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Cranberry Juice Consumption Lowers Markers of Cardiometabolic Risk, Including Blood Pressure and Circulating C-Reactive Protein, Triglyceride, and Glucose Concentrations in Adults[1–4]

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Abstract

Background: Cardiometabolic risk is the risk of cardiovascular disease (CVD), diabetes, or stroke, which are leading causes of mortality and morbidity worldwide.

Objective: The objective of this study was to determine the potential of low-calorie cranberry juice (LCCJ) to lower cardiometabolic risk.

Methods: A double-blind, placebo-controlled, parallel-arm study was conducted with controlled diets. Thirty women and 26 men (mean baseline characteristics: 50 y; weight, 79 kg; body mass index, 28 kg/m^2) completed an 8-wk intervention with LCCJ or a flavor/color/energy–matched placebo beverage. Twice daily volunteers consumed 240 mL of LCCJ or the placebo beverage, containing 173 or 62 mg of phenolic compounds and 6.5 or 7.5 g of total sugar per 240-mL serving, respectively.

Results: Fasting serum triglycerides (TGs) were lower after consuming LCCJ and demonstrated a treatment × baseline interaction such that the participants with higher baseline TG concentrations were more likely to experience a larger treatment effect (1.15 ± 0.04 mmol/L vs. 1.25 ± 0.04 mmol/L, respectively; $P = 0.027$). Serum C-reactive protein (CRP) was lower for individuals consuming LCCJ than for individuals consuming the placebo beverage [ln transformed values of 0.522 ± 0.115 ln(mg/L) vs. 0.997 ± 0.120 ln(mg/L), $P = 0.0054$, respectively, and equivalent to 1.69 mg/L vs. 2.71 mg/L back-transformed]. LCCJ lowered diastolic blood pressure (BP) compared with the placebo beverage (69.2 ± 0.8 mm Hg for LCCJ vs. 71.6 ± 0.8 mm Hg for placebo; $P = 0.048$). Fasting plasma glucose was lower ($P = 0.03$) in the LCCJ group (5.32 ± 0.03 mmol/L) than in the placebo group (5.42 ± 0.03 mmol/L), and LCCJ had a beneficial effect on homeostasis model assessment of insulin resistance for participants with high baseline values ($P = 0.035$).

Conclusion: LCCJ can improve several risk factors of CVD in adults, including circulating TGs, CRP, and glucose, insulin resistance, and diastolic BP. This trial was registered at clinicaltrials.gov as NCT01295684. *J Nutr* 2015;145:1185–93.

Keywords: polyphenol, flavonoid, cardiovascular disease, blood lipids, diabetes, inflammation

Introduction

Cardiometabolic risk is a term that refers to a clustering of physiologically related conditions, including cardiovascular disease (CVD)[7], diabetes, and stroke. These are 3 diseases that pose great risk to adults in the developed world and are modifiable by lifestyle changes. CVD is the leading cause of death worldwide (1), accounting for almost 930,000 deaths annually in the United States (2) and >4 million deaths annually in Europe (3). Diabetes is a considerable risk factor of CVD, and its prevalence continues to rise in the United States and around the world. In the United States, nearly 26 million people have diabetes (4). The WHO estimated the worldwide prevalence of

[1] Supported by Ocean Spray Cranberries, Inc., and the USDA. C Khoo and Ocean Spray Cranberries, Inc., provided the beverages used in this study and were involved in discussions about the design but were not involved in the conduct, analysis, or interpretation of the results.

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[3] Mention of trade names or commercial products in this publication is solely for the purpose of providing specific information and does not imply recommendation or endorsement by the USDA.

[4] Supplemental Table 1 is available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.

[7] Abbreviations used: BP, blood pressure; CRP, C-reactive protein; CVD, cardiovascular disease; LCCJ, low-calorie cranberry juice; MTP, microsomal transfer protein.

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diabetes in 2000 was 171 million, with the expectation of it reaching 366 million by 2030 (5).

Lifestyle modification is a long-recognized approach to lowering incidence of chronic disease. Consuming flavonoids and other polyphenols is a simple and potentially heart healthy lifestyle modification. Cranberries are rich in a number of polyphenols, including procyanidins, quercetin, myricitrin, and anthocyanins (6), several of which have been associated with reducing biomarkers of chronic disease risk, particularly risk of heart disease. Quercetin has been shown effective in reducing blood pressure (BP) in animal models (7–10) as well as in humans (11–13). Procyanidin-rich extracts have reduced C-reactive protein (CRP) in rats fed a high-fat diet (14, 15). In addition, procyanidin-rich grape seed extract has been shown to inhibit foam cell formation in vitro (16). Myricitrin is capable of interfering with atherosclerotic plaque development in an apoE deficient mouse model (17). Anthocyanin-rich products have lowered TGs in animal models (18–20) and inflammatory factors in human studies (21, 22).

