



# Blueberries Decrease Cardiovascular Risk Factors in Obese Men and Women with Metabolic Syndrome<sup>1–3</sup>

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## Abstract

Among all fruits, berries have shown substantial cardio-protective benefits due to their high polyphenol content. However, investigation of their efficacy in improving features of metabolic syndrome and related cardiovascular risk factors in obesity is limited. We examined the effects of blueberry supplementation on features of metabolic syndrome, lipid peroxidation, and inflammation in obese men and women. Forty-eight participants with metabolic syndrome [4 males and 44 females; BMI: 37.8 ± 2.3 kg/m<sup>2</sup>; age: 50.0 ± 3.0 y (mean ± SE)] consumed freeze-dried blueberry beverage (50 g freeze-dried blueberries, ~350 g fresh blueberries) or equivalent amounts of fluids (controls, 960 mL water) daily for 8 wk in a randomized controlled trial. Anthropometric and blood pressure measurements, assessment of dietary intakes, and fasting blood draws were conducted at screening and at wk 4 and 8 of the study. The decreases in systolic and diastolic blood pressures were greater in the blueberry-supplemented group (–6 and –4%, respectively) than in controls (–1.5 and –1.2%) ( $P < 0.05$ ), whereas the serum glucose concentration and lipid profiles were not affected. The decreases in plasma oxidized LDL and serum malondialdehyde and hydroxynonenal concentrations were greater in the blueberry group (–28 and –17%, respectively) than in the control group (–9 and –9%) ( $P < 0.01$ ). Our study shows blueberries may improve selected features of metabolic syndrome and related cardiovascular risk factors at dietary achievable doses. J. Nutr. 140: 1582–1587, 2010.

## Introduction

Nutritional epidemiology provides some evidence regarding the cardio-protective effects of foods high in polyphenols, such as berries, tea, soy, and cocoa products (1–4). Blueberries are particularly high in polyphenolic flavonoids in addition to containing significant amounts of micronutrients and fiber (5–7). American blueberries include the lowbush or wild blueberry (*Vaccinium angustifolium* Aiton) and the highbush or cultivated blueberry (*Vaccinium corymbosum* L.), both of which have superior ranking among fruits and vegetables for their antioxidant capacity, mainly due to their high anthocyanin content (93–235 mg/100 g berries) (6,7). In a comprehensive analysis of the antioxidant potential of commonly consumed polyphenol-rich beverages in the United States, blueberry juice was ranked among the top 4 contributors of dietary antioxidants after pomegranate juice, red wine, and concord grape juice (8).

Berries have been commercialized as fresh or frozen whole fruits, freeze-dried berries, puree, juice, or wine (9–11). Although most processing methods cause a significant decrease in the anthocyanin content (10–12), freeze-drying has been reported to cause the least reduction in total polyphenol content of berries (11).

Several mechanistic studies provide evidence of antioxidative (13,14), antiinflammatory (14,15), antihypertensive (16,17), antidiabetic (18,19), antiobesity (20), and antihyperlipidemic (20,21) effects of blueberries, providing possible rationale for cardio-protective mechanisms. Based on these mechanistic studies, consuming blueberries might favorably alter individual components of metabolic syndrome, a rapidly escalating public health problem in the US (22). Metabolic syndrome has been characterized by abdominal adiposity, dyslipidemia (high triglycerides, low HDL cholesterol), hypertension, impaired glucose tolerance, elevated oxidative stress, inflammation, and increased risks for type 2 diabetes and atherosclerotic cardiovascular disease (CVD)<sup>7</sup> (22–24). Berry supplementation using

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<sup>7</sup> Abbreviations used: CRP, C-reactive protein; CVD, cardiovascular disease; HbA<sub>1c</sub>, hemoglobin A<sub>1c</sub>; HNE, hydroxynonenal; IL-6, interleukin-6; MDA, malondialdehyde; MPO, myeloperoxidase; ox-LDL, oxidized LDL; RD, registered dietitian; sICAM-1, soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1.

chokeberries, cranberries, or a combination of berries has been shown to improve features of metabolic syndrome such as dyslipidemia, hypertension, or impaired fasting glucose in participants with existing cardiovascular risk factors (25–27). However, there is a paucity of clinical data on the cardiovascular health benefits of blueberries per se.

