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Beneficial changes in total cholesterol, LDL-C, biomarkers of intestinal inflammation, and vitamin E status in adults with metabolic syndrome consuming almonds as snack foods: a randomized controlled clinical trial

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ABSTRACT

Chronic inflammation and gut barrier breakdown contribute to the progression of metabolic syndrome and affect the development of cardiometabolic diseases, especially in persons consuming low-quality diets with limited bioactive compounds. Almonds are a rich source of bioactive compounds with antioxidant and anti-inflammatory properties. We hypothesize almond consumption can help disrupt metabolic syndrome progression by improving gut and cardiometabolic health and decreasing inflammation and oxidative stress. To test this hypothesis, adults with metabolic syndrome were randomized to consume either almonds (2 oz, whole, dry roasted, $n = 38$) or crackers (control, equal caloric content, $n = 39$), as a daily snack for 12 weeks, and samples were collected (0, 4, and 12 weeks). Compared with participants consuming crackers, almond consumption resulted in lower plasma total and low-density lipoprotein-cholesterol concentrations, a modest improvement in waist circumference (week 4), and improved dietary intakes of α-tocopherol, soluble fiber, copper, biotin, magnesium, polyunsaturated fatty acids, and monounsaturated fatty acids. Almond consumption raised plasma α-tocopherol concentrations (relative to cholesterol concentrations) and increased excretion of a vitamin E biomarker (α-CEHC). Almond consumption improved biomarkers of gut barrier function and intestinal inflammation (fecal calpro-

Abbreviations: α-CEHC, α-carboxy ethyl hydroxychromanol; BMI, body mass index; BP, blood pressure; CRP, C-reactive protein; CD14, cluster of differentiation 14; ECD, electrochemical detection; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; HPLC, high performance liquid chromatography; ICP-OES, inductively coupled plasma-optical emission spectroscopy; IL-6, Interleukin-6; LBP, lipopolysaccharide-binding protein; LDL-C, low-density lipoprotein cholesterol; MDA, malondialdehyde; MetS, metabolic syndrome; TBA, 2-thiobarbituric acid.

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tectin, myeloperoxidase) in participants with elevated inflammation at baseline. Total body weight, caloric intake, and markers of carbohydrate metabolism (glucose, insulin), systemic inflammation (plasma interleukin-6, C-reactive protein, lipopolysaccharide-binding protein, CD14), and oxidative damage (malondialdehyde) were not altered by almond consumption. In conclusion, daily almond snacking improves nutrient intake and decreases gut inflammation in participants with metabolic syndrome. These beneficial dietary and inflammatory changes may contribute to the improvements in cardiovascular health observed.

1. Introduction

Metabolic syndrome (MetS) affects more than a billion people worldwide and 35% of adults in the United States [1,2]. The MetS diagnosis is based on the presence of at least 3 of 5 cardiometabolic criteria: hypertension, hyperglycemia, central adiposity, hypertriglyceridemia, or low concentrations of high-density lipoprotein cholesterol (HDL-C) [3]. As symptoms progress, individuals are at increased risk for numerous health complications, such as type 2 diabetes, heart disease, and metabolic dysfunction–associated steatotic liver disease, as well as a high burden of health care costs [1]. There is a critical need to develop strategies to help mitigate these metabolic dysfunctions to prevent further health deterioration. Although progression of some symptoms can be managed with medications, easily accessible dietary interventions could be beneficial and may improve overall health [4–7]. Intestinal (gut) barrier dysfunction and chronic inflammation play key roles in MetS progression that can be targeted by dietary interventions as a potential strategy to mitigate disease [8–12].

Gut barrier dysfunction is often observed in people with MetS and is associated with increased intestinal permeability, local mucosal inflammation, and the release of bacterial endotoxin into circulation [13,14]. This cascade of events can further amplify oxidative stress, promote intestinal inflammation, cause a loss of intestinal barrier integrity, and perpetuate systemic inflammation that can potentially damage both the liver and the pancreas [8,11,15]. The precise cause of gut barrier dysfunction in MetS is not clear, but a poor diet, especially a low intake or poor bioavailability of micronutrients, is implicated [16–18].

Much of the US population, especially those with MetS, are at risk for deficiencies of micronutrients and dietary factors including vitamin E (α-tocopherol) and magnesium [19,20]. We have shown previously that vitamin E status is compromised in persons with MetS [17,21]. Almonds are accessible, easily incorporated into a diet as a healthy snack, a “good source” of vitamin E, and are also high in many other bioactive ingredients including polyphenols, mono- and poly-unsaturated fatty acids, fiber, and minerals (e.g., magnesium) [22–24]. Thus, almonds may act as a potent, naturally occurring functional food to help fill nutritional gaps found in people with MetS [19,20]. Adults with more advanced conditions, like diabetes and cardiovascular disease, have been shown to gain cardiometabolic benefits from eating almonds [7,25–37]. High almond and tree nut consumption also correlates with a decreased prevalence of MetS [4–6,38], but to date, only a few intervention studies have specifically evaluated if almonds are beneficial in people with MetS [39–41]. Many of the bioactive components found in almonds have the potential to improve gut health, decrease inflammation, and reduce oxidative stress, and almond consumption has been shown to affect the composition of the gastrointestinal microbiome [42–44]. Although the data suggest that increased almond consumption may improve the conditions that define MetS, it is not yet known if almond consumption can decrease inflammation and gut barrier dysfunction in individuals with MetS that are at risk for cardiometabolic disease [4–6,23].

To test the hypothesis that almonds improve gut barrier dysfunction, and decrease inflammation and oxidative stress, we conducted a human feeding trial in participants with MetS. The primary objectives of this study were to determine the extent to which almond consumption altered indicators of cardiometabolic health, increased α-tocopherol status, and decreased intestinal inflammation, systemic inflammation, and oxidative stress. The secondary objectives were to evaluate the extent to which almond consumption affected mineral status, polyphenol concentrations, glycemic control, and anthropometric measures of health.

2. Methods and materials

2.1. *Participants and study design*

All study activities were approved by the Oregon State University Institutional Review Board, were registered on clinicaltrials.gov (IRB-2022-1435, NCT05790564, respectively), and procedures were followed in accordance with ethical standards. The study was conducted in the Linus Pauling Institute and the Moore Family Center metabolic kitchen at Oregon State University from November 2022 to May 2024. Figure 1 is a CONSORT diagram of the study. Women and men, ages 35–60 years old, were recruited from the Corvallis, Oregon, region. The study was conducted with support from the Oregon State Center for Healthy Aging Research, LIFE Registry. Participants provided informed consent for screening based on eligibility criteria. Inclusion criteria included willingness to: (1) maintain current eating patterns; (2) stop eating nuts and sunflower seeds (except almonds provided by the study); (3) complete food intake diaries during the study; and (4) stop taking mul-