An analysis of NHANES 2005–2008 data demonstrated that a significantly higher proportion of cranberry beverage consumers were predicted to be normal weight (BMI < 25 kg/m^2; P = 0.001) with lower waist circumferences (P = 0.001) and had significantly lower TGs and CRP (23). However, past human intervention studies targeting the role of cranberry products in protecting against cardiometabolic risk have produced a mix of positive (24–31) and null results (24, 32). Reasons for inconsistent results may be the short length of some of the trials, small sample size, and the lack of a fully controlled diet or appropriate control. We conducted a double-blind, placebo-controlled, parallel-arm, human intervention study with low-calorie cranberry juice [LCCJ; 40 kcal per reference amounts customarily consumed as defined in the 21 Code of Federal Regulation, sections 101.60(b) and 101.12] that was longer in length than previous studies and that included a fully controlled diet. Biomarkers of cardiometabolic risk, including serum total cholesterol, LDL cholesterol, HDL cholesterol, TGs, and high-sensitivity CRP, BP, fasting plasma glucose, and fasting serum insulin, were measured before and after the intervention.

Methods

Volunteers. Potential volunteers were recruited from the Washington, DC, metropolitan area to participate in a controlled feeding study. Study volunteers were aged 25–65 y with a BMI between 20 and 38 kg/m^2, nondiabetic, nonsmokers, and in basic good health, with fasting TGs < 3.39 mmol/L (300 mg/dL). Potential volunteers were excluded if any of the following applied: use of cholesterol-lowering medications, use of BP medications, history of bariatric or weight-loss surgery, recent weight loss, history of gastrointestinal or malabsorption disorders, kidney disease, liver disease, gout, hyperthyroidism, untreated or unstable hypothyroidism, cancer, pancreatic disease, or other metabolic disorders. Eligibility was determined by routine blood and urine screening and health history questionnaire. All procedures were approved by the MedStar Health Research Institute Institutional Review Board (Hyattsville, MD) and were conducted in accordance with the Helsinki Declaration of 1975 as revised in 1983. Volunteers provided written informed consent after attending an informational meeting and before screening. Sixty subjects were enrolled according to a power calculation for LDL cholesterol based on data previously collected in our laboratory. Subjects were assigned to 1 of 2 treatment groups using an adaptive randomization method to achieve balance in sex, BMI, age, and LDL cholesterol at baseline. This trial was registered at clinicaltrials.gov (NCT01295684).

TABLE 1 Composition of cranberry juice and placebo treatment beverages[1]

	Treatment beverage	
	Placebo	Cranberry juice
Energy, kcal	40	40
Sugar, g	7.5	6.5
Sucrose	0.1	0.1
Fructose	5.6	4.6
Dextrose	1.7	1.8
Ascorbic acid, mg	60	60
Organic acids, mg	1.7	2.1
Total phenolics, mg	62	173
Anthocyanins, mg	0	10.3
Proanthocyanidins, mg	0	118

[1] Values represent content per 240-mL serving with 2 servings (480 mL) consumed daily.

Design. The study was a placebo-controlled, double-blind, parallel-arm study with 2 treatment groups. Volunteers consumed LCCJ or a color/flavor/energy–matched beverage for 8 wk as part of a controlled diet. Beverage products (240 mL/bottle) were supplied by Ocean Spray Cranberries, Inc., and the products were differentiated by labels marked in the colors blue or green but were otherwise identical in all other aspects including bottle shape, size, and color. Neither the investigators nor the participants knew which product was cranberry juice vs. placebo, and the product code was not lifted until all analyses were complete and the data set was locked. Compositions of treatment beverages are shown in **Table 1**. Volunteers consumed 2 bottles of beverage product daily for a daily total of 480 mL, which provided a total of 80 kcal. During weekdays, treatment beverages were supplied at breakfast and dinner (240 mL at each meal) so that the products could be consumed under supervision of study staff. On weekends, products were consumed off-site, and empty bottles were returned to the USDA Nutrition Center as a check of compliance. All analyses were completed before the blinding code was revealed.