Thus, this study was designed to test the hypothesis that blueberry supplementation, in the form of a freeze-dried beverage, will improve features of metabolic syndrome and decrease biomarkers of lipid and lipoprotein oxidation and inflammation in study participants compared with a control group consuming equivalent amounts of fluids, in a randomized controlled trial.

## Materials and Methods

**Participants.** Sixty-six obese men and women with metabolic syndrome (mean age,  $50.0 \pm 3.0$  y) were enrolled in this randomized controlled study. They were screened for the qualifying criteria: 3 of 5 features of metabolic syndrome as defined by the National Cholesterol Education Program, Adult Treatment Panel (22). Recruitment and interventions were conducted at the General Clinical Research Center at the University of Oklahoma Health Sciences Center, and at the Nutritional Sciences Clinical Assessment Unit at Oklahoma State University. Participants were recruited through flyers and campus e-mail advertisements at both sites. Each potential recruit received an initial telephone screening prior to the screening visit. They were excluded if they were younger than 21 y of age; taking medications for any chronic disease, including hypoglycemic, hypolipidemic, antiinflammatory, or steroidal medications; or had liver, renal, or thyroid disorders or anemia. Potential recruits also were excluded if they were consuming antioxidants or fish oil supplements on a regular basis, were current smokers, consuming alcohol on a regular basis (except social drinking ~1–2 drinks/wk), or were pregnant or lactating. This intervention study was approved by the Institutional Review Board at the University of Oklahoma Health Sciences Center and at Oklahoma State University. All participants provided written informed consent.

**Intervention.** Freeze-dried blueberries provided by the US Highbush Blueberry Council (Folsom, CA) were a blend of 2 blueberry cultivars, Tifblue and Rubel, in a 1:7 ratio of freeze-dried: fresh berries, with no additives (Table 1). Participants received a daily dose of 50 g freeze-dried blueberries that were reconstituted in 480 mL water and vanilla extract or Splenda was added based on the preference of the participants. The participants were asked to consume 1 cup (240 mL) in the morning and the second in the evening at least 6–8 h apart. Because the beverage made with reconstituted freeze-dried blueberries was thick and sticky in consistency, participants were also asked to rinse out each cup with an additional cup of water, thus leading to the consumption of ~960 mL fluids/d in the blueberry group. The control group was asked to consume 960 mL water to match the fluid intake of the blueberry group and was provided with containers to measure out the prescribed amount of water.

**Study design.** This was a single-blinded controlled study in which participants were randomized to the blueberry or control group for 8 wk. Those in the blueberry group made 3 visits/wk to their study site (Monday, Wednesday, and Friday) to ensure compliance by consuming the first cup in the morning under observation by the research staff. Participants were instructed to keep the drink under refrigeration, to avoid exposing it to direct heat or light, and to avoid consuming it with any other snack or with lunch or dinner, because other foods might interfere with the absorption of the blueberry polyphenols. Participants were asked to return any unconsumed blueberry drink. Controls were provided with containers to measure 4 cups water to be consumed on a daily basis. All participants returned for follow-up visits at 2, 4, 6, and 8 wk of the study. The research staff were instructed not to discuss diet or weight issues with participants consuming blueberries to avoid potential confounding factors that might arise as a result of frequent visits of the

**TABLE 1** Composition of freeze-dried blueberries<sup>1</sup>

Nutrients/antioxidant activity	unit/50 g
Energy, <sup>2</sup> kcal	174.0
Protein, g	1.7
Carbohydrates, g	42.3
Total sugars, g	30.0
Dietary fiber, g	9.3
Vitamin C, mg	86.0
Calcium, mg	15.0
Iron, mg	0.5
Potassium, mg	204.0
Sodium, mg	8.0
Phenolic components, mg	1624
Anthocyanins, mg	742
Oxygen radical absorbance capacity, mmol TE	17.8

<sup>1</sup> Source: U.S. Highbush Blueberry Council (Folsom, CA). Fresh weight replacement: 1 to 7 (freeze-dried to fresh).