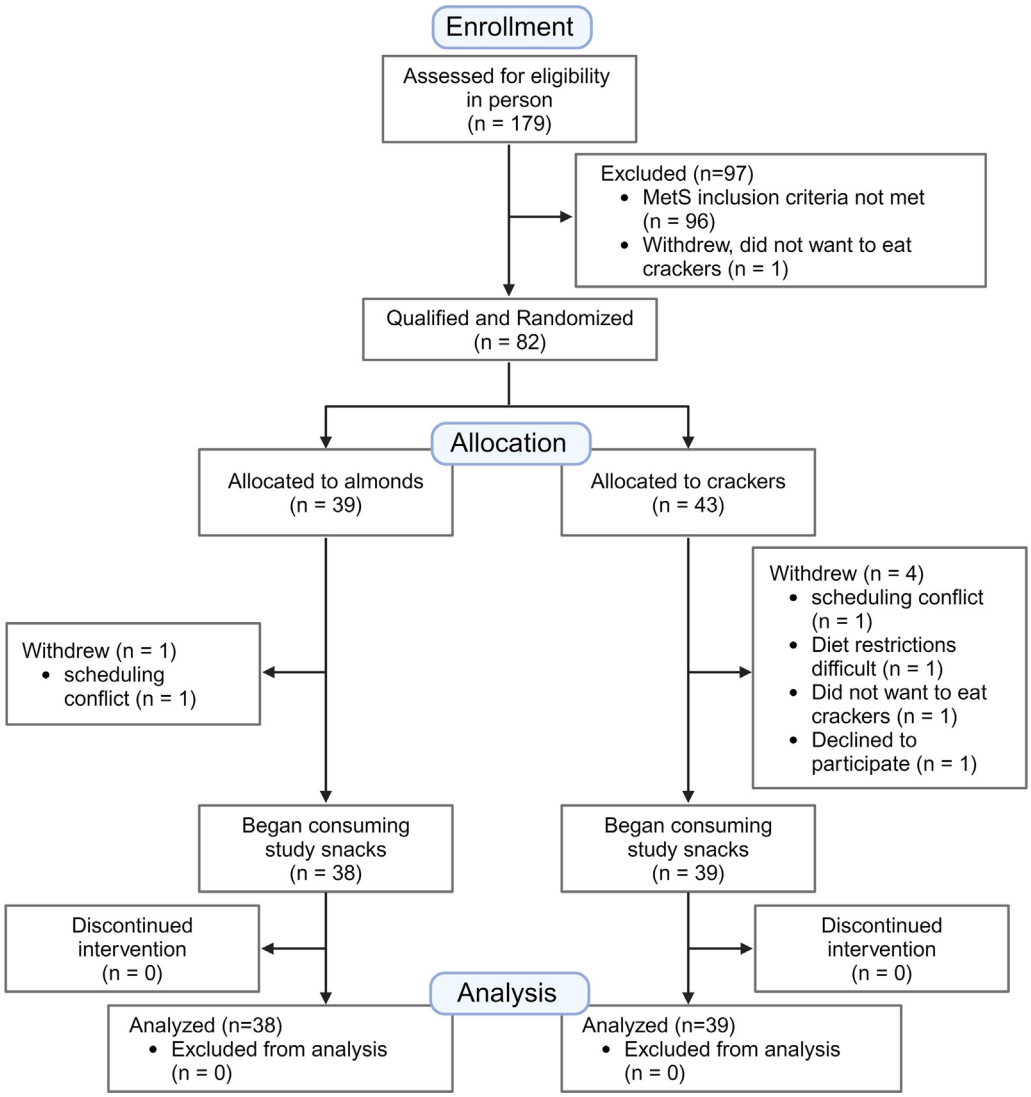

Fig. 1 – Flow diagram of study participants with metabolic syndrome. The illustration shows the progress of study participants through the randomized controlled trial examining effects of 12-week daily consumption of almonds. Created in BioRender. Beaver, L. (2025) https://BioRender.com/b73u712. MetS, metabolic syndrome.

tivitamins and supplements containing probiotics, vitamin E, magnesium, calcium, iron, zinc, and copper for 1 week before and during the study. Exclusion criteria included: (1) weekly consumption of >2 oz of almonds, hazelnuts, peanuts, and sunflower seeds; (2) nut, wheat, or gluten allergy/intolerance; (3) tobacco use; (4) body mass index (BMI) <25.0 or >35.0 kg/m^2; (5) pregnancy or breastfeeding; (6) use of oral antibiotic medication within past month; (7) extensive vigorous exercise (7+ hours per week); (8) use of ezetimibe or orlistat; (9) diagnosis of hemochromatosis; (10) >2 alcoholic drinks consumed daily; (11) history of bariatric surgery, gastrointestinal procedures, or disorders; (12) chronic use of anti-inflammatory medication (past 30 days); (13) history of cardiovascular disease, liver disease, or cancer treatment by chemotherapy, radiation, or immunotherapy (past 5 years); (14) regular use of vitamin E supplements; (15) regular use of multivitamins within past 3 months; and (16) physician-prescribed use of probiotics, vitamin E, magnesium, calcium, iron, zinc, or copper supplements. Eligibility of participants was confirmed by an in-person interview.

One hundred and seventy-nine participants met the eligibility criteria, provided written informed consent, and were screened for MetS by the study nurse. Eighty-three participants were confirmed for MetS and met 3 or more of the following criteria: (1) hypertension (systolic blood pressure [BP] 130–179 mm Hg or diastolic BP 85–119 mm Hg); (2) hyperglycemia (fasting glucose 100–599 mg/dL); (3) central obesity (waist circumference ≥40.1 inches [males] or ≥34.6 inches [females]); (4) hypertriglyceridemia (150–499 mg/dL); and (5) low HDL-C (<40 mg/dL [males] or <50 mg/dL [females]). Six participants withdrew between the screening and the baseline collection of samples. The remaining 77 participants were randomized to either the almonds (n = 38) or crackers placebo group (n = 39) and were free living. Those that met the eligibility criteria were assigned to study treatment groups by the study statistician (G.B.) using a randomized block design,

blocking by sex (male/female) and screening MetS criteria (4 categories qualified based on having elevated: (1) blood pressure and glucose, (2) blood pressure and lipids, (3) glucose and lipids, or (4) lipids and glucose and blood pressure). The laboratory staff who analyzed samples were blinded to treatments through the use of a study key that contained only deidentified information. Study nurse coordinator, staff preparing the food, study statistician, and study participants were not blinded to treatment groups.

One week before baseline collection and during the 12-week study, participants were instructed to avoid consuming foods and beverages containing nuts and sunflower seeds (outside of study-provided almonds) and supplements containing probiotics, vitamin E, calcium, magnesium, iron, zinc, and copper including multivitamins. Participants provided baseline blood, urine, and stool samples at the 0-week visit. After the 0-week visit, participants began eating daily snacks and returned every 4 weeks to receive more study foods. At the 4- and 12-week study visits, urine, blood, and stool samples were also provided by participants. The study ended when enough participants in each treatment group completed the study.

2.2. Study snacks and dietary records

Participants consumed almonds (2 oz of whole dry roasted [58 g]) or crackers (non–whole grain) as a daily snack for 12 weeks. Snacks in both treatment groups were matched in caloric content, 320 calories per day. Nutritional content of snacks is described in Table 1. Almonds were from Stewart & Jasper Orchards (Newman, CA) and provided by the Almond Board of California. The daily crackers snack consisted of 1 serving (28 g) of original Cheez-it crackers (Kellanova, Walmart) and 1.5 servings (42 g) of animal crackers (Kirkland brand, Costco). The crackers acted as a control without the fiber, healthy fats, or micronutrients found in almonds. Because weight gain is a concern for persons with MetS, participants were advised to decrease intake of other foods to match the calorie content of the snack. A registered dietitian assisted in making these recommendations. The almond snack contained more α-tocopherol, fiber, monounsaturated fat, polyunsaturated fat, protein, and magnesium than the cracker snack (Table 1). The almond snack also contained less saturated fat, carbohydrates, and sodium than the cracker snack. Participants self-reported intake of study foods in a snack log and returned empty food wrappers, which were counted and analyzed for compliance. Participants also recorded all foods (including study snacks), medications, and supplements that they consumed in an intake diary for 24 hours before the 0-, 4-, and 12-week study visits. Diet records were analyzed using Food Processor SQL (ESHA, Salem, OR), as described previously [45].

