Tree Nut Consumption and Adipose Tissue Mass: Mechanisms of Action

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Abstract

There is concern that tree nuts may cause weight gain due to their energy density, yet evidence shows that tree nuts do not adversely affect weight status. Epidemiologic and experimental studies have shown a reduced risk of chronic diseases with tree nut consumption without an increased risk of weight gain. In fact, tree nuts may protect against weight gain and benefit weight-loss interventions. However, the relation between tree nut consumption and adiposity is not well understood at the mechanistic level. This review summarizes the proposed underlying mechanisms that might account for this relation. Evidence suggests that tree nuts may affect adiposity through appetite control, displacement of unfavorable nutrients, increased diet-induced thermogenesis, availability of metabolizable energy, antiobesity action of bioactive compounds, and improved functionality of the gut microbiome. The gut microbiome is a common factor among these mechanisms and may mediate, in part, the relation between tree nut consumption and reduced adiposity. Further research is needed to understand the impact of tree nuts on the gut microbiome and how the gut microbial environment affects the nutrient absorption and metabolism of tree nuts. The evidence to date suggests that tree nut consumption favorably affects body composition through different mechanisms that involve the gut microbiome. A better understanding of these mechanisms will contribute to the evolving science base that addresses the causes and treatments for overweight and obesity. *Curr Dev Nutr* 2018;2:nzy069.

Introduction

The CDC estimates that ~71% of adults are overweight or obese in the United States (1). Excess body fat and visceral adiposity are risk factors for chronic diseases, including ischemic heart disease, type 2 diabetes (T2D), nonalcoholic fatty liver disease, metabolic syndrome, and hypertension, among others (2). Although excess adiposity is the result of biological, behavioral, and environmental factors, lifestyle changes can be made to achieve a healthy weight.

Tree nut consumption, as part of a healthy diet, has been recommended to achieve and maintain a healthy body weight (3, 4). The high energy density of tree nuts has raised concerns for weight gain; however, observational and experimental studies report that tree nuts do not adversely affect weight status and can benefit body composition (3, 5–7). Cross-sectional studies have reported an inverse association between nut consumption and BMI and waist circumference (WC) (3, 8). O'Neil et al. (3) analyzed NHANES data ($n = 4386$) and reported that greater tree nut consumption [>7 g (0.25 ounces)/d] was associated with lower BMI ($P = 0.004$) and WC ($P = 0.008$) compared with low tree nut consumption [<7 g (0.25 ounces)/d]. Prospective studies have also reported an inverse association between nut consumption and BMI and WC and have suggested that nut consumption may blunt age-associated weight gain over time (3, 5–7, 9–12). Mozaffarian et al. (12) analyzed a subsection of data from the Nurses' Health Study, Nurses' Health Study II, and the Health Professionals Follow-Up Study ($n = 120,877$), and examined multiple lifestyle changes, both independently and jointly, on weight status over 12–20 y in increments of 4 y. The authors reported that the average weight gain across the cohorts was 1.52 kg, or 2.4% of

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Abbreviations used: DIT, diet-induced thermogenesis; EE, energy expenditure; ET, ellagitannin; FFAR3, free fatty acid receptor 3; FMO3, flavin-containing mono-oxygenase 3; GIT, gastrointestinal tract; HFD, high-fat diet; ME, metabolizable energy; MT, melatonin receptor; T2D, type 2 diabetes; TMA, trimethylamine; TMAO, trimethylamine N-oxide; UCP, uncoupling protein; WC, waist circumference.

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body weight, during each 4-y period, which corresponds to a weight gain of 7.64 kg over a period of 20 y. However, an inverse association with weight gain was observed with increased consumption of nuts (−0.26 kg) per serving per day. Smith et al. (5) used the same data set to investigate the association between protein consumption and 4-y weight change. The authors reported that greater consumption of tree nuts was associated with weight reduction over a 16- to 24-y follow-up (−0.36 to −0.64 kg; $P < 0.001$) after adjusting for other lifestyle factors. Meta-analyses and reviews of cross-sectional, prospective cohort, and randomized controlled trials have all reported a beneficial relation between nut consumption and body composition (4, 6, 12).

The majority of experimental studies showed that tree nut consumption did not promote weight gain (4, 13–15). Fraser et al. (14) conducted a randomized, crossover free-living trial in generally healthy men and women ($n = 81$). Participants were supplemented with almonds (~320 kcal) for 6 mo and reported nonsignificant weight gains over the supplementation period (+0.4 kg); yet, the expected weight gain would be 6.4 kg on the basis of Atwater factor calculations. Kranz et al. (16) provided 75 g walnuts (490 kcal) or no walnuts to 19 men for 8 wk in a crossover study. The investigators instructed participants to maintain current physical activity levels and assessed dietary data using food records. The authors reported that participants did not completely substitute walnuts for other foods. The walnuts displaced 152 kcal, suggesting that individuals were consuming an additional 338 kcal/d that would equate to an increase in 2.5 kg over an 8-wk period. However, participants' weight did not increase during the walnut diet. The error associated with dietary record data could confound the results, but the maintenance of participant body weight suggests that additional mechanisms account for this.