<sup>2</sup> 1 kcal = 4.184 kJ.

blueberry group (compared with the biweekly visits of the control group). Participants received monetary compensation during their follow-up visits. They were asked to refrain from consuming any other source of berries or related products derived from berries such as juices, jams, and desserts. They were also asked to refrain from consuming green tea, cocoa, and soy products while participating in the study, because these were the most commonly consumed flavonoid-rich foods by the enrolled participants as identified by a screening FFQ specific for flavonoids. Participants maintained their usual diet, physical activity, and lifestyle while on the study and were also asked to record their food intakes. Body weight, height, waist circumference, and systolic and diastolic blood pressures were measured by trained personnel and blood draws were performed by registered nurses at screening and wk 4 and 8 of the study. All laboratory staff were unaware of treatment groups.

**Anthropometrics and blood pressure.** Participants removed shoes and items in dress pockets and were weighed on a flat, uncarpeted surface with the SECA 644 Multifunctional Hand Rail Scale (SECA) and recorded to the nearest 0.1 kg. Height was measured without shoes using the Accustat Genentech Stadiometer and recorded to the nearest 0.1 cm. Systolic and diastolic blood pressures were measured in millimeters Hg using Spot Vital Signs Device (Welch Allyn). Participants were asked to lie down and relax for ~8–10 min, following which 3 blood pressure measurements were recorded at intervals of 5 min. Waist circumference was measured at the superior iliac crest using the Gulick II Tape Measure (Vital Signs). All measurements were conducted in fasting participants at screen and at wk 4 and 8 of the study.

**Dietary analyses.** Study participants were required to record daily food intake for 3 d at 3 time points throughout the study: screen and wk 4 and 8. Each time, the registered dietitian (RD) carefully instructed the participants on accurate food record completion using visual tools such as food models and common household measuring utensils. Instructions were also given on careful recording of details needed for recipes. Three day averages of micro- and macronutrient intakes were analyzed using Nutritionist Pro (version 3.2, 2007, Axxya Systems). All data entry was performed by RD trained and certified in using the software. All dietary data entry was verified by a second RD as a measure of quality control. If a participant ate a food that was not in the database, a food with very similar nutrient composition was chosen. Nutrient information was also obtained through food labels or recipes from participants, online sources, or at grocery stores.

**Clinical analyses.** Blood samples were collected immediately after each draw and serum was transported to the University of Oklahoma Medical Center Laboratory for analyses of fasting glucose, insulin, lipid profile (total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol),

and other blood variables, including safety variables (hemoglobin, platelets, white blood cells, liver enzymes, creatinine, blood urea nitrogen, electrolytes, albumin, total protein, and thyroid-stimulating hormone), using automated diagnostic equipment (Abbott Architect Instruments) following standard protocols at the University of Oklahoma Medical Center. Serum hemoglobin A<sub>1C</sub> (HbA<sub>1C</sub>) was analyzed using a DCA 2000+ (Bayer). Insulin resistance was evaluated by homeostasis model assessment calculated as [fasting insulin (mU/L) × fasting glucose (mmol/L)]/22.5.

For assays to determine serum malondialdehyde (MDA) and hydroxynonenal (HNE) and plasma oxidized-LDL, myeloperoxidase (MPO), adiponectin, interleukin-6 (IL-6), high sensitivity C-reactive protein (CRP), soluble intercellular adhesion molecule-1, and soluble vascular cell adhesion molecule levels, serum and EDTA-plasma samples were collected, separated by centrifugation at 1800 × g for 10 min at 4°C, and stored at -80°C for subsequent analyses. NMR-determined lipoprotein subclass profile was performed in first-thaw plasma specimens using a 400-MHz proton NMR analyzer at LipoScience as described previously (28).