Table 1 – Nutritional content of study snacks per day

	Crackers[a]	Almonds[b]
Calories[c]	320	320
Snack weight (g)	70	58
Fat (g)	11.5	28
Saturated fat (g)	3.75	2
Polyunsaturated fat (g)	3.5	7
Monounsaturated fat (g)	4.25	18
Carbohydrates (g)	49	12
Sodium (mg)	330	0
Protein (g)	6	12
Fiber (g)	<1	8
α-Tocopherol (mg)[d]	1.3	10.3
Magnesium (mg)	18	176
Copper (mg)	0.1	0.7
Zinc (mg)	0.6	2
Iron (mg)	1.8	1.6
Calcium (mg)	150	157

[a] Crackers were 28 g Cheez-It and 42 g animal crackers.
[b] Almonds were 58 g whole dry roasted almonds.
[c] Food labels are the source for calorie and macronutrient content in study snacks.
[d] α-Tocopherol and mineral content is the mean amount in study foods as determined by high-performance liquid chromatography with electrochemical detection and inductively coupled plasma-optical emission spectroscopy (n = 15–21), respectively. α-Tocopherol and mineral contents were consistent in study foods throughout the duration of the study.

2.3. Biospecimen sample collection and cardiometabolic and anthropometric measures

We evaluated fasting glucose, insulin, homeostatic model assessment for insulin resistance (HOMA-IR), waist circumference, BP, total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglyceride concentrations of participants. Participants fasted for at least 8 hours before blood collection. Whole blood (10–20 mL) was collected by venipuncture from a vein in the antecubital fossa into serum separator tubes (Becton, Dickinson [BD]) for insulin measurement and lithium heparin plasma separator tubes (BD and Greiner Bio-One) for glucose and lipid profiles. Whole blood was also collected in a sodium heparin vacutainer (BD) for other assays conducted on plasma. Blood glucose and lipid profiles (total cholesterol, LDL-C, HDL-C, and triglyceride) were obtained by ACE Excel autoanalyzer and insulin by Tososh 360AIA analyzer (Oregon State University's Student Health Services clinical laboratory and Quest Diagnostics-Seattle, WA, both CLIA-certified laboratories). LDL-C was calculated using Martin/Hopkins method [46]. HOMA-IR was calculated as previously published [40]. Additional plasma samples were stored at −80°C for bioassays.

Blood pressure was measured manually using a sphygmomanometer and a stethoscope. Waist circumference was measured at the iliac crest using a Gulick II measuring tape. Height was determined with Tanita HR-200 wall mounted stadiometer (Arlington Heights, IL). Weight was measured with a Seca 869 scale (Chino, CA). Complete urine collections were obtained by participants during the 24 hours before each study visit. Urine jugs were kept cold to stabilize metabolites. Upon receipt, urine was weighed, aliquoted, frozen, and stored at −80°C. Stool samples were collected in the evening or morning before study visit by study participants. Stool was collected using a sterile collection device and placed into cryoELITE tissue vials (Wheaton, Millville, NJ), and myeloperoxidase fecal sample collection tubes (Epitope Diagnostic Inc, San Diego, CA). Fecal samples were kept cold after sample collection and transferred to −80°C storage during study visit.

2.4. α- and γ-tocopherols and α-carboxy ethyl hydroxychromanol quantification

Plasma, almond, and cracker α- and γ-tocopherol concentrations were quantified by high-performance liquid chromatography (HPLC) with electrochemical detection (ECD) [47]. Briefly, samples (1 g pulverized almonds, crackers, or 100 µL plasma) were saponified with alcoholic potassium hydroxide and 1% ascorbic acid solution, cooled, and extracted with hexane. The extract was dried under nitrogen and then resuspended in ethanol-methanol solution (1:1; v/v). Samples were injected onto a Synergi Hydro-RP column (Phenomonex, Torrence, CA) with an Alliance 2695 HPLC system (Waters, Milford, MA) coupled to an amperometric ECD detector (LC-4B ECD, Bioanalytical Systems Inc., West Lafayette, IN). Mobile phase consisted of methanol/water (99:1, v/v) containing 0.1% (w/v) lithium perchlorate. Tocopherols were identified using authentic standards, and the peak areas were integrated using Waters Empower Pro software package, then were quantitated by comparison to authentic standard areas.

α-Carboxy ethyl hydroxy chromanol (α-CEHC) was determined using a modified method of Li et al. [48]. Briefly, urine was added to 0.8 mL of Milli-Q water and 0.5 mL of 2% ascorbic acid solution. Samples were acidified with HCl and refluxed for 1 hour at 60°C. CEHCs were extracted with diethyl ether and an aliquot of the ether fraction collected and dried under nitrogen. The samples were resuspended in water:methanol (1:1; v/v) containing Trolox (Sigma) as the internal standard and injected into a Acquity UPLC BEH C18 column on a Waters Acquity H Class UPLC system coupled to a Waters XEVO TQD (Milford, MA) with an electrospray ionization source operated in negative mode. The analytes were detected using multiple reaction monitoring of the following transitions: α-CHEC (m/z 277/163) and Trolox (m/z 249/163). Sample peaks were analyzed by comparison to authentic standard compounds and adjusted using the internal standard.

2.5. Mineral analyses

Mineral (Zn, Fe, Cu, Ca, Mg) concentrations in plasma, almonds, and crackers were determined by inductively coupled plasma-optical emission spectroscopy (ICP-OES), as previously described with minor modifications [49]. One hundred microliters of plasma or 50 mg almonds or crackers were digested overnight in 1 mL of nitric acid (OmniTrace nitric acid, EMD Millipore, Billerica, MA). Acid-digested samples were diluted with Chelex-treated nanopure water to a final concentration of 10% (v/v) nitric acid followed by centrifugation to remove particulates. Samples were analyzed using the Prodigy High Dispersion ICP-OES instrument (Teledyne Leeman Labs, Hudson, NH) against known mineral standards. ICP-OES analyses were done at the W.M. Keck Collaboratory for Plasma Spectrometry at Oregon State University.

2.6. Urinary polyphenol quantification

Urinary polyphenols were estimated in an aliquot of the 24-hour urine sample, using a variation of the Folin-Ciocalteu assay with gallic acid as a standard and measured in a 96-well Biotek Synergy H1 plate reader (Agilent, Santa Clara, CA) at 570 nm, as described [50]. Outcomes are reported, as corrected for creatinine excretion.

2.7. Quantification of inflammation and gut health biomarkers

Biomarkers of inflammation and gut health associated with MetS were measured in participants' plasma or fecal samples, as determined by ELISA per manufacturer's procedures. C-reactive protein (CRP), a liver protein induced during inflammation and found in plasma, was measured using High Sensitive CRP enzyme immunoassay test kit (Origene, Rockville, MD) [51]. Lipopolysaccharide-binding protein (LBP) enhances a host response to lipopolysaccharide and was measured using a human LBP ELISA kit (Thermo Fisher Scientific, Waltham, MA) [52]. Interleukin-6 (IL-6) is a proinflammatory cytokine that was measured using human IL-6 Quantikine ELISA (Biotechne R&D Systems) [53]. Cluster of differentiation 14 (CD14) is a human macrophage protein that was measured using a human CD14 Quantikine ELISA kit (Biotechne R&D Systems) [54]. Fecal calprotectin was measured using Human S100A8/S100A9 Heterodimer DuoSet ELISA kit (Biotechne R&D Systems) [55]. Fecal myeloperoxidase was measured using EDI Quantitative fecal/urine myeloperoxidase ELISA kit (Epitope Diagnostic) [56].