Diets. Complete diets were provided to study volunteers, and volunteers were instructed to eat all foods and only foods provided to them by the USDA Nutrition Center. Background diets provided 15% energy protein, 32% energy fat, and the remainder from carbohydrate, and all foods were scaled in 836-kJ (200 kcal) increments to meet individual energy requirements so that volunteers neither gained weight nor lost

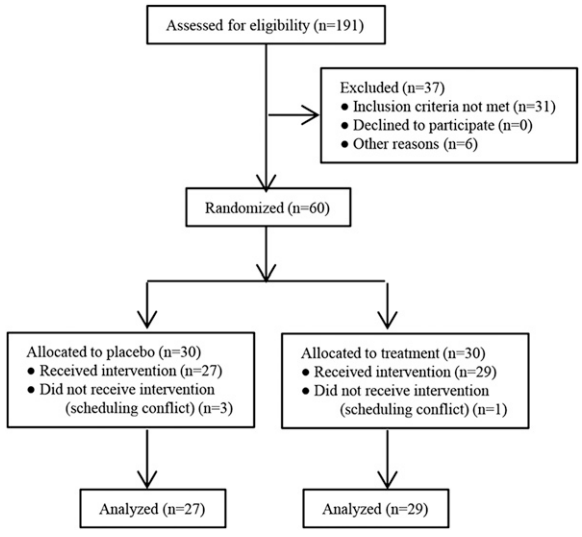

FIGURE 1 CONSORT diagram for study trial. CONSORT, Consolidated Standards of Reporting Trials.

TABLE 2 Characteristics of study volunteers at baseline[1]

	Treatment group			
	Placebo		Cranberry juice	
	Enrolled in intervention (n = 30)	Completed intervention (n = 27)	Enrolled in intervention (n = 30)	Completed intervention (n = 29)
Weight, kg	82.3 ± 5.4	82.2 ± 16.1	76.6 ± 13.9	76.6 ± 14.1
BMI, kg/m^2	28.9 ± 4.5	29.1 ± 4.7	27.8 ± 3.8	27.8 ± 3.9
Age, y	50.0 ± 11.6	51.3 ± 11.1	49.8 ± 11.1	49.8 ± 11.3
Men, n	14	12	15	14
Women, n	16	15	15	15

[1] Values for weight, BMI, and age represent means ± SDs. Statistical comparisons were made by ANOVA. No differences between groups were observed at baseline.

weight during the study (as confirmed by daily weighing). If patterns of weight gain or loss were observed, diets were adjusted such that weight maintenance was achieved. Background diets consisted of typical American foods, and 3–5 servings of fruits or vegetables daily (328–618 g/d depending on energy intake). The study food items are shown in **Supplemental Table 1**. Coffee and tea intake was limited to 2 cups/d (480 mL/d), which is similar to the mean US per capita intake of coffee and tea, both of which are <2 cups/d (33). Breakfast and dinner were consumed at the USDA Nutrition Center, and lunch and weekend meals were packed for carryout.

Clinical assessments and sample collection and analysis. BP measurements were taken in triplicate at the beginning and end of the study treatment period. Volunteers were asked to rest in a quiet, dimly lit

TABLE 3 BP and fasting serum lipids, lipoproteins, CRP, and adhesion molecules in adults at baseline and after 8 wk of consuming cranberry juice or placebo as part of a controlled diet[1]

