to one of three diets for 3 months: (1) 'full-dose nut diet' (n = 40): a diet with 2.0 MJ (477 kcal) per 8.4 MJ (2000 kcal) energy provided as mixed nuts (75 g/day); (2) 'full-dose muffin diet' (n = 39): a diet with 1.97 MJ (471 kcal) per 8.4 MJ (2000 kcal) energy provided as three whole-wheat muffins (188 g/day	↓HbA1c −2.0 mmol/mol (95% CI −3.8, −0.3 mmol/mol),
Arti Muley et al... /2020(93)	type 2 diabetes	a systematic review of Fifteen trials / three month or earlier to 12 months	Tree nuts	667 patients with DM type 2, tree nuts investigated Separately and combine duration of intervention was three month or earlier to 12 months	↓FBS (MD -0.26 mmol/L), ↓HbA1c(-0.11%)in tree nuts combined group, ↓FBS(MD of -0.45, 0.16, and-0.90mmol/L, respectively)in walnuts ,almonds, and hazelnut group,↓HbA1c-0.17% in walnut group
Alyssa M Tindall et al./2019(75)	prediabetes or type 2 diabetes	meta-analysis of 40 randomized controlled trials/1 to 12 months	Almonds, cashews, pecans, pistachios, walnuts, nut oil	Median duration of 3 months (range: 1–12 months), and the dose of nuts tested varied from 20 to 113 g/d (median: 52 g/d).	↓ HOMA-IR (WMD: −0.23; 95% CI: −0.40, −0.06; I2 = 51.7%), ↓ fasting insulin (WMD: −0.40 μIU/mL; 95% CI: −0.73, −0.07 μIU/mL; I2 = 49.4%) in tree nuts or peanuts group, ↔FBS, ↔HbA1c
Ling Yang et al./2020(94)	Non-healthy or healthy; with or without medical diagnosis of disease	systematic review and meta-analysis of 14 randomized clinical trials/ 5 weeks to 12 months	Walnut	823 participants non-healthy or healthy dose of walnut varied between 60 g/week to 15−57 g/day and duration of intervention 5 weeks to 12 months	↑leptin (weighted mean difference (WMD): 2.502 g/mL; 95 % CI:2.147–2.856, p < 0.001), diponectin (WMD: 0.440 ng/mL; 95 % CI: 0.323 to 0.557, p < 0.001), ↔HbA1c, ↔FBS
Elizabeth P Neale et al./2020(95)	Healthy, Metabolic syndrome, type 2 diabetes	a systematic review and meta-analysis of 16 RCT/four days, to one year	Walnut	1620 823 participants non-healthy or healthy dose of walnut varied between 30 grams to 56 grams per day and duration of intervention four days, to one year	↔FBS, ↔HbA1c, ↔ HOMA-IR, ↔fasting insulin

Reference	Subjects Study	Design/Period	Nut Type	Diet Intervention	Results
Jane Bowen et al./2019(96)	obese adults with elevated fasting blood glucose	randomized controlled trial/ 8 weeks	Almond	76 adults randomly assigned to daily consumption of either almond 56 g/day (n=37) or 72 gr/ day snakes(n=39)	↔Plasma glucose, ↔ Serum insulin, ↔↔HbA1c, ↔CRP, ↔ IL-6, ↔ TNFa
Mengxiao et.al Ren/2020(53)	Type 2 Diabetes	randomized controlled trial/ 3 months	Almond	Forty-five participants with T2DM, including 22 in the almond-based 56 g/day (a-LCD) group and 23 in the low-fat diet (LFD) group for 3 months	↓ HbA1c ($p < 0.01$) in a-LCD group, ↑ GLP-1 concentration in a-LCD group (.017)
Khadijeh et al. Rabiei/2018(97)	type 2 diabetic	double-blind, placebo controlled clinical trial/ 7 weeks	hydroalcoholic extract of walnut	20 received hydroalcoholic extract of walnut and 20 received placebo for 7 weeks	↓ postprandial glucose ($P = 0.030$), ↓ HbA1c ($P = 0.028$), ↔ blood glucose, ↔ HOMA-IR
Natasha Godwin et al. /2019(91)	Healthy, Obese, and Overweight	Two-Arm Randomized Controlled Trial/	Mixed Nuts	Subjects were instructed to consume the snack of 42 g of mixed nuts or 69 g of Snyder's mini unsalted pretzels along with 16 oz of water within 5 min. Blood was collected 1 h after consumption of the snacks. Samples were centrifuged at 1200 g for 10 min at 4C to separate serum, which was stored at -80C for later use. Two 24-h recalls were filled out for the 2 days leading up to the testing period.	↑ glucose ($P < .001$), ↑ insulin ($P < .001$) in pretzels, ↔ glucose, ↔ insulin in nuts group