2.8. Malondialdehyde quantification

Plasma malondialdehyde (MDA) concentrations, a measure of lipid peroxidation, were measured, as described previously [57]. Briefly, plasma samples were subjected to alkaline hydrolysis with NaOH, followed by acidification with phosphoric acid, and an aliquot reacted with 2-thiobarbituric acid (TBA; Sigma-Aldrich, St. Louis, MO). The MDA-TBA adducts were extracted with butanol and measured by HPLC with fluorescence detection (532 nm excitation and 553 nm emission). Quantitation was done using an external standard of 1,1,3,3-tetraethoxypropane (Sigma-Aldrich, St. Louis, MO). The MDA-TBA adducts were quantified relative to the standard.

2.9. Statistical analyses

Statistical significance was determined using GraphPad Prism 10 software (La Jolla, CA). Data testing the effect of treatment and time were analyzed by fitting a mixed effects full model using Geisser-Greenhouse correction for sphericity. Multiple comparisons were performed when a significant interaction was found using Tukey's multiple comparisons test, which corrects for multiple comparisons using statistical hypothesis testing. Paired *t*-tests were used to compare 0- and 12-week results in almond consumers (data were normally distributed). For other measures, the primary comparisons were the change in the almond group (before and after treatment) compared with the change in the cracker group (before and after treatment). This value was calculated for each subject by subtracting the measurement at 4 or 12 weeks of snack consumption from the baseline value measured at week 0. For the comparison of baseline values and comparison of the changes in both groups, Mann-Whitney was used because most of the data were not normally distributed. We additionally tested for

subgroup responses to treatment using Fisher's exact test. All tests were 2-sided. Differences were determined to be significant when $P \leq .05$.

To detect significant differences among our primary objectives our biostatistician performed a power analysis using a urinary biomarker of vitamin E intakes called α-CEHC. The urinary α-CEHC concentrations (corrected for creatinine) were compared on week 4 as compared to week 0. We used the change in urinary α-CEHC in response to vitamin E from hazelnuts using data from our published paper as the source of data for the power calculation [58]. The vitamin E biomarker (urinary α-CEHC) increases during the study period in response to hazelnuts were 0.29 ± 0.10 (μmol/g creatinine, mean ± standard error of the mean). Thus, 34 subjects per group were sufficient with an α of 0.05 and 80% power.

3. Results

3.1. *Participant characteristics and compliance*

Seventy-seven participants completed the 12-week study (Figure 1). There were no statistically significant differences between groups in baseline characteristics, including age (~50 y), BMI (~31 kg/m^2), sex, or race (Table 2). Participant food intake records indicated compliance with avoiding confounding food items, and 92% of participants reported maintaining a similar diet throughout the study. Participants in the almond group and the cracker group each consumed 96% of snacks provided (compliance rate), and there was no change in snack consumption over the 12-week study period. There were no significant differences in compliance between the treatment groups ($P = .28$). A majority (69%) of participants reported they ate the study foods as snacks, whereas 26% of participants ate the study foods both as snacks and with meals. Only 5% of participants ate the study foods during meals only. In general, the almonds and crackers were well tolerated by participants although mild abdominal discomfort (upset stomach) was experienced by 5% of participants (3 participants in the almond group and 1 in the cracker group). Discomfort was experienced between the 0- and 4-week visits, and when it occurred, we recommended the snacks be eaten throughout the day (as opposed to all at once) and not eaten on an empty stomach. Discomfort was resolved in all participants by the next study visit.

3.2. *Almond snacking improved some indicators of cardiovascular health*

Almond consumption was not associated with a change in body weight, but it was associated with a modest but significant decrease in waist circumference (0.8 cm) at 4 weeks of study intervention, compared to cracker consumers (Figure 2, Supplemental Table 1). Twelve weeks of almond snacking tended to decrease waist circumference, compared to cracker consumers ($P = .07$). Almond and cracker snacking in the MetS study population was not associated with significant changes in systolic or diastolic BP, fasting glucose, insulin, or HOMA-IR (Supplemental Table 1).

Twelve weeks of almond snacking significantly decreased total cholesterol and LDL-C, relative to cracker consumption (Figure 2). Specifically, 11 of 38 individuals in the almond group observed a large decrease in both plasma total cholesterol and LDL-C concentrations (greater than 25 or 22 mg/dL, respectively) compared to 3 of 38 individuals in the cracker group (Fisher's exact $P = .03$). Almond consumption did not significantly alter HDL-C or triglyceride concentrations.

3.3. *Effect of snack consumption on dietary and participant vitamin E status*

To better understand potential causes of the almond-associated improvements in waist and cholesterol concen-

Table 2 – Demographic information for participant with metabolic syndrome

Treatment groups	Crackers ($n = 39$)	Almonds ($n = 38$)	P value[a]
Age (years)[b]	50.1 ± 6.9	48.4 ± 7.3	.311
Weight (kg)	93.0 ± 13.7	88.6 ± 13.0	.155
Body mass index (kg/m²)	31.0 ± 3.3	30.0 ± 2.9	.150
Gender[c,d]	**n (%)**	**n (%)**	.999
Male	19 (49)	20 (53)	
Female	19 (49)	17 (45)	
Transgender	1 (3)	0	
Nonbinary	0	1 (3)	
Race			.819
White	31 (79)	29 (76)	
Non-White[e]	8 (20)	8 (21)	
Unknown	0	1 (3)	

[a] Comparisons between the control and treatment groups were made using t-tests (continuous variables) or Fisher's exact tests (categorical variables). There were no statistically significant differences in demographic characteristics between the cracker and almond groups.

[b] Age, weight, and body mass index values represent mean ± standard deviation.

[c] Gender and race values are number of participants (percentage of study population) for each treatment group. Percentages may not add up to 100 due to rounding.

[d] Fisher's exact tests were conducted without including transgender, nonbinary, or unknown groups.

[e] Includes participants that self-reported as Asian (6.5% of total population), American Indian and Alaska Native (1.6%), Black (1.3%), Other (1.3%), and more than 1 race (10.4%).