		Baseline[3]		8 wk[4]		
		Treatment group		Treatment group		
	Analysis[2]	Placebo	Cranberry juice	Placebo	Cranberry juice	P[5]
Total cholesterol, mmol/L	Per Prot	5.09 ± 0.16	5.00 ± 0.13	5.09 ± 0.06	5.08 ± 0.06	0.93
	ITT	5.14 ± 0.18	4.98 ± 0.13	5.10 ± 0.05	5.09 ± 0.05	0.91
LDL cholesterol, mmol/L	Per Prot	3.25 ± 0.11	3.21 ± 0.11	3.28 ± 0.05	3.31 ± 0.05	0.67
	ITT	3.27 ± 0.12	3.21 ± 0.11	3.28 ± 0.04	3.31 ± 0.04	0.64
HDL cholesterol, mmol/L	Per Prot	1.24 ± 0.07	1.19 ± 0.05	1.27 ± 0.02	1.23 ± 0.02	0.18
	ITT	1.24 ± 0.06	1.19 ± 0.05	1.26 ± 0.02	1.23 ± 0.02	0.21
TGs,[6] mmol/L	Per Prot	1.28 ± 0.11	1.28 ± 0.10	1.25 ± 0.04	1.15 ± 0.04	0.027
	ITT	1.39 ± 0.17	1.28 ± 0.09	1.31 ± 0.04	1.18 ± 0.04	0.022
apo A-I, mg/dL	Per Prot	129.9 ± 3.6	127.6 ± 3.3	128.2 ± 1.4	127.4 ± 1.4	0.67
	ITT	130.7 ± 3.7	127.6 ± 3.2	129.0 ± 1.3	127.6 ± 1.3	0.47
apo A-II, mg/dL	Per Prot	30.6 ± 0.7	30.2 ± 0.7	29.4 ± 0.5	30.4 ± 0.5	0.14
	ITT	31.3 ± 1.0	30.2 ± 0.7	29.8 ± 0.5	30.6 ± 0.5	0.24
apoB, mg/dL	Per Prot	78.7 ± 3.2	78.8 ± 2.5	79.2 ± 1.3	79.6 ± 1.3	0.81
	ITT	79.8 ± 3.8	78.8 ± 2.4	79.7 ± 1.2	80.0 ± 1.2	0.85
sICAM, ng/mL	Per Prot	265.4 ± 15.8	263.0 ± 15.2	278.9 ± 7.9	263.6 ± 7.6	0.17
	ITT	277.7 ± 16.1	263.0 ± 14.7	284.7 ± 7.2	268.3 ± 7.2	0.11
sVCAM, ng/mL	Per Prot	471.3 ± 41.0	444.0 ± 29.2	451.5 ± 14.3	469.2 ± 13.8	0.38
	ITT	469.1 ± 37.3	444.0 ± 28.2	450.7 ± 13.1	468.1 ± 13.1	0.35
Diastolic BP, mm Hg	Per Prot	68.1 ± 1.5	73.9 ± 1.6	71.6 ± 0.8	69.2 ± 0.8	0.048
	ITT	68.4 ± 1.4	73.9 ± 1.6	71.5 ± 0.7	69.2 ± 0.7	0.11
Systolic BP, mm Hg	Per Prot	111.5 ± 2.4	121.9 ± 3.2	116.1 ± 1.1	115.2 ± 1.1	0.57
	ITT	111.9 ± 2.4	121.9 ± 3.1	116.3 ± 1.0	115.0 ± 1.0	0.41
CRP,[7] ln(mg/L)	Per Prot	0.800 ± 0.186	0.708 ± 0.0.180	0.997 ± 0.120	0.522 ± 0.115	0.005
	ITT	0.768 ± 0.176	0.724 ± 0.175	0.938 ± 0.113	0.539 ± 0.113	0.014

[1] BP, blood pressure; CRP, C-reactive protein; ITT, intention to treat; Per Prot, per protocol; sICAM, soluble intercellular adhesion molecule; sVCAM, soluble vascular cell adhesion molecule.
[2] Analyses were conducted Per Prot (analysis of volunteers who completed the intervention: n = 29 for cranberry juice, n = 27 for placebo) and ITT (analysis of all volunteers enrolled: n = 30 for cranberry juice, n = 30 for placebo).
[3] Values are means ± SEs from samples collected before dietary intervention (pretreatment).
[4] Values are least-squares means ± SEs from an ANOVA linear mixed model that included covariates of age, baseline (pretreatment), BMI, and sex.
[5] Values are for the placebo vs. cranberry juice comparison at 8 wk.
[6] For TGs, there was a significant baseline × treatment interaction (P = 0.0005 for ITT analysis) such that individuals with higher baseline TG concentrations had a greater lowering effect after consumption of cranberry juice.
[7] ANOVA of high-sensitivity CRP was based on log-transformed data. Back-transformed means (for volunteers completing intervention) are as follows: placebo baseline concentration of 2.23 mg/L, cranberry juice baseline concentration of 2.03 mg/L, placebo 8-wk concentration of 2.71 mg/L, cranberry juice 8-wk concentration of 1.69 mg/L.

room for 5 min. BP was then measured by an automated cuff 3 times at 2.5-min intervals. The mean of those 3 BP measurements was used for statistical analysis.

Blood was collected at the beginning and end of the study treatment period, on 2 different mornings separated by 1 d. Blood was collected after a 12-h fast by a certified phlebotomist using sterile blood collection supplies. Blood in serum separator tubes was allowed to sit at room temperature (25°C) for 30 min, and then serum was removed, immediately aliquoted into cryovials, and stored at −80°C until analysis. EDTA-coated vacutainers were centrifuged at 2000 × *g* for 10 min, and then plasma was removed, aliquoted into cryovials, and stored at −80°C until analysis. Blood for glucose analysis was collected in a tube containing sodium fluoride, immediately inverted, set on ice for ~10 min, and then stored in cryovials at −80°C until analysis.