Effect of nuts consumption on BMI: The body mass index (BMI) is the metric system defining a person's weight in kilograms divided by the square of height in meters in adults and for classifying (categorizing) them into groups (26).

A meta-analysis of nut intervention studies evaluating adiposity parameters reported favorable alteration in BMI (96, 97). A meta-analysis of 27 RCTs of walnut intake (15 to 108 g/d for 14 days to 24 months) found no significant differences on body mass index (BMI) ($p = 0.703$), but when walnut intake increased to 35 g/day BMI was reduced significantly ($p = 0.041$). (97). Xia analysis 8 randomized controlled trials to investigate the effects of pistachio intake on adiposity. They found the pistachio diet group found less BMI values ($P<.001$) (Xia et al., 2020). Contrary to meta-analysis studies described (96, 97), there were two meta-analyses that investigated the effect of almonds on BMI (98) and the intake of nuts or nut products (99), which didn't have a significant effect on BMI. A clinical trial that was not included in the meta-analysis (96-99) showed a significant effect of flaxseed oil consumption on reducing BMI ($P=0.004$) BMI reduced significantly in both groups (walnuts/ for diet prescriptions <1500 kcal/day, or diet prescriptions that were ≥1500 kcal/day for 12 weeks). Human interventions evaluating the effect of nut consumption on BMI are shown in Table 5.

Effect of nut consumption on CHD risk:

Coronary heart disease happens as a consequence of developing atherosclerosis in the coronary arteries, leading to myocardial infarction. Myocardial infarctions are responsible for the death of more than 9 million people annually worldwide. Risk factors for CHD are obesity, diabetes, hypertension, malnutrition, and hypercholesterolemia which act via, oxidative stress, inflammation, and endothelial dysfunction. Studies showed nut consumption could reduce CHD. Crews investigated studies about nuts and CHD. She reported that nut consumption could reduce the risk of CHD (100). Hu investigated studies about nuts and CHD. They reported that nut consumption less than5 times per week could reduce the risk of both fatal CHD and non-fatal myocardial infarction by 35% in women (101). A meta-analysis of 12 cohort studies investigated the association between nut intakes and CHD risk and the dose-response, found a 24% decrease in the relative risk of CHD (102). An inverse relationship between nut intake and death from CHD was found in postmenopausal women, but it wasn't statically significant (103).

Nuts and intermediate biomarkers of CHD: Some trial studies investigated the underlying mechanisms by which nuts have protective effects on CHD. They found that nut consumption with a control diet improved lipid profile, antioxidant status, oxidative stress, chronic endothelial dysfunctions, and inflammation (104).

Lipid and lipoprotein profile: It is completely understood that elevated serum cholesterol levels lead to atherosclerosis and CHD (105). Nut consumption by reducing LDL-c and increasing HDL-c could decrease the formation of plaque (106).