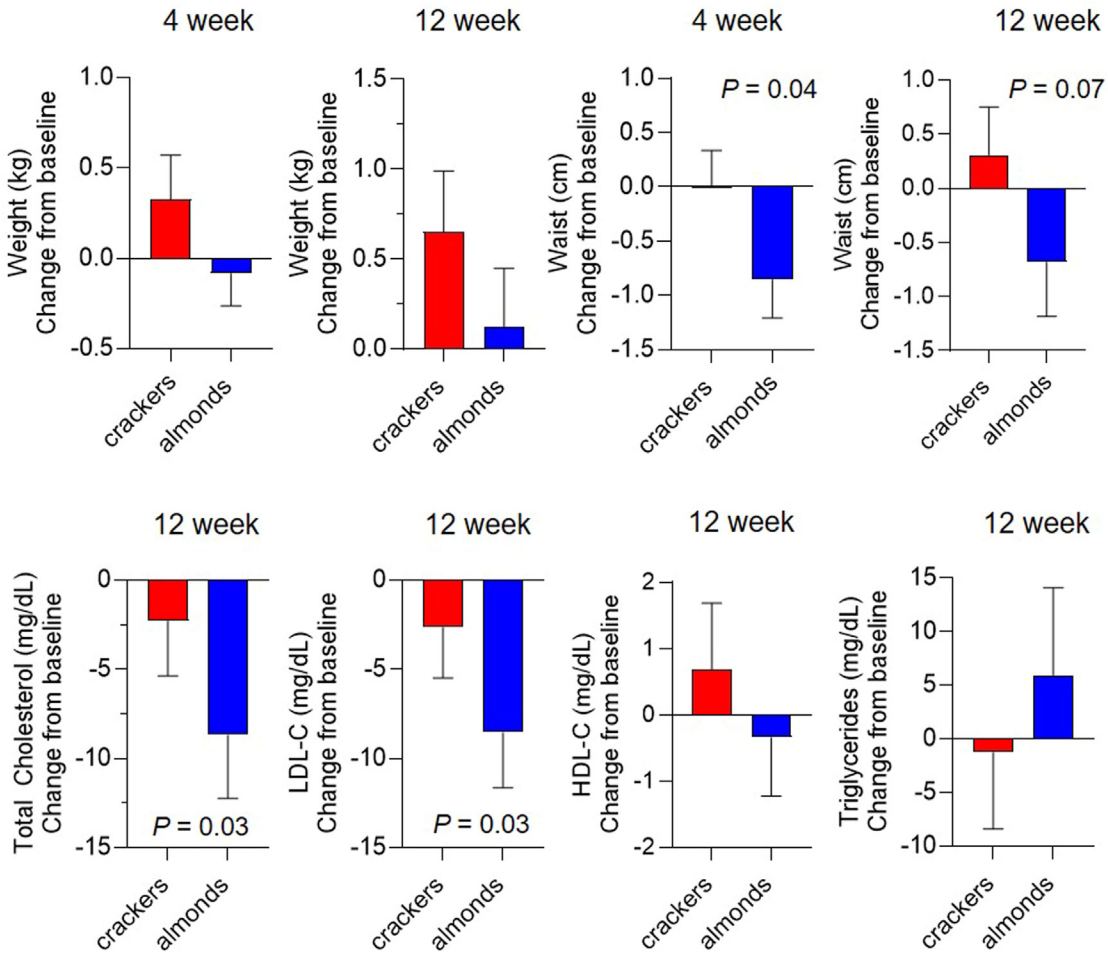

Fig. 2 – Almond consumption decreased waist circumference, total cholesterol, and LDL-C concentrations in participants with metabolic syndrome. Data are change from baseline results (post-pre), where bars indicate the mean change (± SEM) in the amount of the indicated parameter at 4 or 12 weeks of snack consumption relative to baseline samples, *n* = 38–39/treatment group. Significant difference between treatment groups was evaluated using Mann-Whitney tests where $P \leq .05$ was considered significant. We additionally tested for subgroup responses to treatment using Fisher's exact test. HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SEM, standard error of the mean.

trations, we determined if almond intake had an influence on overall nutrient intakes. At baseline, the cracker and almond treatment groups were similar in total intake of calories, macronutrients, and other dietary components (Supplemental Figure 1). Almond or cracker consumption did not change the estimated daily caloric intake. In crackers consumers, the only significant change in the reported dietary records was a modest decrease in dietary protein and magnesium intake at the 4-week study visit, compared to baseline. Based on food intake records, almond snacking was associated with significant increases in dietary soluble fiber, copper, biotin, magnesium, polyunsaturated fatty acids (primarily from omega-6 fatty acids), and monounsaturated fatty acids at both the 4- and 12-week study visits, compared to baseline and the cracker control group (Supplemental Figure 1). Because fat consumption increased in almond participants at 4- and 12-week study visits, but calorie intake was stable, we examined which macronutrients were altered and observed that there was a decrease in total carbohydrate consumption compared to their baseline consumption (paired *t*-test, $P = .02$), whereas no significant change in protein intake was noted among almond consumers relative to baseline.

For vitamin E status, participants consumed, on average, about 5 mg dietary α-tocopherol daily at baseline; by 4 weeks, those in the almond group increased α-tocopherol intakes to more than 17 mg daily and maintained this amount of intake over 12 weeks (Figure 3**A**). Because α-tocopherol is carried in plasma entirely within lipoproteins, we evaluated both plasma α-tocopherol concentrations (Figure 3**B**) as well as ratios of α-tocopherol to cholesterol (Figure 3**C**) [59]. In the almond consumers, plasma α-tocopherol was increased over the 12 weeks of the study compared to baseline (Figure 3**B**, paired *t*-test, $P = .01$). When expressed as a ratio of α-tocopherol relative to cholesterol, a significant time by treatment interaction ($P < .01$) was observed, with almond consumers showing markedly increased ratios of α-