Serum total, HDL and LDL cholesterol, and TG concentrations were determined by enzymatic procedures using a Vitros Clinical Chemistry Analyzer (Vitros 5,1; Ortho-Clinical Diagnostics, Inc.). Serum apo A-I, apo A-II, and apoB were measured by immunoturbidimetric assay (Bacton Assay Systems and Express 550 Plus analyzer, Siemens Healthcare Diagnostics). Serum IL-10, IL-1β, IL-6, TNF-α, and CRP were analyzed with sandwich-type immunoassay methods using electrochemiluminescence detection (Meso Scientific Discovery). Plasma glucose concentrations were determined using an automated enzymatic/colorimetric assay (Vitros 5,1). Serum insulin concentrations were measured using a sandwich-type immunoassay method (EMD Millipore Corp.) performed on a Dynex system (Dynex Technologies, Inc.). All analytes were measured in duplicate. HOMA-IR was calculated by the following equation: fasting glucose × fasting insulin/22.5 (34), where glucose was expressed in millimoles per liter and insulin was expressed in milliunits per liter. HOMA-β was calculated by the following equation: 20 × fasting insulin/(fasting glucose − 3.5) (34), where glucose was expressed in millimoles per liter and insulin was expressed in milliunits per liter.

Statistical analysis. A power calculation was based on data from previous studies in our laboratory. Our target detectable difference was a 10% change in LDL cholesterol. With anticipated mean LDL cholesterol of 110 mg/dL for the recruited population, we aimed to detect a difference of 11 mg/dL. Based on previous research in our laboratory with similar dietary interventions, we found an SD of the difference of treatment to be 12.5 mg/dL. A sample size calculation was performed for a 1-factor ANOVA for a parallel-arm study with 90% power to detect a change of 11 mg/dL at $P = 0.05$. Twenty-seven participants per group were needed, and 30 per group were enrolled to allow for attrition.

Values for analytes on the 2 blood days at the beginning or at the end of the intervention were averaged, and those mean values were used in the statistical analysis. To determine the effect of treatment (cranberry juice), statistical analyses were performed in SAS (version 9.3; SAS Institute, Inc.) using an ANOVA linear mixed model with covariates of age, baseline (pretreatment), BMI, and sex retained in all models. Interactions of these covariates with treatment were removed from the model if not significant. Data were tested for normality with the Shapiro-Wilk statistic and by inspection of stem-leaf plots and normal probability plots of residuals. The data for CRP were skewed and therefore were ln transformed before statistical analysis. Model effects are reported as least-squares means. A per protocol analysis was conducted to predict the true potential efficacy of cranberry juice for improving risk factors of cardiometabolic disease, and intention-to-treat analysis was performed to allow estimation of population effects in the presence of some noncompliance, with data for dropped participants handled by standard approaches (35).

Results

Of 191 individuals who completed a study application and informed consent form, 60 individuals were selected to participate in the study, and 56 completed the intervention (**Figure 1**). Four subjects dropped out because of scheduling difficulties. Twenty-nine volunteers finished the cranberry juice arm (15 women, 14 men), and 27 volunteers finished the placebo arm (15 women, 12 men). Characteristics of volunteers enrolled in the protocol and completing the protocol are shown in **Table 2**.

Serum total cholesterol, LDL cholesterol, and HDL cholesterol were not different after 8 wk of consumption of LCCJ compared with placebo (**Table 3**). In addition, serum apo A-I, apo A-II, and apoB were not different (Table 3). Serum TGs were lower for those consuming cranberry juice compared with placebo (Table 3). In addition, there was a baseline × treatment interaction such that individuals with higher baseline TG concentrations experienced a greater lowering of serum TG after consuming cranberry juice (**Figure 2**A). For volunteers with the highest baseline TG concentrations, there was a 0.54-mmol/L difference in TG concentration at the end of the intervention between cranberry juice and placebo consumption. Diastolic BP was lower for the cranberry juice group than for the placebo group, whereas systolic BP was not different (Table 3). Note that baseline systolic BP was different between the groups; however, the baseline values were included in the statistical model to account for this difference.