Although supplementation with tree nuts does not appear to elicit weight gain or weight loss, tree nut consumption has been shown to favorably affect body composition (15, 17). Alvarez-Perez et al. (17) analyzed a subgroup of individuals from PREDIMED (Prevención con Dieta Mediterránea; $n = 351$), a trial in which participants with T2D (~49%) or increased risk of cardiovascular disease consumed a Mediterranean diet plus 30 g mixed tree nuts/d, a Mediterranean diet plus 1 L extra virgin olive oil/wk, or a lower-fat control diet and reported significant within-group reductions in WC and total body weight in the nut group after 1 y. A 2-period crossover, controlled-feeding trial provided isocaloric diets that included 42.5 g almonds/d or a muffin control to generally healthy individuals who were overweight ($n = 48$) (18). The authors reported that the almond diet significantly reduced abdominal mass (mean percent change ± SE; −0.28 ± 0.09 kg), abdominal fat mass (−0.13 ± 0.03 kg), leg fat mass (mean change ± SE; −0.26 ± 0.06 kg), and WC (−1.7 ± 0.4 cm) compared with the muffin control diet (−0.09 ± 0.09 kg, − 0.06 ± 0.03 kg, − 0.14 ± 0.06 kg, and −0.9 ± 0.4 cm, respectively) after 6 wk. Moreover, studies have shown that tree nuts may benefit weight-loss diets (19, 20). Dhillon et al. (19) conducted a randomized controlled trial ($n = 79$) that evaluated the effect of an energy-restricted diet with almonds on body composition and reported a greater reduction in truncal fat (mean change ± SE; −1.2% ± 0.26% compared with −0.48% ± 0.24%; $P = 0.025$) and total fat (−1.79% ± 0.36% compared with −0.74% ± 0.33%; $P = 0.035$) compared with a nut-free, energy-restricted diet. The purpose of this review is to explore the mechanisms that could account for the association between tree nut consumption and reduced adipose tissue mass.

Several mechanisms have been proposed to explain the relation between nut consumption and adiposity. Each tree nut has a unique nutrient and bioactive profile that contributes to various mechanisms of action reviewed in this article (**Table 1**). Here we discuss the evidence suggesting that tree nuts may affect adiposity through discrepancies in available metabolizable energy (ME), appetite control, displacement of less healthy foods/nutrients, increased diet-induced thermogenesis (DIT), antiobesity effects of melatonin and phenolics, and changes in the gut microbiome. Limitations in our current knowledge and future directions are also discussed.

Current Status of Knowledge

Discrepancies in ME value compared with calculated energy value

Tree nut supplementation studies have shown that even when tree nuts are not isocalorically substituted for other foods in the habitual diet, the expected increase in body weight does not occur (13, 16). The increase in energy intake from nuts without a concurrent increase in body weight may be explained by the discrepancies in Atwater factor calculations, which are used to estimate the ME of foods, or the "available" food energy with a physiologic fuel value. Atwater general factors are based on the heat of combustion of protein, fat, and carbohydrate and are corrected for losses in digestion, absorption, and excretion of urea. This approach assigns an energy value to each macronutrient (4 kcal/g carbohydrate, 4 kcal/g protein, 9 kcal/g fat, and 7 kcal/g alcohol) and does not take into account food or diet complexity. The Atwater factors are the standard used to estimate the energy content of food (21), but they have significant shortcomings.

The coefficients assigned to determine the gross energy value of dietary proteins, fats, and carbohydrates suggest that the energy available in 1 g fat is always the same, regardless of food source (27). However, the digestibility of nuts is likely variable due to their botanical and compositional diversity (28). The gross energy content and digestibility of macronutrients are not constant and other chemical components contribute energy, which may influence the ME of the macronutrients (29). Re-examination of the accuracy of the Atwater factors has highlighted differences between the actual and the predicted ME.

Few studies have evaluated the ME of tree nuts. However, walnuts, almonds, and pistachios are reported to have a lower actual ME value than the predicted Atwater factors value (25, 28, 30). USDA scientists conducted 3 crossover, controlled-feeding trials to evaluate the actual ME of each nut and reported marked differences between the calculated Atwater value and the actual value. The authors reported overestimation of almonds (Atwater general factors overestimate ME value by 32%), walnuts (21%), and pistachios (5%) (see **Table 2**). This discrepancy shows the need for further investigation of the actual ME of tree nuts. The overestimation of the caloric content of tree nuts may provide an explanation for their benefits on body weight.

Improved appetite control

Acute studies have shown that tree nuts favorably affect satiety (31, 32). One proposed mechanism is that nut consumption modulates gut

TABLE 1 Average nutrient composition of tree nuts in a 42.4-g (1.5-ounce) serving[1]

	Energy, kcal	Total fat, g	SFAs, g	MUFAs, g	PUFAs, g	Protein, g	Fiber, g	Melatonin, mg	Total phenolics,[2] mg	ET,[2] mg
Almonds	246	21.2	1.6	13.4	5.2	9.0	5.3	NR	19.9–177.7	20.8–26.8
Brazil nuts[3]	280	28.5	6.9	10.2	10.4	6.1	3.2	NR	47.6–131.8	NR
Cashews	235	18.7	3.3	10.1	3.3	7.8	1.4	NR	58.2–116.5	NR
Hazelnuts	267	25.8	1.9	19.4	3.4	6.4	4.1	NR	123.7–354.9	NR
Macadamia nuts	305	32.2	5.1	25.0	0.6	3.4	3.7	NR	19.6–66.3	NR
Pecans	294	30.6	2.6	17.4	9.2	3.9	4.1	NR	545.7–856.8	128.0
Pine nuts[3]	286	29.1	2.1	8.0	14.5	5.8	1.6	NR	13.6–28.9	NR
Pistachios	238	19.3	2.5	10.0	6.1	8.6	4.5	9.6–9.9[4]	368.5–704.2	NR
Walnuts	278	27.7	2.6	3.8	20.1	6.5	2.8	0.0001–0.0003[5]	662.2–690.6	2.6–349.8

[1]Nutrients and energy values for raw nuts from USDA database (21). ET, ellagitannin; NR, not reported.
[2]Data from reference 22.
[3]Values are for dried nuts.
[4]Data from reference 23.
[5]Data from references 24–26.