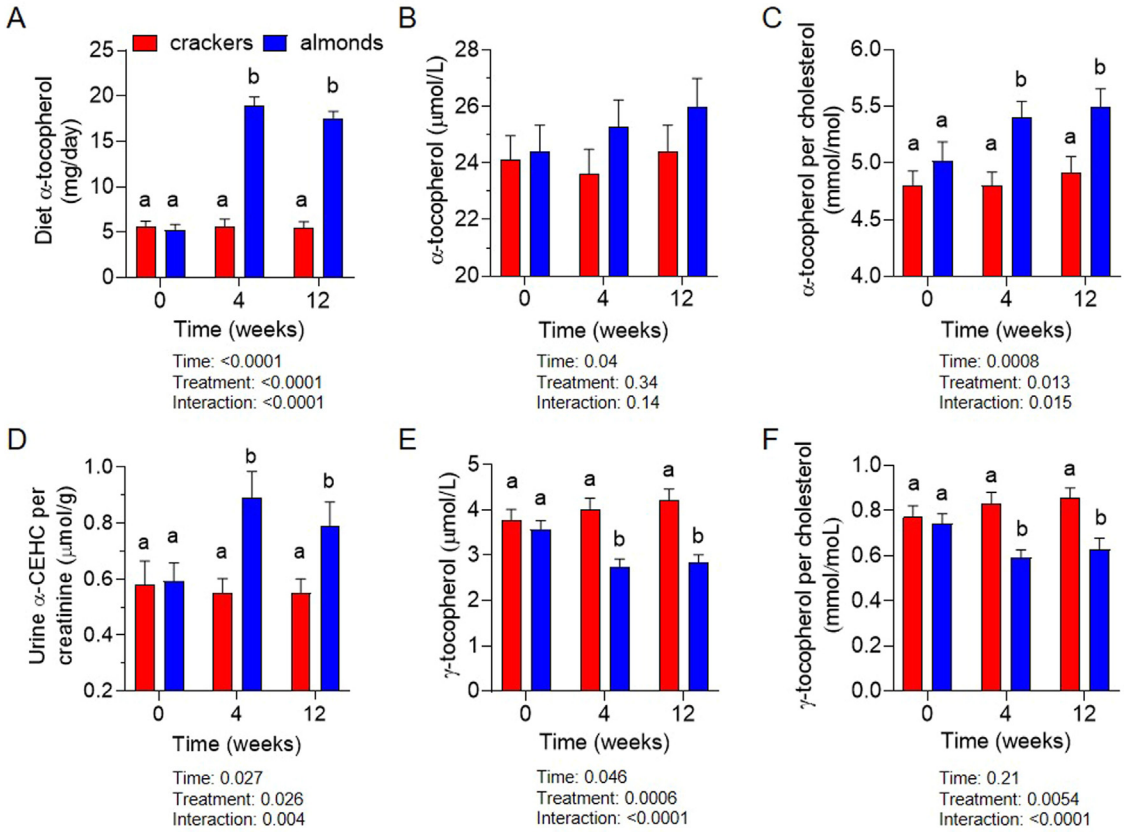

Fig. 3 – Effect of almond or cracker consumption on vitamin E status in participants with metabolic syndrome. Diet records, fasting plasma, and 24-hour urine samples were obtained at baseline (0), 4, and 12 weeks of snack intervention from participants, who consumed either almonds ($n = 38$, blue bar) or the caloric equivalent as crackers ($n = 39$, red bar). Bars indicate the mean (± SEM) in the amount of: A: α-Tocopherol intakes, B: plasma α-tocopherol concentrations, C: Plasma α-tocopherol/cholesterol ratios, D: Urinary α-CEHC per creatinine, E: plasma γ-tocopherol concentrations, F: Plasma γ-tocopherol/cholesterol ratios. Significant difference between treatment groups was evaluated using a mixed effects model and P values are given where $P \leq .05$ was considered significant. When a significant interaction was found, letters indicate significant difference between treatment groups. α-CEHC, α-carboxyethyl hydroxychromanol; SEM, standard error of the mean.

tocopherol to cholesterol at both 4 and 12 weeks (60% increase week 4, 58% increase week 12 as compared to crackers group, Figure 3**C**). This was in part attributed to a significant decrease in plasma total cholesterol following both 4 or 12 weeks daily almond intake ($P = .01$ and $P = .03$, respectively; Figure 2 and data not shown). Similarly, excretion of α-CEHC, a urinary marker that increases with improved α-tocopherol status, was increased significantly (interaction $P = .004$) at both 4 and 12 weeks (Figure 3**D**). In contrast to the improved α-tocopherol status, plasma γ-tocopherol concentrations (or the ratios of γ-tocopherol to cholesterol, Figures 3**E and F,** respectively) decreased at both 4 and 12 weeks compared to baseline, a phenomenon observed previously [60]. Taken together, these data demonstrate that a daily snack of almonds can improve α-tocopherol intakes, as well as vitamin E status.

3.4. *Snack consumption did not affect plasma mineral status or total polyphenol concentrations in urine*

The almonds contained ~10 times more magnesium than the crackers (Table 1), so we evaluated if plasma mineral concentrations changed with snacking (Supplemental Table 2). Plasma magnesium concentrations were consistently 21 μg/mL across treatment groups and at 0- and 12-week time points; thus, plasma magnesium concentrations were not significantly affected by our treatments. Plasma zinc, copper, iron, and calcium concentrations were unaffected by either snack treatment as well. Similarly, although almonds are a rich dietary source of polyphenols, no significant change in total polyphenol concentrations in urine was observed between the treatment groups or over the study duration (Supplemental Figure 2).

3.5. *Almond consumption improved biomarkers of gut barrier function and inflammation without affecting systemic inflammation or oxidative stress*

Fecal calprotectin is an indicator of gut inflammation and neutrophil migration into the gastrointestinal tissue [55,61]. Fecal myeloperoxidase is a marker of oxidative stress and inflammation derived from neutrophils and monocytes in the intestine [62,63]. At baseline, only 30%–31% of the participants had fecal calprotectin or myeloperoxidase concentrations at a concentration that is considered elevated (>50 μg/g calprotectin or >2 μg/g myeloperoxidase). Almond consumption improved calprotectin concentrations in the majority of people with elevated baseline calprotectin values (Figure 4**A,** 4**B**). Specifically, in the almond group, 11 of 12 individuals displayed a large decrease (>20 μg/g) in calprotectin concentrations at 4 weeks, compared to 7 of 15 individuals in the cracker group (Fisher's exact $P = .02$). Similar beneficial changes were observed at 12 weeks (9 of 12 individuals in the almond group, compared to 5 of 15 in the cracker group, Fisher's exact $P = .05$). In contrast, no significant effects of treatment were observed on calprotectin values when participants with no indications of baseline gut barrier dysfunction were included in the analysis (Supplemental Figure 3). In the population of participants with elevated myeloperoxidase concentrations at baseline, 4 weeks of almond treatment improved myeloperoxidase concentrations ($P = .05$) (Figure 4**C**). Almond consumption also significantly improved fecal myeloperoxidase concentrations at 4 weeks when all participants were considered ($P = .02$, Supplemental Figure 3).

We next tested if 4 weeks of daily almond consumption would reduce systemic inflammation by evaluating various plasma inflammation biomarkers. Almond consumption did not alter plasma CRP, IL-6, LBP, and CD14 concentrations (Figure 5**A-D**). CD14 concentrations decreased significantly with 4 weeks of cracker consumption, compared with the almond treatment group (Figure 5**D,** $P = .01$). Normal CRP concentrations (<0.3 mg/dL) were found in 49% of the participants, whereas the remaining participants had minor or moderate elevations in concentration of CRP that have been previously associated with obesity [64]. When statistical analysis was performed using data from only participants with elevated CRP, no effect of treatment was observed on plasma CRP, IL-6, LBP, or CD14 concentrations (data not shown). Further, plasma MDA concentrations, a biomarker of oxidative stress, was unaffected by the almond or cracker consumption in the entire study population (Figure 5**E**). Taken together, almond snacking modestly improved inflammation and gut barrier integrity in participants with preexisting elevated calprotectin and myeloperoxidase concentrations (Figure 4), but this local anti-inflammatory effect did not decrease overall systemic biomarkers of inflammation nor oxidative stress.

4. Discussion

This work demonstrates in persons with MetS that daily almond consumption improves some measures of cardiovascular health and gut health but does not change the amount of systemic inflammation or oxidative stress as was hypothesized. More specifically, among MetS participants with elevated intestinal inflammation at baseline, we show for the first time that 4 weeks of almond consumption decreased fe-

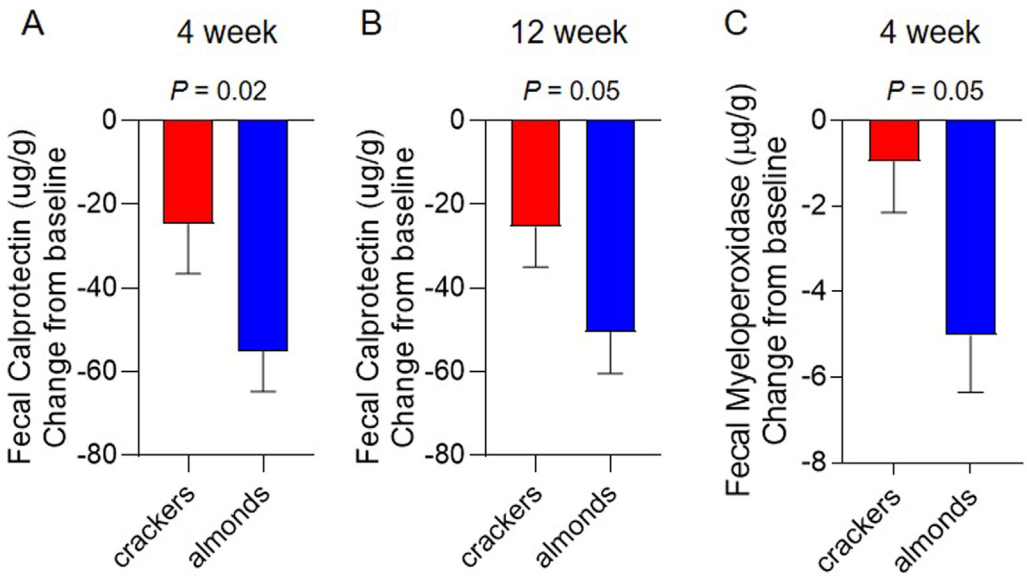

Fig. 4 – Almond consumption improved indicators of gut barrier function among participants with metabolic syndrome who had elevated calprotectin or myeloperoxidase concentrations at the beginning of the study. Data are change from baseline results (post-pre), where bars indicate the mean change (± SEM) in the amount of the indicated parameter at 4 or 12 weeks of snack consumption relative to baseline samples. A-B: Participants were included in the analysis when they had >50 μg/g calprotectin, or C: >2 μg/g myeloperoxidase, in their fecal samples at the baseline visit ($n = 11$–15/treatment group). Significant differences at $P \leq .05$ between treatment groups were tested using Mann-Whitney tests. We additionally tested for subgroup responses to treatment using Fisher's exact test. SEM, standard error of the mean.

