Blueberries improve biomarkers of cardiometabolic function in participants with metabolic syndrome-results from a 6-month, double-blind, randomized controlled trial

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BACKGROUND

- Metabolic syndrome (MetS) affects approximately one-third of Westernized populations and has been widely reported to increase the risk of type 2 diabetes, cardiovascular (CV) disease, and CV-related mortality.
- Blueberries and their main bioactive constituents (anthocyanins) have been identified as candidates to improve CV-related endpoints and the components of MetS.
- The clinical management of MetS is initially through lifestyle modifications, with statins and antihypertensive medications added to ongoing lifestyle guidance as MetS severity increases.
- Previous studies have shown that higher anthocyanin intakes are associated with lower all-cause mortality, reduced risk of type 2 diabetes and myocardial infarction, reduced insulin resistance and hypertension and lower weight gain.
- Identifying effective dietary approaches has clinical relevance throughout MetS progression, as a preventive strategy in nonmedicated individuals, and as an adjunct to those receiving standard pharmacologic therapies.

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AIM

- The aim of this study was to investigate the effects of 6-mo blueberry intake (at 2 dietarily achievable levels) on biomarkers of insulin resistance, vascular function, lipid status, and anthocyanin metabolism in adults with MetS.

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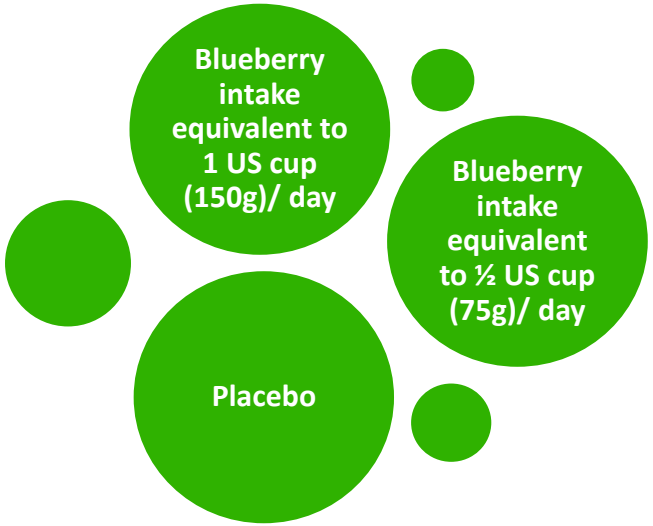
METHODS

Study design

- Double-blind, placebo-controlled, parallel study
- Overweight and obese (BMI≥25 kg/m2) adults, aged 50–75 y, with MetS (≥3 MetS components, i.e., impaired fasting glucose, hypertension, central adiposity, hypertriglyceridemia, and low levels of HDL cholesterol).
- Study duration: 6 months

Randomly assigned to 1 of 3 arms:



- The 3 types of intervention foods were isocaloric and carbohydrate-matched (glucose 31%, fructose 30%, sucrose 0%).
- 1-cup, ½ cup, and placebo treatments contained 364, 182, and 0 mg anthocyanin, and 879, 439, and 0 mg phenolics, respectively.

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METHODS

- Following a 21-d run-in period of dietary restrictions (e.g. blueberry abstinence), insulin resistance and cardiometabolic endpoints were assessed at baseline and 6-mo after intervention.

- A sub study of peripheral and hepatic insulin sensitivity was conducted on 20 consenting participants from the main study (n= 10 from each of the 1-cup blueberry and placebo groups).

Linear mixed-effect models were used to assess the effectiveness of the intervention, including “participant” as a random effect, time, and treatment group, with the time × treatment group interaction taken as the principal analysis of effect.

Primary outcome

– Change (Δ 0 to 6 mo) in insulin resistance (HOMA-IR).

Secondary outcomes

Changes (Δ 0 to 6 mo) in:

– Vascular function [flow-mediated dilatation (FMD), augmentation index (AIx), carotid-to-femoral pulse wave velocity (cfPWV), and blood pressure (BP)]

– Biomarkers of cardiometabolic health [lipid status, nitric oxide (NO) intermediates, glycated hemoglobin (HbA1c), and glucose]

– Blueberry (phenolic) metabolites.

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RESULTS I

- In total, 115 participants (age 63±7 y; 68% male; BMI 31.2±3.0 kg/m2) completed the study [n=37, n=39, n=39; 1 cup (150 g) blueberries, ½ cup (75 g) blueberries, and placebo, respectively].
- No favorable effects of the intervention were shown for the primary endpoint HOMA-IR or indices of glucose control (QUICKI, HbA1c) and peripheral, hepatic, and adipose tissue insulin sensitivity was unchanged (confirmed by clamp assessment in a subgroup).
- After 6 mo of 1 cup blueberries/d compared to other treatments:
  - %FMD significantly increased in the 1 cup group, compared to placebo. This FMD difference translates to a 13% reduction in future CV events. The ½ cup group showed no difference to placebo.
  - AIx was significantly reduced in the 1 cup group, but not in the ½ cup group, compared to placebo.
  - Mean plasma cyclic guanosine monophosphate (cGMP) concentrations significantly increased in the 1 cup group, but not in the ½ cup group, compared to placebo.
- The intervention had no effect on BP or other biomarkers of vascular function and systemic redox status (total free thiols).