hormones (33), but study findings are contradictory (34). The dose, timing, and variety of nut may play an important role in appetite regulation. For example, Hull et al. (31) assessed the energy intake and appetite regulation of ad libitum meals after consuming 0 g, 28 g (173 kcal), or 42 g (259 kcal) of almonds and reported a dose-dependent decrease in calorie intake at lunch and dinner after both doses of almonds [$F(1, 31) = 47.3$; $P < 0.0001$] compared with the 0-g almond treatment, with no difference in net daily energy intake ($n = 32$). Participants also reported higher ratings of fullness on the higher (42 g) almond day compared with the lower (28 g) ($P = 0.03$) and the no-almond (0 g) day ($P = 0.005$). The authors speculated that these findings may be due to changes in gastrointestinal peptide release; however, gastrointestinal peptide release was not measured in this study. Rock et al. (34) conducted a crossover postprandial study in adults with overweight ($n = 28$) that compared the gastrointestinal peptide response to a walnut-containing meal (~54% of energy from walnuts) with a control meal high in cream cheese (~54% of energy from cream cheese) and reported no differences in peptide YY, cholecystokinin, and ghrelin response between meals. A recent parallel study assessed the effects of 28 g almond consumption on postprandial appetite and neural responses to visual food stimuli compared with a 40 g isocaloric, macronutrient-matched baked biscuit ($n = 22$) in which investigators utilized visual analog scales and fMRI (35). The authors reported that there were no differences in postprandial hunger, desire to eat, fullness, or neural responses to visual food stimuli between food items. However, the authors noted that the

TABLE 2 Human trials investigating the actual ME of tree nuts compared to Atwater factor predictions[1]

Study (ref)	Study design	Subjects	Treatment	Duration	Results[2]
Baer et al. (30)	Randomized, crossover, controlled-feeding	Healthy men and women ($n = 16$)	No nuts, 42 g and 84 g pistachios/d	18 d	Atwater calculation of 5.66 kcal/g overestimated the ME value of pistachios by 5.40 kcal/g (5% overestimation)
Novotny et al. (27)	Randomized, crossover, controlled-feeding	Healthy men and women ($n = 18$)	No nuts, 42 g and 84 g almonds/d	18 d	Atwater calculation of 6.0–6.1 kcal/g overestimated the ME value of almonds at 4.6 ± 0.8 kcal/g (34% overestimation; $P \leq 0.001$)
Baer et al. (28)	Randomized, crossover, controlled-feeding	Healthy men and women ($n = 18$)	No nuts and 42 g walnuts/d	3 wk	Atwater calculation of 6.61 kcal/g overestimated the ME value of walnuts at 5.22 ± 0.16 kcal/g (21% overestimation; $P < 0.0001$)

[1]PubMed search terms included the following: "nuts AND metabolizable energy", "nuts AND Atwater factors", "almonds AND Atwater factors", "Brazil nuts AND Atwater factors", "cashews AND Atwater factors", "hazelnuts AND Atwater factors", "macadamia nuts AND Atwater factors", "pecans AND Atwater factors", "pine nuts AND Atwater factors", "pistachios AND Atwater factors", "walnuts AND Atwater factors". Studies were included based on the inclusion criteria of human clinical trials. ME, metabolizable energy; ref, reference.
[2]Results are displayed as mean ± SE.

study may have been underpowered and the MEs of the almonds and biscuit were not measured, which may have affected the outcome and interpretation of this study. Similar appetite ratings between the 2 foods may represent greater hunger suppression after almond consumption because almonds have been shown to have less available energy due to their fiber content compared with the calculated energy value (27). The dose used in this study may have also been too low to elicit a reduction in feelings of hunger that have been reported previously with higher doses (31, 32)

Nut fiber may be important in appetite control due to its prebiotic function (36). Fiber is a substrate for gut bacteria and promotes the growth of bacteria that benefit the host through production of SCFAs (37). Postprandial studies have shown changes in satiety and hunger hormones in addition to increased concentrations of SCFAs after consumption of a high-fiber meal compared with a low-fiber meal (38). SCFAs are essential for the maintenance of intestinal epithelial cells, and evidence suggests that they also play a role in adiposity signaling. After SCFA production occurs via microbial conversion, SCFAs can be taken up via sodium-dependent monocarboxylate transporter 1–mediated transport or diffusion into colonocytes (39) and are capable of directly activating G-coupled receptors, inhibiting histone deacetylases and serving as energy substrates (40). Acetate is the most abundant SCFA in the peripheral circulation and may play a role in appetite control (39). Frost et al. (41) used a mouse model to explore this mechanism. The authors reported that acetate can cross the blood-brain barrier and hypothesized that acetate may affect satiety through alteration of the hypothalamic anterior cingulate cortex and AMP-activated protein kinase activities, producing downstream changes in neuropeptide expression. Propionate (C3:0) is produced from methylmalonate via succinate conversion or through lactate conversion to acrylate (39). Similar to acetate, propionate may also play a role in appetite suppression (42) in addition to regulation of hepatic lipogenesis (43) despite the relatively low peripheral concentrations. Propionate is a ligand for free fatty acid receptor 3 (FFAR3), which is expressed in gut epithelial cells (39), white adipose tissue, and the portal vein (44). Kimura et al. (45) showed that FFAR3-deficient mice became obese when fed a normal diet compared with mice that overexpressed FFAR3 in adipose tissue and remained lean even after being fed a high-fat diet (HFD). However, the authors also acknowledged that SCFA-mediated activation of FFAR3 suppresses insulin signaling in adipocytes, which inhibits fat accumulation in adipose tissue and promotes the metabolism of unincorporated lipids and glucose in other tissues. Lin et al. (46) conducted a 4-arm parallel trial in FFAR3-deficient mice fed an HFD (control) or an HFD and supplemented with butyrate (5%), propionate (4.3%), and acetate (3.7%) and reported the SCFA supplementation protected against diet-induced obesity compared with the control. The authors reported that the gut microbiota may alter host metabolism through SCFA-mediated gut hormone stimulation and food intake inhibition. Animal studies have also provided evidence for an association between SCFAs and appetite control. Endogenous SCFA production may be a beneficial link between tree nuts and appetite control. In the colon, fiber from tree nuts is fermented to generate SCFAs, which, in turn, promote appetite regulation and mitigate overconsumption of energy. However, studies are needed to identify which tree nuts, dose, and meal timing may promote satiation, and the mechanisms of action need to be clarified.