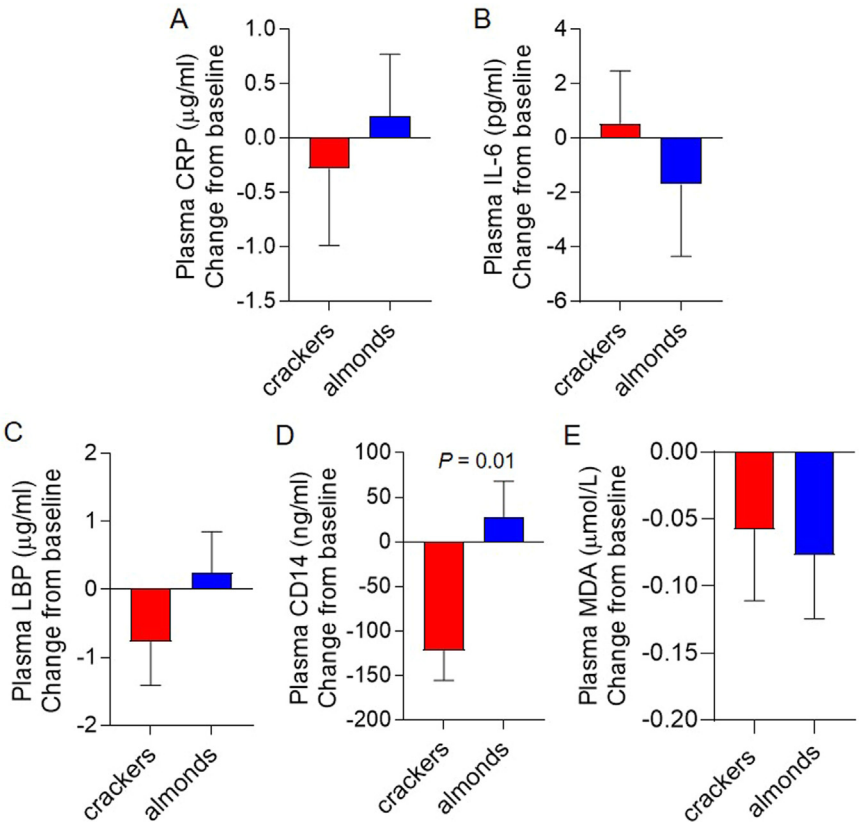

Fig. 5 – Four weeks of almond consumption did not significantly affect systemic inflammation or oxidative stress in participants with metabolic syndrome. Biomarkers of inflammation and oxidative stress measured are: A: CRP, B: IL-6, C: LBP, D: CD14, and E: MDA. Data are change from baseline results (post-pre), where bars indicate the mean change (± SEM) in the amount of the indicated parameter at 4 weeks of snack consumption relative to baseline samples, $n = 38–39$/treatment group. Significant differences at $P \leq .05$ between treatment groups were tested using Mann-Whitney tests. We additionally tested for subgroup responses to treatment using Fisher's exact test. CD14, cluster of differentiation 14; CRP, C-reactive protein; IL-6, interleukin-6; LBP, lipopolysaccharide-binding protein; MDA, malondialdehyde; SEM, standard error of the mean.

cal calprotectin and myeloperoxidase, 2 biomarkers associated with intestinal inflammation and gut barrier dysfunction. Almond snacking by participants with MetS also decreased total cholesterol, LDL cholesterol, and caused a modest decrease in waist circumference. Almond snacking did not cause significant changes in participants' weight or calorie intake. The high compliance rate and few adverse events observed herein show that incorporating 2 servings of roasted unsalted almonds into the daily diet was achievable and improved vitamin E status and intakes of other important dietary components like mono- and poly-unsaturated fatty acids, soluble fiber, magnesium, copper, and biotin.

Only a few studies have specifically intervened with an almond snack in persons with MetS, but many studies have explored the beneficial effects of almonds in populations with similar metabolic disorders (obesity/overweight, hyperlipidemia, hypercholesterolemia, prediabetes, type 2 diabetes, etc.) [37,39–41,65,66]. The improvements in plasma total cholesterol and LDL-C observed here are consistent with improvements in cholesterol observed in these diverse study populations [37,65]. The decrease in waist circumference with almond consumption observed herein was small (and only a statistical trend at week 12), suggesting this finding may not be generalizable to other populations. Despite this caveat, a recent meta-analysis of 37 papers found almond consumption was associated with an improvement in waist circumference, body fat percentage, body weight fat mass, and hunger scores in subjects with <30 kg/m^2 BMI and a study length longer than 12 weeks [65]. Other studies, focused on weight management, have found that almond consumption enhances satiety, positively influences central adiposity, and decreases body fat percentage [67]. To further benefit cardiovascular health, almond snacking may complement other interventions such as increased physical activity, adopting a Mediterranean diet, reducing caloric and/or refined carbohydrate intake, and the use of pharmaceutical agents to manage MetS conditions [40,66,68,69].

There is much interest in examining whether almond consumption improves glycemic regulation. Our conclusions are consistent with a recent meta-analysis of studies conducted in people with type 2 diabetes, which showed that almond consumption did not impact fasting glucose, insulin,

or HOMA-IR [70]. Other studies, often in which almonds were given in the context of a low-carbohydrate diet, have reported benefits of these diets and almond consumption on glycemic regulation [32,33,35,39,40,71]. It is noteworthy that almond consumers in the present study choose voluntarily to eat fewer carbohydrates (compared to their baseline carbohydrate intake, Supplemental Figure 1).

Almond consumption also improved vitamin E status and intakes of several nutrients associated with higher quality diets. Perhaps the most nutritionally significant observation is the improvement in vitamin E status because vitamin E has been listed continuously as a nutrient of concern since the 2015 *Dietary Guidelines for Americans* [72]. The dietary change due to almond consumption was associated with a decrease in plasma total cholesterol (Figure 2) [30]. Because α-tocopherol is carried entirely within lipoproteins, ratios of α-tocopherol to cholesterol are a more appropriate measure to evaluate changes due to these dietary manipulations [59]. We observed a significant improvement in vitamin E status (Figure 3), documented by increases in the ratios of α-tocopherol to cholesterol, decreases in the ratio of γ-tocopherol to cholesterol, as well as an increase in urinary α-CEHC. It is remarkable that the relatively small increase in α-tocopherol intake (approximately 10 mg per day) was sufficient to improve these parameters. Notably, plasma γ-tocopherol decreased, as expected, likely because of the function of the hepatic α-tocopherol transfer protein, which is known to preferentially facilitate the retention of plasma α-tocopherol, whereas the catabolism of non–α-tocopherols, as well as excess α-tocopherol, is a function of the catabolic pathway mediated by cytochrome P450 4F2 [73]. An adequate intake of α-tocopherol, as was obtained here with almonds, is especially important because it may protect against the development of liver complications (metabolic dysfunction-associated fatty liver disease, steatohepatitis, hepatic carcinoma) that persons with MetS are at an increased risk of developing. Vitamin E supplements have been used with significant benefit to treat steatohepatitis, but concern about vitamin E supplements has limited their use [74–78].