Decreased Oxidative Stress: Nuts are a food source of antioxidants, such as phytosterols, selenium, tocopherols, and other antioxidants. Oxidative stress is an imbalance between the production and removal of reactive oxygen species (ROS), which leads to CHD by oxidation of LDL-C and vascular endothelial cells damage. Interventional, in vivo and in vitro studies showed that nut consumption remarkably reduced oxidative stress. (10). Brazilian nut consumption significantly increased the glutathione peroxidase 3 (GPx3) activity and

significantly reduced the oxLDL by 3.25% (66.31 U/L ± 23.59 U/L to 60.68 U/L ± 20.88 U/L) at end of 12 weeks(107).Moreover, oxidized glutathione (GSSG) was significantly reduced and oxygen radical absorbance capacity (ORAC) levels significantly increased with the consumption of walnuts and cashews (63–108 g/day for each nut), compared to the baseline (108). Based on recent and previous studies, unsaturated fat MUFA, which is abundant in pistachios, pecans and almonds, could have beneficial antioxidant effects and potentially reduce oxidative stress (109, 110).

Endothelial dysfunctions: Endothelial dysfunction, which is characterized by decreasing bioavailability of nitric oxide and increasing expression of inflammatory cytokines, promotes vascular diseases (111). Nitric oxide bioavailability decreases in the vascular endothelium by TNF-α inflammatory cytokine. Furthermore, endothelial activators including ICAM-1, E-selectin and VCAM-1 increased by TNF-α and led to smooth muscle cell proliferation and plaque development. (112). Studies reported that nuts reduced endothelial dysfunction by reducing inflammatory mediators and other mediated pathways. (113, 114).

Inflammation: Inflammation plays a major role in pathogens of atherogenesis and metabolic syndrome (111). Studies have showed several pro-inflammatory cytokines and adipokines, such as CRP, TNF-α, IL-6, MCP-1 and VCAM-1, develop CHD, DT2M, blood pressure and some other diseases by different mechanisms (115). Lifestyle plays a key role in the development of inflammation, such as immobility, nutrition, and stress. Studies showed that nuts contain several nutrients and bioactive components, which may significantly decrease inflammatory atherosclerosis biomarkers, including CRP, TNF-α, MCP-1, IL-6and VCAM, such as alpha-linoleic acid, polyphenols, fiber and L-arginine (9, 116).

CONCLUSION: In conclusion, habitual nut intake can play a role in decreasing the risk of cardiovascular risk factors and CHD via the modification of lipid and glucose metabolism, reducing inflammation, improving endothelial function, weight maintenance and reduced oxidative stress. The nutrient profile of nuts could have key role in their protective effects, although the exact mechanisms underlying these effects are unclear in human intervention studies. Therefore, human clinical trial investigations are necessary to identify the exact and important underlying mechanisms by which nuts reduce cardiovascular risk factors and CHD. Furthermore, human clinical trials are needed to find the exact and most effective pathways by which nuts prevent or reduce cardiovascular risk factors.

Abbreviation list: SFA: Saturated fatty acid; MUFAs: Monounsaturated fatty acids; PUFAs: Polyunsaturated fatty acids; BMI: Body mass index; HMGCoA: β-hydroxy β-methulglutaryl-CoA; DASH: Dietary approaches to stop hypertension; NPC1L1: Niemann-Pick C1-Like 1; ABC: ATP-binding cassette; CE: Cholesterol ester; HepG2: Human hepatocellular carcinoma cell line; Caco2: Human colon adenocarcinoma cell line; LXR: Liver X receptor; PPAR: Nuclear receptors peroxisome proliferator-activated receptor; HNF-4: Hepatocyte nuclear factor-4; SREBP: Sterol-regulatory element-binding protein; NFkB: Nuclear Factor kappa-light-chain-enhancer of activated B cells; NOS: Nitric oxide synthase enzyme; CRP: C-reactive protein; TNF-α: Tumor necrosis factor alpha; IL-6: Interleukin 6; EDHF: Endothelium-derived hyperpolarizing factor; JNK: JunN-terminal kinases; Gpr: G-protein-coupled receptors; ROS: Reactive oxygen species; GPx3: Glutathione peroxidase 3; ORAC: Oxygen radical absorbance capacity; ICAM-1: Intercellular adhesion molecule-1; VCAM-1: Vascular cell adhesion protein-1; MCP1: Monocyte chemo attractant protein-1.

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