Displacement of less healthy foods and/or nutrients

The consumption of tree nuts may displace less-healthy nutrients with favorable nutrients, leading to a healthier dietary pattern. Some tree nut supplementation studies have shown improved dietary quality, particularly when nuts are consumed as a snack (47, 48). Jaceldo-Siegl et al. (49) conducted a crossover controlled study and observed favorable dietary modifications in healthy individuals after 52 g (~307 kcal) almond supplementation/d for 6 mo ($n = 81$). The authors collected dietary recall data on 7 separate occasions during each diet period and reported that dietary MUFAs, PUFAs, fiber, vegetable protein, α-tocopherol, and magnesium increased ($P < 0.05$) and *trans*-FAs, animal protein, sodium, cholesterol, and added sugars decreased ($P < 0.05$) compared with the habitual diet ($n = 81$). The SFAs in almonds were almost completely displaced (98%), whereas PUFAs (26%) and MUFAs (16%) were only partially displaced, indicating that almonds increased the unsaturated FA content of participants' habitual diets. Displacement estimates of 100% indicate that the specific nutrient from almonds replaced an equal amount of that nutrient in the diet supplemented with almonds by reducing the intake of the nutrient from other foods. Estimates >100% indicate that the nutrient from almonds more than fully displaced that nutrient in the diet supplemented with almonds and, therefore, the diet contained less of that particular nutrient. Jaceldo-Siegl et al. (49) estimated the displacement for carbohydrates (246%) and sugars (626%) with almond supplementation. This indicates full displacement of the carbohydrate and sugar content found in almonds and a reduction in the carbohydrate and added-sugar content of the overall background diet. SFA and added-sugar consumption is negatively associated with weight maintenance, and displacement of these nutrients may contribute to favorable effects on body weight (50–52). One study showed that displacement was not always optimized with nut supplementation (16), and an increase in unfavorable nutrients, such as SFAs, may occur. Kranz et al. (16) reported minimal displacement of energy and nutrients when 75 g (490 kcal) walnuts were added to participants' usual diets ($n = 19$). Results showed the walnuts displaced 25% of energy, 15% of total fat, and 15% of SFAs in participants' habitual diets. This partial displacement indicates that participants were not making recommended isocaloric dietary substitutions, but rather, were replacing 25% of the energy from walnuts, but 75% of the energy from walnuts was not displaced. This resulted in an increase in overall energy intake. Extra calories would be expected to increase body weight, but there was no weight gain during walnut supplementation. However, the reporting error associated with dietary recall data could have affected the results. Participants may have made more dietary changes with walnut consumption than what was captured from dietary recall data. These could have included decreasing portion sizes and misreporting foods consumed, which could have overestimated energy intake and affected dietary quality.

Replacing foods associated with higher chronic disease risk is an important strategy for incorporating tree nuts into a healthy dietary pattern. Dietary displacement, or substitution, of a portion of protein from animal origin for plant protein may elicit metabolic changes and have favorable effects on weight status. Studies have shown that the consumption of phosphatidylcholine and L-carnitine, nutrients primarily found in red meat and animal products, resulted in gut microbiota production of trimethylamine (TMA) (53, 54). TMA can

be taken up by the liver and oxidized to form trimethylamine-N-oxide (TMAO), an organic compound that has received attention due to its potentially atherogenic and obesogenic properties (54, 55). Emerging evidence suggests that the link between gut microbe-derived TMA and adipose tissue function corresponds to flavin-containing monooxygenase 3 (FMO3), a hepatic enzyme that produces TMAO (56). Schugar et al. (56) reported protection against HFD-induced obesity in FMO3-knockout mice partially through stimulating the beiging of white adipose tissue. In addition, the authors observed a positive association between FMO3 and markers of adiposity, such as BMI, and a negative correlation between FMO3 and beige/brown marker genes, such as uncoupling protein (UCP) 1, in 3 separate cohorts ($n = 435$).

Reducing TMA and therefore TMAO production may be possible through increasing consumption of plant protein and decreasing animal protein. In an exploratory study, Koeth et al. (54) compared plasma and 24-h urine TMAO and heavy isotope–labeled TMAO after an L-carnitine challenge [227 g (8 ounces) sirloin steak, corresponding to ~180 mg L-carnitine] plus a capsule containing 250 mg of heavy isotope–labeled L-carnitine in an individual ($n = 1$) following a vegan diet (> 5 y) compared with individuals ($n = 5$) following an omnivorous diet. Postprandially, omnivores showed an increase in TMAO and labeled TMAO concentrations in the plasma and urine samples compared with vegans, who produced nominal TMAO. Furthermore, the authors tested whether the gut microbiota affected TMAO formation from dietary L-carnitine through prescribing antibiotics to volunteers to suppress intestinal microbiota for 1 wk, and then they repeated the L-carnitine challenge. After the antibiotic treatment, there appeared to be near complete suppression of endogenous TMAO in both plasma and urine. This study, despite its limited sample size and exploratory nature, suggests that the gut microbiota play a major role in TMAO production and following a vegan diet may result in a gut microbiome that has a decreased capacity to produce TMAO compared with omnivores when challenged with a red meat–containing meal (54). However, additional studies in larger sample sizes are needed to confirm these findings. Shifting from animal-based proteins to plant-based proteins may promote a microbial environment that is less likely to produce TMA, the precursor to obesity-associated TMAO.

In summary, tree nuts are a source of plant-based protein, unsaturated FAs, minerals, and other constituents that could aid in weight maintenance through displacing other nutrients. Consumption of tree nuts in place of less healthy foods and nutrients can lower the risk of weight gain. Substitution of animal protein with plant protein may reduce the production of obesity-associated TMAO. Tree nuts contain nutrients, such as fiber, that are associated with a lower risk of developing obesity; therefore, substitution of foods that contain unfavorable nutrients with tree nuts may be protective against weight gain.