Several serum markers of inflammation were measured. Serum CRP was lower in the cranberry juice group than in the placebo group (Table 3). For the group of volunteers that completed

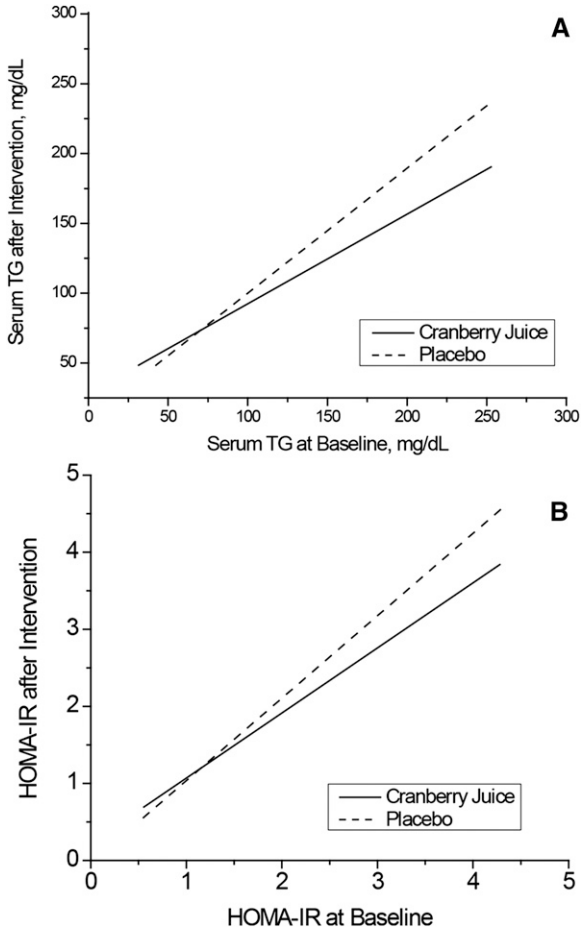

FIGURE 2 Relation between baseline serum TG concentration and postintervention TG concentration (A) and between baseline HOMA-IR and postintervention HOMA-IR (B) in adult volunteers who consumed cranberry juice or placebo as part of a controlled diet for 8 wk. Cranberry juice had a TG-lowering effect for volunteers with baseline TG concentrations and lowered the HOMA-IR for volunteers with high baseline concentrations.

the intervention, the log-transformed values back-transform to 1.69 mg/L for LCCJ (95% CI: 1.35, 2.11) and 2.71 mg/L for placebo (95% CI: 2.14, 3.43). The median CRP concentrations at 8 wks were 1.47 mg/L for LCCJ vs. 2.63 mg/L for placebo; thus, median CRP concentrations for participants consuming cranberry juice were 44% lower than those for participants consuming the placebo. Other serum markers of inflammation (IL-6, IL-10, IL-1β, and TNF-α) were not significantly different between groups.

The group consuming the LCCJ had significantly lower fasting plasma glucose concentrations than the group consuming the placebo (**Table 4**). Fasting serum insulin was not significantly different between groups. For HOMA-IR, there was a significant baseline × treatment interaction such that individuals with higher baseline HOMA-IR concentrations experienced a greater lowering of HOMA-IR after consumption of cranberry juice (Figure 2B). Thus, with increasing baseline HOMA-IR, there was greater improvement of insulin sensitivity for the group consuming cranberry juice than for the group consuming placebo. HOMA-β was not significantly different between groups (Table 4).

The intention-to-treat analysis suggested a trend that did not reach statistical significance for lower soluble intercellular adhesion molecule concentrations when consuming cranberry juice ($P = 0.11$; Table 3). Concentrations of soluble vascular cell adhesion molecule did not differ between groups.

Discussion

Heart disease kills more people throughout the world than any other cause of death (1). Polyphenols hold promise for lowering risk of CVD (36, 37). In our study, consumption of an LCCJ for 8 wks resulted in lowering of several CVD risk factors, including diastolic BP, CRP, TGs, blood glucose, and HOMA-IR, with a trend for improved soluble intercellular adhesion molecule.