Participants with MetS were shown here to consume less than the recommended amount of omega-6 polyunsaturated fatty acids when entering the study. Adding 2 servings of roasted almonds improved the intake of monounsaturated fatty acids and importantly improved the amount of omega-6 fatty acids consumed to a value that is recommended by the American Heart Association [79,80]. Consumption of omega-6 fatty acids, like linoleic acid, which is abundant in almonds, has been shown to improve blood lipoprotein profiles, as observed here in persons with MetS, and a higher intake of omega-6 fatty acids has been associated with reduced risk for coronary heart disease [79,80]. In future studies, we will measure if the increased intake of health promoting lipids with almond consumption is associated with improvements in the plasma fatty acid and oxylipin profiles. In addition to improving vitamin E and omega-6 status, almond consumption may also bridge the gap of other nutrition deficiencies in MetS subjects by increasing intakes of magnesium, soluble fiber, copper, biotin, and polyphenols [81]. Deficiencies in some of these dietary components have been associated with the development of health conditions including type 2 diabetes, osteoporosis, and hypertension [82–84]. Although we did not observe almond-induced improvements in plasma magnesium concentrations, circulating magnesium only represents 0.8% of total magnesium stores. Previous studies have established that blood-based measurements of magnesium are not considered a sensitive and specific biomarkers of dietary magnesium intake or status and can easily mask deficiency [85]. Similarly, changes in urinary total polyphenol concentrations, which would represent absorbed and excreted polyphenols, were not observed here; however, this result was not unexpected. Polyphenols are not well absorbed in the intestine, but nonetheless they can act locally in the gut to decrease inflammation through multiple mechanisms [86,87].

Inflammation and oxidative stress are unquestionably linked to the pathogenesis of MetS, and MetS is linked to the development of intestinal dysbiosis and increased intestinal permeability [88]. Consumption of a Mediterranean diet with mixed nuts (almond, walnut, hazelnuts) has been shown in persons with MetS to enhance plasma antioxidants and decrease xanthine oxidase activity, but similarly to our study, these authors did not observe changes in markers of oxidative damage [89]. We found that almond consumption was associated with improvements in biomarkers of intestinal inflammation and gut barrier dysfunction (particularly among participants with elevated intestinal inflammation at baseline) but did not affect systemic inflammation. These data indicate that the changes we observed in the gut barrier function, although important, were not sufficient to mediate a systemic change in inflammation in the context of our MetS population. A recent study in persons with MetS, who were given a green tea extract, also found that the treatment improved gut barrier function without affecting systemic inflammation [62]. It is possible that the bioactive ingredients, like polyphenols, that are affecting inflammation are poorly absorbed, and thus there was only improvements in inflammation in gastrointestinal tissues. It is also possible that longer term exposure to almonds would be necessary to improve systemic inflammatory processes. More research is needed in additional populations to confirm our findings of improvements in calprotectin and myeloperoxidase concentrations with almond consumption. Importantly, our results complement literature showing the consumption of almonds can improve colonic microbiota, by promoting the growth of beneficial bacteria [33,44,81,90–95]. Some mechanisms by which almonds have been proposed to promote intestinal health include increased intake of fiber, healthy fats, almond polysaccharide (AP-1), and polyphenols, which can promote the production of short chain fatty acids, improve intestinal barrier function, and increase the ratio of symbiotic to pathogenic bacteria [43,90,96–99]. To explore this possibility, we further measured short chain fatty acids concentrations in fecal samples (0, 4, and 12 week) of our participants. There were no significant changes with almond consumption in acetic, propionic, butyric, valeric, or lactic acid concentrations, when compared to baseline (data not shown). Future work will examine whether the gut microbiota composition was altered with almond consumption in this population.

Our study had some limitations. One limitation was that no healthy volunteers were included, and thus it was not possible to directly compare the inflammatory and oxidative stress re-

sults to those from healthy individuals. Furthermore, we were limited in the duration of the almond intervention, number of time points, and measures of inflammation we could examine, and enrolled relatively healthy individuals with MetS, where only half of the enrolled subjects had plasma CRP concentrations elevated above normal values. Those with higher amounts of inflammation may have demonstrated a greater response to the almond intervention, but further research is needed on this point. Although the study population was relatively balanced in terms of biological sex, the participants were generally Caucasians (expected because of local demographics), which is a limitation of this study. Almond consumption has been associated with decreases in oxidative stress/MDA in other populations like regular smokers with increased oxidative stress [96,100,101], which is in contrast to the outcomes reported here. Thus, the lack of inclusion of smokers may contribute to these different findings observed here.

In summary, the present work identified novel benefits of daily almond snacking in people with MetS that may help to slow the development of ensuing chronic disorders like cardiovascular diseases, stroke, and other associated disorders. Although progression of various MetS symptoms, such as hypertension or hyperglycemia, can be managed with medications, this work is significant because the results, in conjunction with other published literature, support dietary recommendations to encourage people with MetS to increase their consumption of almonds, an accessible and naturally occurring functional food, that could help reduce the public health burden associated with MetS.

Author Declarations

Laura Beaver and Emily Ho report financial support was provided by the Almond Board of California. Emily Ho reports financial support was provided by the National Institute of Food and Agriculture, Agricultural Experimental Station. Emily Ho reports financial support was provided by the Oregon Agricultural Experiment Station. Emily Ho reports financial support was provided by the National Institutes of Health. Emily Ho reports a relationship with Haleon Scientific Advisory Board that includes board membership. Emily Ho reports a relationship with Vytology Scientific Advisory Board that includes board membership. Emily Ho reports a relationship with Amway Scientific Advisory Board that includes board membership. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Laura M. Beaver: Conceptualization, Visualization, Investigation, Data curation, Resources, Writing – original draft, Supervision, Project administration, Formal analysis, Funding acquisition, Writing – review & editing. **Scott W. Leonard:** Investigation, Resources, Formal analysis, Writing – original draft, Writing – review & editing. **Sandra L. Uesugi:** Investigation, Resources, Project administration, Writing – review & editing. **Carmen P. Wong:** Investigation, Resources, Formal analysis, Writing – original draft, Writing – review & editing. **Lily-Marie Lytle:** Visualization, Resources, Formal analysis, Writing – review & editing. **Anusha Vasudevan:** Visualization, Data curation, Resources, Formal analysis, Writing – review & editing. **Ethan M. Papenhausen:** Investigation, Resources, Formal analysis, Writing – review & editing. **Yashasvini Jupudi:** Formal analysis, Writing – review & editing. **Deborah Bella:** Methodology, Resources, Writing – review & editing. **Gerd Bobe:** Conceptualization, Formal analysis, Writing – review & editing. **Maret G. Traber:** Conceptualization, Visualization, Supervision, Formal analysis, Writing – original draft, Funding acquisition, Writing – review & editing. **Emily Ho:** Conceptualization, Resources, Supervision, Project administration, Funding acquisition, Writing – review & editing.

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Declaration of generative AI and AI-assisted technologies in the writing process

No AI was used in the writing of this manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nutres.2025.04.011.

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