Increased DIT

A limited number of clinical trials have examined the effect of tree nuts on energy expenditure (EE). Although peanuts are not a tree nut, high-oleic peanuts have been shown to have a thermic effect (57, 58). One study compared the effects of acute ingestion of 56 g high-oleic peanuts, 56 g conventional peanuts, or control biscuits that had similar energy density on energy metabolism in men with overweight or obesity ($n = 70$) (58). The authors reported that high-oleic peanuts significantly increased postprandial EE (9.25%) compared with conventional peanuts (6.46%; $P < 0.05$), yet there was no difference when compared with the control biscuits (9.04%; $P > 0.05$). The authors noted that the protein used in the control biscuit may have confounded these results because whey protein, an animal-based protein, was used and differences have been reported in the oxidative activity of plant proteins compared with animal proteins (59). The unique high-oleic peanuts appear to have a favorable effect on DIT similarly to isocaloric control biscuits made with whey protein compared with conventional peanuts. Oleic acid is found in tree nuts; however, the effects of tree nuts on DIT are not well studied. Agebratt et al. (60) studied the effects of 7 kcal · kg body weight^{-1} · d^{-1} of fruit or nuts (peanuts and tree nuts) on basal metabolic rate using indirect calorimetry in healthy individuals ($n = 30$). The investigators reported that basal metabolic rate increased in the nut group compared with baseline (mean ± standard deviation; 1931 ± 221 kcal/24 h compared with 2031 ± 294 kcal/24 h; $P = 0.028$) but was not different between groups ($P = 0.52$) or in the fruit group from baseline (1787 ± 278 kcal/24 h compared with 1845 ± 240 kcal/24 h; $P = 0.26$).

Two constituents of tree nuts that may be essential in eliciting DIT are protein and unsaturated FAs. Protein has been reported to be an important macronutrient for weight loss and weight maintenance (61–65). Weight-loss diets often emphasize protein instead of carbohydrates (66). Evidence suggests favorable, protein-generated body-composition changes are related to greater DIT for protein compared with other macronutrients (64) and increased fat oxidation for higher- compared with lower-protein diets (59). The high metabolic cost of protein turnover, relative lack of storage sites in the body, and upregulation of mitochondrial UCPs, such as UCP2, may all contribute to the DIT activity of proteins (67, 68). A 42.5-g (1.5-ounce) serving of tree nuts provides 3.4–9.0 g protein and minimal digestible carbohydrate. The protein and unsaturated FA content of tree nuts may provide benefits related to body weight and composition when replacing refined carbohydrates due to the differences in digestion and metabolism (20).

The FAs in tree nuts may play a key role in the mechanisms related to adiposity. Emerging evidence suggests that MUFAs and their metabolites are key adiposity mediators (69, 70). The effects of PUFAs on body composition are less clear (15, 71, 72) and there appear to be differences between n–3 and n–6 PUFAs (73). Liu et al. (69) conducted a crossover controlled-feeding trial that reported a reduction in android fat mass in men after 4 wk with a diet containing canola oil (62.8% MUFAs) and high-oleic canola oil (72.0% MUFAs) compared with a diet containing flax and safflower oil (17.9% MUFAs). One proposed mechanism of action for dietary FAs altering body composition involves the MUFA metabolite oleoylethanolamide (70). Oleoylethanolamide is produced from oleic acid in the intestine and, after absorption, functions as an agonist of PPAR-α. PPAR-α is a transcription factor that can enhance lipid utilization and fat oxidation and affect lipid concentrations in tissues and circulation (70).

Most tree nuts are lipid rich (46–76% total fat) and, similar to canola oil, contain a proportionally large amount of MUFAs compared with PUFAs. Walnuts are the only exception and contain primarily PUFAs (74). A review of dietary FA composition and body weight maintenance included studies that compared MUFAs, PUFAs, and SFAs and measured DIT, EE, or fat oxidation post–high-fat meal and

concluded that unsaturated fats induced greater EE, DIT, and/or fat oxidation compared with SFAs (75). The unsaturated FA content in tree nuts may have positive effects on DIT but requires further exploration. Most tree nuts are high in MUFAs, which may upregulate DIT, similarly to protein, and positively affect weight maintenance.

Melatonin as a bioactive nutrient

Melatonin, known as *N*-acetyl-5-methoxy tryptamine, is synthesized in the pineal gland and neuroendocrine cells of the gastrointestinal tract (GIT) mucosa (76). Melatonin can also be obtained in the diet from foods such as wine, tomatoes, and some tree nuts. Although foods that have melatonin contain relatively low amounts and bioavailability is only ∼15%, bioactive compounds can evoke metabolic effects even at very small concentrations (77). The melatonin content in walnuts is 3.5–7.5 ng/g (24–26) and 226,900–233,000 ng/g in pistachios (23). The significant range in melatonin concentrations that have been reported may be explained by the use of different methods of analysis and nut varieties; standardized methodology could provide more precise results. Although only one study has reported the melatonin content of pistachios, this amount correlates with ∼12.7–13 mg melatonin in 57 g pistachios. Melatonin content in over-the-counter supplements ranges from 1 to 20 mg. Melatonin acts on the melatonin 1–3 receptors (MT1, MT2, and MT3), which are present on numerous human cells, including adipocytes and cells within the GIT (78). Melatonin is also important in promoting sleep and maintaining circadian rhythm. As such, there is a growing body of evidence examining the correlation between sleep deprivation and greater risk of obesity. Studies to date suggest that increasing melatonin concentrations via over-the-counter supplements may improve sleep outcomes and also lower obesity risk, but further investigation is needed (79, 80). Although melatonin is produced endogenously, increased concentrations through dietary intervention may provide benefits. The effect of melatonin derived from the consumption of melatonin-containing foods on body composition has not been examined to our knowledge; clinical trials are needed to evaluate the potential benefits on body weight and composition. A review of the Mediterranean-style diet suggested that melatonin may be a key factor that contributes to chronic disease risk–reducing benefits associated with the Mediterranean diet (81). The Mediterranean diet contains several foods that contain melatonin including wine, extra-virgin olive oil, tomatoes, and tree nuts.