In the present study, participants consuming LCCJ had lower diastolic BP after 8 wks than those consuming the placebo, which is in accord with other intervention studies of polyphenol-rich products (38–42), although a few other studies showed no effect (29, 43–46). Animal studies support these findings. One study showed that BP dropped in vasculature of anesthetized rats when infused with dilute buffered cranberry juice (47), and another study showed that cranberry juice prevented a high-fat diet–induced increase in BP in hamsters (48). One mechanism may be decreased angiotensin-converting enzyme, as suggested by human studies with pomegranate juice (38) and chokeberry extract (40) and by in vitro studies with polyphenols (49–55). Cranberries are a good source of quercetin (6), which has also been shown to reduce BP both in humans (11–13) and in animal models (7, 9, 10). Proposed mechanisms include reduction of oxidative stress (56–59), improved endothelium-dependent vasodilation (56, 58, 59), and inhibition of angiotensin-converting enzyme I (60, 61), an important target in hypertension therapy (49, 62). The magnitude of the change in BP observed in this study is consistent with that obtained with recommended dietary patterns to reduce BP, such as the Dietary Approaches to Stop Hypertension Trial diet (63) or with a low-sodium diet (64). The magnitude of the change observed in the current study could be associated with a 15% decrease in risk of stroke and a 10% decrease in risk of coronary heart disease (65).

Cranberry juice lowered TGs, in accord with other studies, including a study in which grape powder decreased TGs after 21 d (66). NHANES 2005–2008 data showed that cranberry juice consumers had significantly lower TGs than nonconsumers (23). In rodent models, TGs were lowered by quercetin (67), lyophilized grape (68), and green tea polyphenols (69). One possible mechanism is inhibition of microsomal TG transfer protein (MTP) (67, 69–72), which would prevent assembly of apoB-containing lipoproteins (chylomicrons and VLDL), but this would also be expected to decrease total cholesterol, LDL cholesterol, and apoB. The magnitude of TG change seen in this study is consistent with other dietary interventions used to lower TGs, such as eliminating *trans* FAs, replacing carbohydrates with MUFAs or PUFAs, or adding marine-derived PUFAs to the diet (73).

CRP was lower for volunteers consuming cranberry juice, as similarly seen in a group of men consuming purple-flesh potatoes (74). Analysis of NHANES 1999–2002 data demonstrated that CRP levels were inversely associated with total flavonoid intake, flavonol intake, quercetin intake, kaempferol intake, and

TABLE 4 Fasting glucose and insulin concentrations, HOMA-IR, and HOMA-β in adults after 8 wk of consuming cranberry juice or placebo as part of a controlled diet[1]

		Baseline[3]		8 wk[4]		
		Treatment group		Treatment group		
	Analysis[2]	Placebo	Cranberry juice	Placebo	Cranberry juice	P[5]
Fasting plasma glucose, mmol/L	Per Prot	5.36 ± 0.08	5.42 ± 0.08	5.42 ± 0.03	5.32 ± 0.03	0.03
	ITT	5.37 ± 0.07	5.41 ± 0.09	5.39 ± 0.03	5.26 ± 0.03	0.04
Fasting serum insulin, IU/mL	Per Prot	7.21 ± 0.82	7.39 ± 0.73	7.39 ± 0.32	7.36 ± 0.30	0.94
	ITT	7.21 ± 0.75	7.39 ± 0.72	7.38 ± 0.29	7.38 ± 0.30	0.99
HOMA-IR[6]	Per Prot	1.74 ± 0.20	1.80 ± 0.19	1.82 ± 0.08	1.76 ± 0.07	0.044
	ITT	1.74 ± 0.19	1.80 ± 0.19	1.81 ± 0.07	1.76 ± 0.07	0.036
HOMA-β	Per Prot	77.8 ± 8.1	78.3 ± 7.3	76.7 ± 3.6	82.5 ± 3.5	0.23
	ITT	77.8 ± 7.6	78.3 ± 7.0	77.1 ± 3.3	82.7 ± 3.3	0.24

[1] ITT, intention to treat; Per Prot, per protocol.
[2] Analyses were conducted Per Prot (analysis of volunteers who completed the intervention: $n = 29$ for cranberry juice, $n = 27$ for placebo) and ITT (analysis of all volunteers enrolled: $n = 30$ for cranberry juice, $n = 30$ for placebo).
[3] Values are means ± SEs from samples collected before dietary intervention (pretreatment).
[4] Values are least-squares means ± SEs from an ANOVA linear mixed model that included covariates of age, baseline (pretreatment), BMI, and sex.
[5] Values are for the placebo vs. cranberry juice comparison at 8 wk.
[6] For HOMA-IR, there was a significant baseline × treatment interaction such that individuals with higher baseline HOMA-IR concentrations had greater lowering of HOMA-IR after consumption of cranberry juice.