**Biomarkers of oxidative stress.** Plasma concentrations of MPO and ox-LDL were measured in duplicate with commercially available ELISA kits: Mercodia MPO ELISA and Mercodia Oxidized LDL Competitive ELISA (Mercodia) according to the manufacturer's instructions. Lipid peroxidation was measured in serum as combined MDA and HNE using a colorimetric assay according to the manufacturer's protocol (LPO-586, Oxis Health Products). The mean intra-assay CV for MPO, ox-LDL, and MDA and HNE were 4.8, 5.2, and 3.6%, respectively.

**Biomarkers of inflammation.** Plasma concentrations of CRP, adiponectin, IL-6, soluble intercellular adhesion molecule-1 (sICAM-1), and soluble vascular cell adhesion molecule-1 (sVCAM-1) were determined using commercially available ELISA kits: Human CRP Quantikine ELISA, Human Total Adiponectin Quantikine ELISA, Human IL-6 Quantikine ELISA, Human sICAM-1 Quantikine ELISA, and Human sVCAM-1 Quantikine ELISA (R&D Systems) according to the manufacturer's protocols. The minimum detectable levels were 15.6, 62.5, 9.4, 15.6, and 15.6 ng/L for each assay, respectively. The inter-assay CV were 6.2, 3.6, 3.1, 3.5, and 7.6%, respectively.

**Statistical analyses.** For all measures, descriptive statistics were calculated and graphs drawn to look for outliers; no data points were determined to be outliers. Differences between blueberry and control groups at baseline were assessed using Student's *t* tests.

Changes in measurements over the 8-wk study period were assessed by calculating the difference between the pre- and postintervention measurements in each group. For each variable, significance was assessed by comparing the change over the 8-wk study period between blueberry and control groups using Student's *t* tests. Target sample size was calculated to include 25 participants/group to detect significant differences in certain dependent variables with 80% power. Multiple hypothesis testing was not accounted for and all statistical tests were 2-tailed with significance level set at 0.05. SPSS for Windows (version 15.0, SPSS, 2006) was used for the statistical calculations.

## Results

In this randomized controlled trial, 66 men and women with metabolic syndrome were enrolled upon qualification. Among 34 enrolled participants in the blueberry group, 9 withdrew on account of side effects, including nausea, vomiting, constipation, and diarrhea following blueberry intervention during the first week of the study, leading to a 27% drop-out rate in the blueberry group. Among 32 participants enrolled in the control group, 1 was excluded on account of smoking, 6 withdrew due to personal reasons (not disclosed), and 2 withdrew due to time constraints, leading to a 28% drop-out rate in the control group. The temporary gastrointestinal discomfort was also reported by

participants who completed the 8-wk blueberry treatment, which did not persist beyond the first week of the intervention. Thus, 48 participants actually completed the 8-wk study of whom 25 were in the blueberry group and 23 were controls. Baseline characteristics, including age, BMI, and safety variables, did not differ between the blueberry and control groups (Table 2). For the 25 participants in the blueberry group, compliance was high, with 96.5% of the blueberry drink consumed and 100% compliance visits/wk. The controls reported 100% compliance in terms of water intake and biweekly visits.

The decreases in systolic and diastolic blood pressures were greater in the blueberry-supplemented group (-6 and -4%, respectively) than in controls (-1.5 and -1.2%) (*P* = 0.003 and *P* = 0.04). Changes in body weight, waist circumference, HbA<sub>1C</sub>, insulin resistance, and serum glucose concentration and lipid profile did not differ between the groups. Blood pressure outcomes remained significantly different when data were analyzed without participants on stable antihypertensive medications in the blueberry and control groups. Those in the blueberry group had a significantly lower baseline serum LDL-cholesterol concentration than controls and no significant changes were noted between groups (Table 3). NMR-based lipid particle concentrations were not significantly affected by blueberry intervention (Supplemental Table 1).