The antiobesity action of supplemental melatonin has been evaluated in cell, animal, and human models that contain measurable amounts of melatonin (79, 81–85). In vitro studies have reported conflicting results using various cell types, such as murine preadipocytes, but reported that melatonin affected expression of transcriptional activators, adipokines, and hormones. Melatonin treatment of preadipocytes increased expression of PPAR-γ coactivator 1α, a transcription factor in mitochondrial biogenesis and adiponectin, an insulin-sensitizing and anti-inflammatory adipokine, but suppressed expression of leptin, a satiety hormone, compared with control cells (85). Although the melatonin in these studies was given at supraphysiologic doses, lower doses in vivo have also reported mixed results (82, 83). In one study, melatonin was injected into obese mice at 500 μg/kg body weight and body weight decreased and the expression of PPAR-γ, a nuclear receptor involved in adipogenesis (83), also decreased. Similarly, another research group investigated the effects of dietary melatonin in mice fed an HFD (60% of energy from fat) (82). The investigators fed mice either a normal feed pellet diet, an HFD, or an HFD + melatonin (50 mg/kg body weight) for 10 wk and reported that melatonin supplementation reversed the HFD-induced whitening of adipose tissue through increased expression of the thermogenic marker UCP1 in brown adipose tissue compared with mice fed an HFD without melatonin supplementation. The authors speculated that the increased UCP1 thermic activity in the melatonin-supplemented group protected against weight gain in mice. Amstrup et al. (79) conducted a randomized, double-blind, placebo-controlled trial in postmenopausal women (n = 81) with osteopenia assigned to 1 of 3 treatments: 1 mg melatonin, 3 mg melatonin, or placebo. After 1 y of treatment, fat mass decreased by 6.9% (P = 0.02) and lean mass increased by 5.2% (P = 0.08) in the combined melatonin groups compared with placebo. An improvement in body composition after 1 y of melatonin supplementation suggests a favorable relation.

Supplementation of melatonin showed improvement in measures of body composition. However, melatonin is a hormone and inappropriate timing of supplementation and supplementation in the presence of common genetic variants could result in adverse endocrine responses, such as an increase in T2D risk (86). Melatonin is a potent bioactive compound and the antiobesity action of supplemental melatonin suggests that it is possible that there are benefits of a diet rich in melatonin, but research is needed to evaluate the effects of dietary melatonin on body composition.

Phenolic compounds' antiobesity action

Tree nuts vary considerably in type and amount of phytochemicals. Many of 6 classes of phytochemicals are present in tree nuts, including alkaloids, phenolics, carbohydrates, and nonnutritive lipids. However, organosulfurs and nonnutritive proteins have not been reported in tree nuts (87). Phytochemicals provide a variety of health benefits, including antioxidative, antitumor, and anti-inflammatory effects (88), and also appear to be correlated with benefits related to body composition (89). Phenolic compounds have been detected in all tree nuts, and growing evidence suggests that there is a favorable association between polyphenol intake and adiposity (90–93). Although all tree nuts contain phenolic compounds, pecans, walnuts, and pistachios contain the highest amounts, respectively (22, 87). Different phenolic compounds are present in tree nuts, including stilbenes, tannins, lignans, phenolic acids, phenolic aldehydes, and flavonoids (87).

Ellagitannins (ETs) are a hydrolyzable tannin that may affect adiposity-related mechanisms and have been detected in walnuts, pecans, and almonds (22, 87). However, to obtain the benefits from ETs, the phenolic must first be metabolized in the GIT to ellagic acid. Ellagic acid can be released from ETs through GIT pH changes and/or gut microbial hydrolysis via tannin-hydrolase and lactonase (94, 95). Kang et al. (96) reviewed ellagic acid as a potential obesity moderator, with an emphasis on in vitro studies, and reported that ellagic acid inhibits adipogenesis, reduces lipogenesis, and alters adipocyte differentiation. In vitro results suggested several possible mechanisms, including the following: decreased expression of PPAR-γ, FA synthase (Fas), FA-binding protein 4 (aP2), and CCAAT/enhancer binding protein α (C/EBPα) (96). However, the authors noted that translation to humans would be challenging because the estimated effective dose of ellagic acid is ∼30–850 mg/d for a healthy individual, which is not easily attainable

through a typical American dietary pattern. Although some studies reported a favorable effect on glucose metabolism in mouse and rat models (95), ET metabolites in muscle, adipose, lung, liver, heart, and kidney have not been detected in pigs (97). Exploration of ET target tissue is essential to understanding the potential role they may play in adiposity. Although other bioactive substrates are also present in tree nuts, ETs appear to have great potential in providing adiposity-related benefits.

Critical role of the gut microbiome

The gut microbiome is a complex, ever-changing environment that plays a major role in human health, including weight status (98, 99). The term *gut microbiome* refers to the collective archaea, bacteria, fungi, parasites, and viruses present in the intestinal tract (100) that are essential for digestion of food, supply of substrates to epithelial cells, and functionality of the host immune system (101). Humans and gut microorganisms have a symbiotic relation. An unfavorable gut microbial environment or *gut dysbiosis* has been linked to digestive diseases (102), cardiovascular diseases (103), sleep disorders (104), cancer (105), and other chronic diseases (106). Gut dysbiosis has also been observed in obese compared with lean states (107). The earliest reported correlation between obesity and the gut microbiome was >1 decade ago and differences in the microbiota's ability to harvest dietary energy were described between lean and obese mice. Turnbaugh et al. (108) transplanted gut microbiotas of lean and obese mice into germ-free mice and reported a significantly greater percentage increase in body fat in mice that received obese donor microbiota compared with mice that received the lean donor microbiota (mean ± SE; 47% ± 8.3% compared with 27% ± 3.6%), with no difference in feed pellet consumption. This finding yielded important insight into the dynamic relation between the gut microbiota and the host. The GIT in mice is anatomically different from the human GIT; still, there appear to be differences between lean and obese gut microbiomes in humans as well (109, 110). Human studies have shown that relatively high microbiota gene content and increased microbial diversity are associated with better metabolic health (40). An increased ratio of bacteria in the Firmicutes phyla and a decrease in the Bacteroidetes phyla have been correlated with increased energy harvest from food and low-grade inflammation (107). In animal and human models, obesity is correlated with reduced microbial diversity, decreased gene richness (number of gut microbial genes), and an increased ratio of Firmicutes to Bacteroidetes (108, 111). Although the abundance of Firmicutes relative to Bacteroidetes is often reported, because these phyla encompass ~90% of the human gut microbiota, detecting functional differences in microbiotas between individuals with obesity and lean individuals is an important factor to consider and requires further analysis.