anthocyanidin intake (75), and NHANES 2005–2008 data showed that cranberry juice consumers had significantly lower CRP than nonconsumers (23). Possible active agents include quercetin, which lowered CRP in a human CRP transgenic mouse model and in a human-like lipoprotein mouse model (apoE-Leiden) (76), and procyanidins, which, when derived from grape seed, lowered CRP in obese Zucker rats fed a high-fat diet (14). Quercetin also suppressed cytokine-induced expression of CRP in Hep3B cells (77), and both quercetin and kaempferol inhibited gene expression and production of CRP in Chang liver cells (78). The median CRP concentration for participants consuming cranberry juice was 44% lower than that for participants consuming the placebo beverage. This decrease is similar to that seen in other studies, such as 32% lower CRP with a Mediterranean-style diet rich in MUFAs, PUFAs, and fiber (79), and 39% lower CRP with a Mediterranean-style weight-loss diet rich in complex carbohydrates (80).

Although the volunteers in this study had fasting blood glucose levels in the normal range, the volunteers consuming cranberry juice had lower fasting glucose at the end of the intervention than those consuming the placebo beverage. Cranberry juice also improved HOMA-IR for those with higher baseline values, suggesting improved glucose tolerance for those becoming insulin resistant. These findings are supported by animal models. In rats, supplementation of a high-fructose diet with cranberry powder lowered fasting glucose and insulin and improved HOMA-IR and β-cell function (81). In addition, cranberry polyphenols also lowered fasting insulin and HOMA-IR in obese mice fed a high-fat diet (82). In a prior placebo-controlled human feeding study of 42 diabetic adults, blueberry leaf extract, which, like cranberries, is high in myricetin, lowered fasting plasma glucose, whereas the placebo did not (83). However, a few other studies have not produced an effect of cranberry juice on glucose management (31, 84).

Multiple outcomes were tested for this study, which increases the possibility of false-positive results, and in this case, with 22 outcome variables tested, 1 false positive could be expected. A Bonferroni-adjusted P value cutoff for 22 tests would allow only a value of $P < 0.002$ to be declared significant, eliminating all 5 positive outcomes, despite the fact that the chance of 5 false-positive results is only 0.3%. For this reason, Bonferroni adjustments are dismissed by many scientists and statisticians as overly conservative because of their disproportionate increase in type II errors (85–89). For a study such as this with 22 outcome variables tested, only 1 false positive would be expected.

This study used an LCCJ that was sweetened with sucralose. Use of low-calorie sweeteners is on the rise in the United States (90, 91). Some early observational, associative, or animal studies with low-calorie sweeteners reported that such sweeteners may be detrimental to weight control (92–94). However, more recent studies have demonstrated that non-nutritive, low-calorie sweeteners are not associated with weight gain (95) but rather are beneficial for weight loss and weight maintenance (96, 97). In a recent clinical intervention trial, participants consuming non-nutritive sweetened beverages lost significantly more weight and reported less hunger than participants consuming water, the "gold standard" for hydration (96). Some studies, particularly rodent studies, have also suggested that non-nutritive, low-calorie sweeteners negatively impact glucose management (98, 99), and others have suggested the opposite (100–105). This human feeding study suggests that cranberry juice sweetened with sucralose has a positive impact on glucose management. Cranberry juice sweetened with sugar contains the same polyphenol content as LCCJ, contains among the highest concentration of polyphenols compared with other juices (106), and contains similar amounts of sugar compared with other juices on the market (106), although effects of sugar-sweetened juice were not tested here.

Dietary guidance has included a recommendation that the majority of fruit be consumed whole rather than as juice (107). However, because fresh cranberries are not typically consumed raw because of their tart and astringent taste and because cranberries are consumed almost entirely as juice in the US diet (108), our study used juice. It is unknown whether the benefits observed here would translate to whole fruit, which would provide fiber in addition to the polyphenols.

In conclusion, consumption of LCCJ for 8 wk resulted in lowering of several factors associated with cardiometabolic risk in an adult population. The magnitude of the significant changes is consistent with the magnitude of changes achieved with other dietary and lifestyle interventions. Lifestyle characteristics, such as consumption of healthful food items, should be encouraged to improve health, reduce incidence of chronic disease and associated morbidities, and ultimately lower health care costs. Consumption of high-polyphenol products such as cranberry juice is a sustainable lifestyle practice that holds notable promise for improving health.

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JAN, DJB, and CK designed the research; JAN, DJB, and SKG conducted the research; CSC performed the statistical analysis; JAN wrote the paper and had primary responsibility for the final content. All authors read and approved the final manuscript.

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