The decreases in oxidized LDL (ox-LDL) and combined MDA and HNE concentrations were greater in the blueberry-supplemented group (-28 and -17%, respectively) than in controls (-9 and -9%) (*P* = 0.009 and *P* = 0.005). Changes in plasma CRP, IL-6, MPO, adhesion molecules (sICAM-1, sVCAM-1), and adiponectin concentrations did not differ between the groups (Table 4).

Changes in dietary intakes did not differ between the blueberry and control groups (Supplemental Table 2).

## Discussion

An emerging body of evidence indicates the role of blueberries as cardio-protective agents, although few human studies have been reported to support this claim. Our test dose of 50 g freeze-dried blueberries, equivalent to ~350 g or 2.3 cups fresh blueberries,

**TABLE 2** Baseline characteristics and serum biomarkers of participants with metabolic syndrome completing 8-wk supplementation with freeze-dried blueberries or control treatment<sup>1</sup>

	Blueberry	Control
<i>n</i>	25	23
Age, <i>y</i>	51.5 ± 3.0	48.0 ± 3.3
BMI, <i>kg/m</i> <sup>2</sup>	38.1 ± 1.5	37.5 ± 3.0
M/F <i>n/n</i>	2/23	2/21
Aspartate aminotransferase, <i>U/L</i>	25.3 ± 1.3	25.7 ± 3.0
Alanine aminotransferase, <i>U/L</i>	33.1 ± 2.6	34.0 ± 4.7
Blood urea nitrogen, <i>mmol/L</i>	4.6 ± 0.2	4.2 ± 0.4
Creatinine, <i>μmol/L</i>	70.7 ± 8.8	80.0 ± 18.0
Albumin, <i>g/L</i>	41.0 ± 1.0	35.0 ± 2.0
Hemoglobin, <i>g/L</i>	138.0 ± 2.0	143.0 ± 2.0
White blood cells, <i>n</i> × 10 <sup>-9</sup>	7.0 ± 0.4	6.8 ± 0.5
Antihypertensive medication users, %	22.0	21.0
Multivitamin users, %	12.0	10.0

<sup>1</sup> Data are means ± SE.

**TABLE 3** Change in anthropometrics, blood pressure, and serum glucose and lipid concentrations in participants with metabolic syndrome after 8-wk supplementation with freeze-dried blueberries or control treatment<sup>1</sup>

Variable	$\Delta$ (0–8 wk)	
	Blueberry	Control
<i>n</i>	25	23
Body weight, kg	-0.4 ± 0.30	0.5 ± 0.40
Waist circumference, cm	-0.4 ± 0.30	-0.5 ± 1.10
Systolic blood pressure, mm Hg	-7.8 ± 2.50*	-2.0 ± 2.80
Diastolic blood pressure, mm Hg	-2.5 ± 1.10*	0.7 ± 2.00
Glucose, mmol/L	0.1 ± 0.20	-0.1 ± 0.20
HbA <sub>1c</sub> , %	0.1 ± 0.10	0.2 ± 0.10
Homeostasis model assessment of insulin resistance	0.7 ± 0.50	-0.2 ± 0.20
Triglycerides, mmol/L	0.0 ± 0.10	0.1 ± 0.20
Total cholesterol, mmol/L	0.2 ± 0.20	0.2 ± 0.30
HDL cholesterol, mmol/L	0.0 ± 0.02	0.0 ± 0.02
LDL cholesterol, mmol/L	0.1 ± 0.10	0.0 ± 0.20

<sup>1</sup> Data are means ± SE. \*Different from control,  $P < 0.05$ .

was overall well tolerated and conforms to the daily fruit and vegetable recommendations of at least 5 servings for US adults (29). We also selected this dose to investigate the therapeutic effects of blueberries in a standard freeze-dried form on features of metabolic syndrome in men and women with low fruit intake (30).