The few studies that have considered the effect of nut consumption on the gut microbiome have focused on bacterial presence and diversity (112–117), as shown in **Table 3**. Ukhanova et al. (112) characterized microbiota in fecal samples collected from healthy volunteers in 2 separate randomized, controlled, crossover feeding studies with 0, 42.5, or 85 g/d treatments of almonds ($n = 18$) or pistachios ($n = 16$) for 18 d with the same base typical, low-fiber American diet. The authors reported differences in diversity and shifts in operational taxonomic units, including a decrease in the operational taxonomic unit closest to a Firmicutes bacterium and to *Clostridium* spp. However, metagenomic and metabolomic analyses were not performed, which precluded determining the effects that almond and pistachio consumption had on gene expression and resulting functional consequences. The components of tree nuts, including fiber, protein, fat, and some bioactives, have the potential to alter the gut microbiome. However, less is known with regard to the effects of nut consumption on the gut environment.

There are challenges in understanding the effects of dietary interventions, including tree nuts, on the microbiome due to the variability in analysis methods and how data are reported. Commonly, authors report taxonomic diversity and composition using 16S ribosomal RNA approaches, which provides information about the bacterial taxonomic classifications present in the sample (118) but explains little about the functionality of the microbes present. To explore bacterial functionality, whole-metagenome shotgun analyses can be used. Metagenomic analyses sequence the DNA of all microorganisms present in the sample (119). However, DNA alone cannot be used to draw conclusions on microbe functionality because sequencing DNA does not provide information about active cellular functions (120). Assessment of interactions between the gut microorganisms and the host requires analysis beyond gut richness, phyla determination, and DNA sequencing. In addition to 16S ribosomal RNA analysis and shotgun metagenomics, analyzing the metatranscriptome (RNA), metaproteome (protein products), and metabolome (metabolic products) is also important to better elucidate the microbe-host interaction. Determining microbial functions carried out at a specific point in time, such as after a dietary intervention, allows for a better understanding of the impact on the host (120).

To identify diets that have antiobesity effects on the gut microbiome, appropriate analytical methodology is necessary. The use of shotgun-metagenomics provides a perspective about the active metabolic pathways that can influence host metabolism. Although there are limited data on the effects that tree nuts have on the gut microbiome, tree nuts contain nutrients that have been reported to favorably influence the gut microbiome, such as fiber, unsaturated FAs, and polyphenols. These nutrients are also associated with a favorable weight status. The microbes present in the gut appear to play a critical role in the regulation of adiposity and can be altered through dietary intervention. Continued research investigating tree nut consumption and the gut microbiome is needed, with an emphasis on the metabolic response of microbes to dietary interventions.

Discussion

The 2015–2020 Dietary Guidelines for Americans recommend tree nuts as part of a healthy dietary pattern for reducing the risk of chronic diseases. Although the energy density of tree nuts has raised concerns about recommendations, particularly for individuals who are overweight or obese, evidence suggests that a moderate intake of tree nuts does not promote weight gain. Epidemiologic studies have reported an inverse relation between body composition and nut consumption, and clinical trials have shown that tree nut consumption does not affect body weight and may improve body composition.

The mechanisms that may explain the effects of nut consumption on body weight and body composition discussed herein represent our current understanding about how nutrients in tree nuts may affect

TABLE 3 Human trials investigating the effect of nut consumption on the gut microbiome[1]

Study (ref)	Study design	Subjects	Treatment	Duration	Related endpoints	Results
Liu et al. (113)	3-arm parallel	Healthy men and women ($n = 46$)	8 g FOSs/d (no nuts), 10 g almond skins/d, 56 g almonds/d	6 wk	Fecal water, pH, bacteria enumeration, enzyme activity	No changes in fecal water or pH All groups increased *Bifidobacterium* spp., *Lactobacillus* spp., with no significant differences between groups Almond skin and FOSs increased β-galactosidase activity β-Glucuronidase activity was decreased after FOSs and almond skin All groups showed decreased nitroreductase activity
Ukhanova et al. (112)	Randomized, crossover feeding trial	Healthy men and women ($n = 18$; almond) ($n = 16$; pistachio)	No nuts, 42.5 g almonds or pistachios/d, 85 g almonds or pistachios/d with base typical low-fiber American diet	18 d	Diversity, OTUs	Pistachios decreased *Lactobacillus* No significant change in bifidobacteria with either nut Both nuts decreased OTUs closest to Firmicutes bacterium and *Clostridium* spp. Both nuts increased butyrate producers
Burns et al. (114)	Randomized crossover trial	Parent-child pairs ($n = 28$)	No nuts, 42.5 g almonds or almond butter/d (parents), 14 g almonds or almond butter/d (children)	3 wk	Diversity, OTUs	No significant differences in diversity No significant differences in OTUs
Holscher et al. (115)	Randomized, crossover feeding trial	Healthy men and women ($n = 18$)	No nuts, 42 g whole almonds/d, 42 g whole, roasted almonds/d, 42 g roasted chopped almonds/d, 42 g almond butter/d	3 wk	Diversity, OTUs	No significant differences in diversity Whole almonds significantly increased *Dialister* Whole roasted almonds significantly increased *Lachnospira* Chopped almonds significantly increased *Lachnospira*, *Roseburia*, and *Oscillospira* No significant differences between almond butter and control Significantly more fungal OTUs after whole almonds
Holscher et al. (116)	Randomized, crossover feeding trial	Healthy men and women ($n = 18$)	No nuts or 42 g walnuts/d	3 wk	Diversity, OTUs, primary and secondary bile acids	No significant differences in diversity Walnuts significantly increased Firmicutes and decreased Actinobacteria Walnuts significantly increased *Faecalibacterium*, *Clostridium*, *Roseburia*, and *Dialister* No significant changes in primary bile acids Walnuts significantly reduced secondary bile acids
Bamberger et al. (117)	Randomized crossover trial	Healthy men and women ($n = 135$)	No nuts or 43 g walnuts/d	8 wk	Diversity, OTUs	Significant dissimilarities between walnut and control Walnuts significantly increased *Ruminococcaceae* and *Bifidobacteria* and decreased *Clostridium* spp.