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RESULTS II

- Relative to placebo, 1 cup increased HDL cholesterol levels significantly, with a trend towards a dose-related increase. When statin users were excluded, a significant difference in HDL cholesterol concentrations was observed between the 1-cup group and the placebo group.
- The 3.09-mg/dL (0.08-mmol/L) difference in HDL cholesterol between statin nonusers (when comparing 1 cup/day with placebo) would equate to 6.2–9.3% lower risk of coronary heart disease, 11.4–14.5% lower risk of CV disease (men and women, respectively).
- Both apoA-I and HDL-P, n were significantly increased (Δ 0 to 6 mo) in the 1-cup group compared with placebo ($P = 0.002$ and $P = 0.013$, respectively), in statin nonusers.
- No effect on total cholesterol and LDL cholesterol levels or the total cholesterol:HDL cholesterol ratio was observed, following intervention.
- In serum and 24-h urine, total concentrations of anthocyanin derived phenolic acid metabolites significantly increased (Δ 0 to 6 mo) following blueberry intake ($P<0.01$ and $P<0.001$, respectively; in a dose-dependent manner, compared with placebo).

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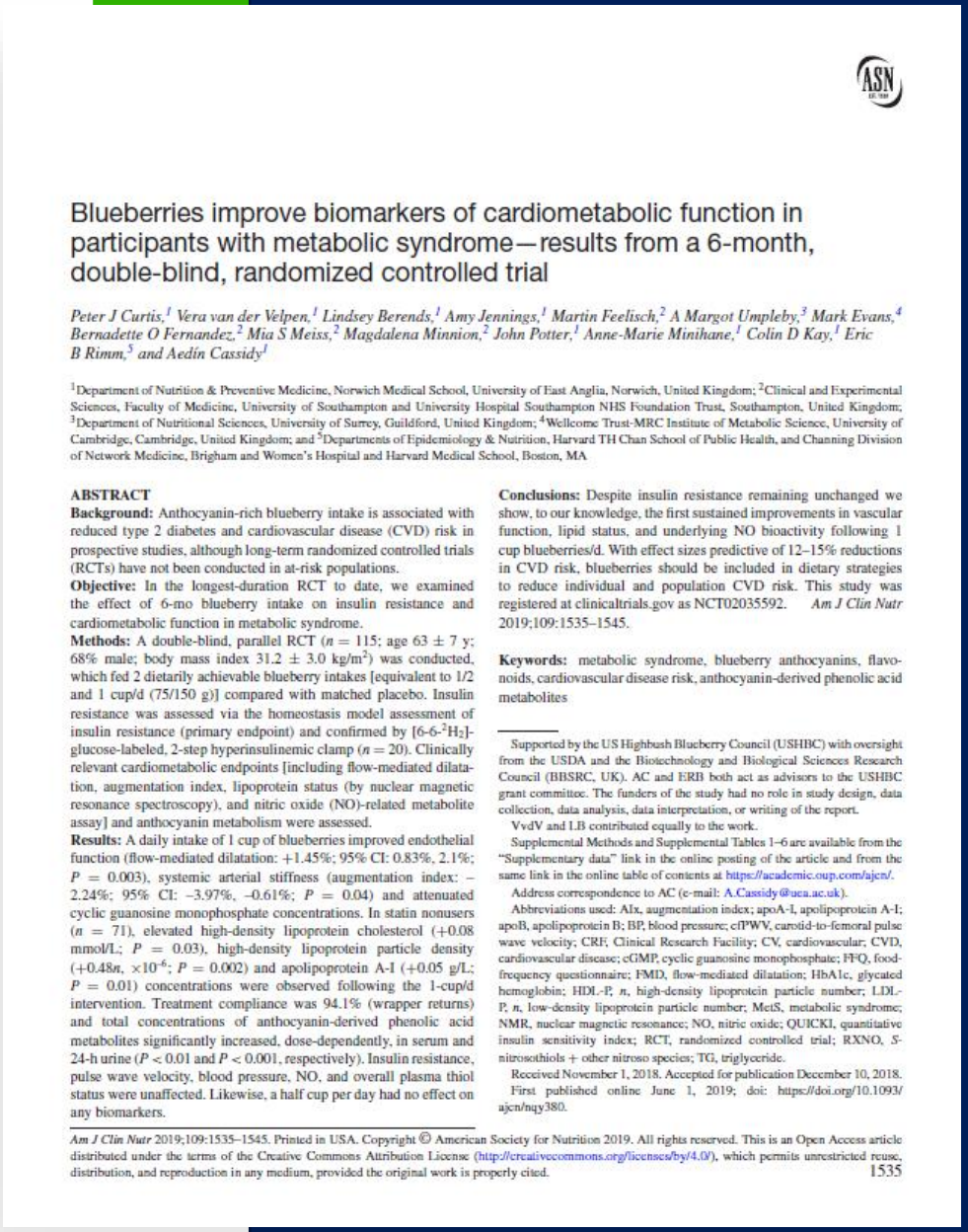
CONCLUSION

"Despite insulin resistance remaining unchanged we show, to our knowledge, the first sustained improvements in vascular function, lipid status, and underlying NO bioactivity following 1 cup blueberries/d. With effect sizes predictive of 12–15% reductions in CVD risk, blueberries should be included in dietary strategies to reduce individual and population CVD risk".