Blueberries have been reported to exert favorable effects on features of metabolic syndrome and type 2 diabetes in animal models of obesity (19,20). Human intervention studies investigating the effects of berries on metabolic syndrome are limited. Clinical trials involving chokeberry juice supplementation showed significant improvements in fasting glucose, lipids, and HbA<sub>1c</sub> in type 2 diabetics, and, cranberry, or bilberry and black currant extract supplementations, were shown to improve dyslipidemia in type 2 diabetics, or hyperlipidemic patients, respectively (25,26,31). However, in our study, blueberry supplementation for 8 wk did not affect fasting serum glucose, insulin, lipid profiles, and body weight or waist circumference. These null effects may be due to the fact that participants with metabolic syndrome in our blueberry intervention group had

**TABLE 4** Change in plasma biomarkers of oxidative stress and inflammation in participants with metabolic syndrome after 8-wk supplementation with freeze-dried blueberries or control treatment<sup>1</sup>

Variables	$\Delta$ (0–8 wk)	
	Blueberry	Control
<i>n</i>	25	23
CRP, mg/L	0.2 ± 0.50	0.4 ± 1.50
siCAM-1, ng/L	-0.1 ± 0.02	0.0 ± 0.03
sVCAM-1, ng/L	-0.1 ± 0.04	0.0 ± 0.05
IL-6, pg/L	0.0 ± 0.01	0.0 ± 0.01
Adiponectin, $\mu$ g/L	0.0 ± 0.01	0.0 ± 0.01
ox-LDL, U/L	-30.0 ± 4.00*	-9.6 ± 9.50
MPO, $\mu$ g/L	2.5 ± 5.00	-2.4 ± 8.50
MDA and HNE, $\mu$ mol/L	-0.2 ± 0.03*	-0.1 ± 0.01

<sup>1</sup> Data are means ± SE. \*Different from control,  $P < 0.01$ .

normal baseline levels of glucose, insulin, and lipids (except low HDL cholesterol). Also, additional dietary adjustments and longer study duration may be needed to affect adiposity in these men and women. On the other hand, blueberry supplementation significantly decreased systolic and diastolic blood pressures in our prehypertensive participants, which conforms to the findings of previous studies on the blood pressure-lowering effects of cranberry intervention in healthy humans or mixed berry supplementation in those with CVD risk factors (27,32). Mechanistic studies explain the role of blueberries or anthocyanins in ameliorating hypertension by significantly increasing endothelial nitric oxide synthase levels in bovine and human endothelial cells (33,34), decreasing vasoconstriction via nitric oxide-mediated pathway, or decreasing renal oxidative stress and, thereby, systolic blood pressure in rodent models of human essential hypertension (16,17). Thus, our study is the first to our knowledge to report that blueberries have antihypertensive effects in people with metabolic syndrome. Because hypertension is an independent and significant CVD risk factor (35) and can be mitigated by dietary practices (36), blueberry supplementation may be a potential therapeutic dietary measure and needs further confirmation in larger controlled studies.

Biomarkers of lipid and lipoprotein oxidation such as MDA and ox-LDL levels are elevated in population with abdominal adiposity and metabolic syndrome and have also been associated with coronary artery disease (24,37,38). In our 8-wk study, decreases in plasma ox-LDL and serum MDA and HNE levels were significantly greater in the blueberry-supplemented group than in controls. Our findings are similar to the previous intervention studies reporting the effects of blueberries, cranberry juice, or freeze-dried strawberries in lowering lipid hydroperoxides in smokers, ox-LDL in healthy volunteers, or MDA and HNE in women with metabolic syndrome, respectively (39–41). The antioxidant effects of blueberries have also been reported by studies using cellular and animal models of oxidative stress (13,14), thus providing mechanistic evidence that needs to be strengthened by larger controlled clinical trials. However, in our study, blueberries did not affect plasma MPO, an independent predictor of CVD and a significant contributor to oxidative stress (42). Thus, further investigation is needed to define the effects of berry polyphenols on MPO in participants with metabolic risk factors.