[1]PubMed search terms included the following: "nuts AND microbiome", "almonds AND microbiome", "Brazil nuts AND microbiome", "cashews AND microbiome", "hazelnuts AND microbiome", "macadamia nuts AND microbiome", "pecans AND microbiome", "pine nuts AND microbiome", "pistachios AND microbiome", "walnuts AND microbiome". Studies were included based on the inclusion criteria of human clinical trials with gut-microbiome outcomes, such as diversity. FOS, fructo-oligosaccharide; OTU, operational taxonomic unit; ref, reference.

adipose tissue mass. Cell and animal models have provided information on several mechanisms of action, including the effect of MUFAs, melatonin, and ETs on thermogenesis. Mouse models have also been instrumental in laying the groundwork for the relation between dietary intervention and the gut microbiome. However, mice have a larger cecum, which is where fermentation occurs, than the proportionally smaller human cecum, where no fermentation occurs. Translation from mouse models to humans can be challenging due to differences in dose and anatomy, highlighting the need for human clinical trials exploring the effect of tree nut consumption on the composition and functionality of the gut microbiome.

The current understanding of the role that the gut microbiome plays in health and disease suggests that there are different "enterotypes" among individuals. Human enterotypes represent a classification based on the ecosystem present in the gut microbiome and may be an important area to target for dietary intervention. Dietary habits have been correlated with various enterotypes and not only play a role in an individual's disease risk but also in how an individual responds to dietary intervention. For example, ETs may be metabolized and utilized differently depending on enterotype. ETs and ellagic acid can be detected in the plasma and urine and persist at relatively high concentrations for days after ET ingestion, suggesting they may provide local benefits within the GIT; however, it is likely that urolithins, an ET metabolite, provide systemic benefits (92). Recent evidence suggests that urolithin production varies among individuals; some individuals possess the ability to produce different types and quantities of urolithins compared with others (89, 121). This dissimilarity can be attributed to variability within gut microbiomes (89, 121–123). Tomás-Barberań et al. (123) analyzed urolithin content in urine and fecal samples collected from 3 separate acute trials that provided participants with 30 g walnuts or 1.9 and 0.9 g pomegranate extract. The authors determined that 3 phenotypes could be observed independently of the volunteers' health status, age, sex, BMI, and amount or type of ET food source ingested; "metabotype A" produced only urolithin A conjugates, "metabotype B" produced isourolithin A and/or urolithin B in addition to urolithin A, and "metabotype 0" did not produce urolithins. These metobotypes may be important in eliciting cardiovascular benefits from ETs (121) and have been correlated with weight status (124). Selma et al. (124) investigated differences in ellagic acid metabolism between healthy individuals with overweight or obesity and normal-weight individuals from 2 separate studies supplying participants with 30 g nuts ($n = 20$) or 450 mg pomegranate extract ($n = 49$). Investigators correlated cardiometabolic risk biomarkers found in the plasma with urolithins in feces and urine and reported metabotype B was most common in individuals with overweight or obesity (31%) compared with normal-weight individuals (20%), whereas metabotype A was higher in normal-weight individuals (70%) compared with participants with overweight or obesity (57%). This study suggests an association with body composition and urolithin metabotype; healthy-weight individuals may have the ability to obtain the greatest benefit from ET consumption. Although the most favorable enterotype or metabotype has yet to be identified, the microbial environment is important to understand how tree nut consumption affects adiposity and it may differ depending on an individual's BMI.

Summary and Conclusions

It is likely that there is no single, unifying mechanism of action that accounts for the association between tree nut consumption and adipose tissue mass. This likely reflects, in part, the diverse nutrient content of tree nuts. Each member of the tree nut family contains a unique nutrient profile and a variety of vitamins, minerals, and phytochemicals that likely affect adiposity through different mechanisms. The combined or individual action of protein and fiber in tree nuts may affect appetite control through the satiating effect of protein and/or the SCFA-producing effect of fiber. Tree nuts are also nutrient-dense and can improve diet quality through nutrient displacement of unfavorable foods and nutrients, such as saturated fats and added sugars, with beneficial nutrients, such as unsaturated FAs, plant-based protein, fiber, and bioactive compounds. The unsaturated FAs in tree nuts may play a role in DIT, primarily observed with MUFAs. Although all tree nuts are high in energy from fat, not all of the lipids may be available for absorption and utilization. Discrepancies have been reported comparing the ME available in tree nuts with the predicted, or calculated, Atwater value for almonds, pistachios, and walnuts. These findings suggest that this discrepancy might be relevant to other tree nuts as well. Two tree nuts, walnuts and pistachios, contain melatonin. Melatonin may affect adipose tissue mass through several mechanisms, such as activation of thermogenesis and promotion of the browning of white adipose tissue. The phenolics in tree nuts may also have an antiobesity effect. In vitro evidence showed that ET and its metabolite ellagic acid can inhibit adipogenesis, reduce lipogenesis, and alter adipocyte differentiation. The benefits derived from ETs and other nutrients found in tree nuts may not be optimized without necessary gut microbiomes. ETs and ellagic acid differ between individuals in how they are metabolized, depending on the microbes present in the GIT.

In conclusion, numerous studies have shown that tree nut consumption has favorable effects on health status and chronic disease risk reduction, without resulting in weight gain. The complex mix of nutrients and bioactive components in tree nuts suggests multiple mechanisms of action that likely contribute in varying degrees to the favorable effect on adiposity. The composition and functionality of the gut microbiome appear to be an underlying theme with limited information on the effects of tree nut consumption. The interaction between tree nut consumption and the gut microbiome warrants further investigation.

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