Blueberries improve biomarkers of cardiometabolic function in participants with metabolic syndrome—results from a 6-month, double-blind, randomized controlled trial

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ABSTRACT

Background: Anthocyanin-rich blueberry intake is associated with reduced type 2 diabetes and cardiovascular disease (CVD) risk in prospective studies, although long-term randomized controlled trials (RCTs) have not been conducted in at-risk populations.

Objective: In the longest-duration RCT to date, we examined the effect of 6-mo blueberry intake on insulin resistance and cardiometabolic function in metabolic syndrome.

Methods: A double-blind, parallel RCT ($n = 115$; age 63 ± 7 y; 68% male; body mass index 31.2 ± 3.0 kg/m^2) was conducted, which fed 2 dietarily achievable blueberry intakes [equivalent to 1/2 and 1 cup/d (75/150 g)] compared with matched placebo. Insulin resistance was assessed via the homeostasis model assessment of insulin resistance (primary endpoint) and confirmed by [6-6-^{2}H$_2$]-glucose-labeled, 2-step hyperinsulinemic clamp ($n = 20$). Clinically relevant cardiometabolic endpoints [including flow-mediated dilatation, augmentation index, lipoprotein status (by nuclear magnetic resonance spectroscopy), and nitric oxide (NO)-related metabolite assay] and anthocyanin metabolism were assessed.

Results: A daily intake of 1 cup of blueberries improved endothelial function (flow-mediated dilatation: +1.45%; 95% CI: 0.83%, 2.1%; $P = 0.003$), systemic arterial stiffness (augmentation index: −2.24%; 95% CI: −3.97%, −0.61%; $P = 0.04$) and attenuated cyclic guanosine monophosphate concentrations. In statin nonusers ($n = 71$), elevated high-density lipoprotein cholesterol (+0.08 mmol/L; $P = 0.03$), high-density lipoprotein particle density (+0.48n, $\times 10^{-6}$; $P = 0.002$) and apolipoprotein A-I (+0.05 g/L; $P = 0.01$) concentrations were observed following the 1-cup/d intervention. Treatment compliance was 94.1% (wrapper returns) and total concentrations of anthocyanin-derived phenolic acid metabolites significantly increased, dose-dependently, in serum and 24-h urine ($P < 0.01$ and $P < 0.001$, respectively). Insulin resistance, pulse wave velocity, blood pressure, NO, and overall plasma thiol status were unaffected. Likewise, a half cup per day had no effect on any biomarkers.

Conclusions: Despite insulin resistance remaining unchanged we show, to our knowledge, the first sustained improvements in vascular function, lipid status, and underlying NO bioactivity following 1 cup blueberries/d. With effect sizes predictive of 12–15% reductions in CVD risk, blueberries should be included in dietary strategies to reduce individual and population CVD risk. This study was registered at clinicaltrials.gov as NCT02035592. *Am J Clin Nutr* 2019;109:1535–1545.

Keywords: metabolic syndrome, blueberry anthocyanins, flavonoids, cardiovascular disease risk, anthocyanin-derived phenolic acid metabolites

Supported by the US Highbush Blueberry Council (USHBC) with oversight from the USDA and the Biotechnology and Biological Sciences Research Council (BBSRC, UK). AC and ERB both act as advisors to the USHBC grant committee. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

VvdV and LB contributed equally to the work.

Supplemental Methods and Supplemental Tables 1–6 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: AIx, augmentation index; apoA-I, apolipoprotein A-I; apoB, apolipoprotein B; BP, blood pressure; cfPWV, carotid-to-femoral pulse wave velocity; CRF, Clinical Research Facility; CV, cardiovascular; CVD, cardiovascular disease; cGMP, cyclic guanosine monophosphate; FFQ, food-frequency questionnaire; FMD, flow-mediated dilatation; HbA1c, glycated hemoglobin; HDL-P, n, high-density lipoprotein particle number; LDL-P, n, low-density lipoprotein particle number; MetS, metabolic syndrome; NMR, nuclear magnetic resonance; NO, nitric oxide; QUICKI, quantitative insulin sensitivity index; RCT, randomized controlled trial; RXNO, S-nitrosothiols + other nitroso species; TG, triglyceride.

Received November 1, 2018. Accepted for publication December 10, 2018.

First published online June 1, 2019; doi: https://doi.org/10.1093/ajcn/nqy380.

Article available at: https://pubmed.ncbi.nlm.nih.gov/31136659/