Biomarkers of inflammation such as CRP, IL-6, and adhesion molecules ICAM-1 and VCAM-1 are significantly elevated in metabolic syndrome and positively associated with CVD (43,44). On the other hand, adiponectin, an antiinflammatory cytokine, is significantly decreased in metabolic syndrome and inversely related to CVD (45). The antiinflammatory effects of berries have been suggested by limited epidemiological observations. The Women's Health Study showed a borderline significant risk reduction of elevated CRP ( $\geq 3$  mg/L) among women consuming higher amounts of strawberries [ $\geq 2$  servings/wk (150 g/wk)], whereas blueberry intake had no significant association with risks of CVD, including CRP levels (46). Analyses of NHANES data (1999–2002) also revealed a significant inverse association between serum CRP and anthocyanin intakes among U.S. adults (47). In our study, changes in plasma levels of adhesion molecules, CRP, IL-6, and adiponectin did not differ between the blueberry and control groups. In a recently reported study, Curtis et al. (48) showed similar null effects of elderberry anthocyanin extracts on inflammatory biomarkers such as CRP and IL-6 in healthy postmenopausal women in a 12-wk study. Thus, longer study duration or a higher dose of berry polyphenols may be needed to lower inflammatory

biomarkers. Berry extracts or anthocyanin treatment has been shown to reduce inflammation-related parameters in animal and cellular models (14,15). Thus, further investigation is needed to define the antiinflammatory effects of berries or anthocyanins in cases of obesity and metabolic syndrome.

Certain limitations of our study include a cohort comprised primarily of women, the side effects and drop-outs following blueberry intervention, and the absence of a dose-response treatment. The gastrointestinal side effects were anticipated as a result of additional fiber intake in the form of a concentrated berry powder, especially in our participants with habitual low fiber and fruit intakes (Supplemental Table 2) (30). Though it led to a 27% drop-out rate in the blueberry arm, those who completed the entire 8-wk study also experienced this temporary gastrointestinal discomfort during the first week, which was later alleviated, and participants reported high compliance to the blueberry beverage. For future studies, administration of reconstituted freeze-dried blueberries in 3 or 4 doses throughout the day, or using 2 cups conventional frozen blueberries, as well as dietary adjustments for total fiber intake may have improved tolerability while exerting similar health benefits. Also, we did not detect parent anthocyanins or metabolites in serum samples as a measure of compliance, mainly because blood draws were conducted in a 10- to 12-h fasting state, which allows complete clearance and excretion of anthocyanins (49). Finally, our control group was consuming plain water to match the fluid intake of the intervention group, whereas a fiber- and energy-matched control beverage may lead to better elucidation of the role of polyphenols in the observed health effects of berries.

In conclusion, our study findings suggest a cardio-protective role of dietary achievable doses of blueberries in men and women with metabolic syndrome, which includes a significant decrease in systolic and diastolic blood pressures and plasma ox-LDL and lipid peroxidation. Our clinical data are supported by previously reported mechanistic studies and limited human intervention studies using single or mixed berries or anthocyanin extracts. However, our findings specifically show the cardio-protective effects of blueberries in improving features of metabolic syndrome. These results warrant further investigation and provide some evidence for including blueberries as part of healthy dietary practices.

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A.B., C.E.A., and T.J.L. designed the intervention study; M.D., M.J.L., K.S., M.W., and A.B. conducted research and laboratory measurements; C.E.A. and N.M.B. analyzed data; and A.B., C.E.A., and T.J.L. wrote the paper. All authors read and approved the final manuscript.

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