Dietary Total Isoflavone Intake Is Associated With Lower Systolic Blood Pressure: The Coronary Artery Risk Development in Young Adults (CARDIA) Study

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The effect of dietary isoflavone intake on systolic blood pressure (SBP) has not been studied in a large community-based cohort inclusive of African Americans. The authors analyzed data from the year 20 examination of the Coronary Artery Risk Development in Young Adults (CARDIA) study, including medical history, physical examination, and dietary intake surveys for 3142 participants. Multivariable linear regression models controlled for age, sex, body mass index, smoking, physical activity, and intakes of alcohol and total energy. Effect modification by race was tested. Overall, patients with hypertension had a lower daily intake of total dietary isoflavones (2.2±5.2 mg/d vs 4.1±11.7 mg/d; $P<.001$). In fully adjusted models, the highest quartile of dietary isoflavone intake was associated with a 4.4 mm Hg lower SBP on average compared with SBP for the lowest quartile. The relationship between dietary isoflavone intake and SBP was more pronounced among African Americans compared with Caucasians (P for interaction $<.001$). Greater dietary intake of isoflavones was independently associated with a lower SBP. *J Clin Hypertens (Greenwich).* 2016;18:778–783. © 2015 Wiley Periodicals, Inc.

Elevated blood pressure (BP) is a major public health concern. According to recent National Health and Nutrition Examination Survey data, approximately 29.3% of American adults have a diagnosis of hypertension.[1] Of these, only about half are being treated adequately.[1] This has a significant negative impact on the health of the nation, with hypertension contributing to one of every seven deaths in the United States. A healthcare system that could better treat the remaining half of hypertensive patients could avoid 46,000 deaths and more than $93.5 billion per year in direct and indirect costs.[2,3]

The impact of dietary composition in treating hypertension was demonstrated by the Dietary Approaches to Stop Hypertension (DASH) trial in 2001, where the DASH diet, with an intermediate sodium level, led to a 5.0 mm Hg lower mean systolic BP (SBP) compared with the control diet.[4] Intervention studies examining the BP-lowering effect of supplemental soy protein have suggested similar efficacy. Soy protein supplementation of 2040 g/d to 40 g/d has been shown in relatively small, randomized, controlled trials to lower BP in select populations.[5–7] Isoflavones, the suspected active ingredients in soy, were directly evaluated in a recent meta-analysis of 14 randomized controlled trials with a total of 789 nonhypertensive participants ingesting 25 mg to 375 mg of soy isoflavones for 2 to 24 weeks where SBP decreased, on average, by 1.9 mm Hg.[8] A separate meta-analysis inclusive of hypertensive participants showed a larger effect of isoflavones on SBP among hypertensive participants with a 5.9 mm Hg reduction on average.[9]

The relationship between dietary isoflavone intake and BP has not been studied in a population-based cohort inclusive of African Americans. This is a group that when compared with Caucasians is at higher risk for hypertension, with an earlier onset, and is more associated with severe end-organ damage, including left ventricular hypertrophy, renal failure, and stroke.[10,11] Our hypothesis was that there would be an inverse and dose-response relationship between dietary isoflavone intake and SBP, and this relationship would be modified by race.

METHODS

The Coronary Artery Risk Development in Young Adults (CARDIA) study is a prospective trial investigating the development and determinants of subclinical and clinical cardiovascular disease. The study began in 1985 to 1986 and enrolled 5115 African American and Caucasian men and women aged 18 to 30 years. Participants were selected so that there would be approximately the same number of people in subgroups of race, sex, education, and age in each of four centers: Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA. These participants were asked to attend follow-up examinations during years 2, 5, 7, 10, 15, 20, and 25. This cross-sectional study is limited to

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participants with nonmissing BP measurements and dietary data at year 20 (n=3142).

At the CARDIA year 20 examination, demographic information and other characteristics were collected from questionnaires and clinical measurements were performed. Age, sex, and smoking habits were ascertained through questionnaires. Positive smoking history was defined as daily smoking in adolescence and/or in adulthood. Body weight was measured with light clothing to the nearest 0.2 lb. Body height without shoes was measured to the nearest 0.5 cm. Body mass index (BMI) was calculated from these measurements (kg/m^2). Physical activity was measured using the interviewer-administered CARDIA Physical Activity questionnaire. The questionnaire asks about participation in 13 specific moderate- and vigorous-intensity activities over the previous year, including sports, exercise, home maintenance, and occupational activities. Each activity was assigned an intensity score (ranging from 3 to 8 metabolic equivalents) and a duration threshold (ranging from 2 to 5 h/wk) to calculate a total activity score. For an approximate reference, a total activity score of 300 exercise units approximates at least 150 minutes of moderate-intensity activity per week.[12] Hypertensive participants (defined as participants with SBP >140 mm Hg and diastolic BP >90 mm Hg based on three BP measurements, after 5 minutes of seated rest, obtained with an Omron oscillometer (Omron Healthcare, Inc, Lake Forest, IL); by a self-reported history of physician-diagnosed hypertension; or known to be taking antihypertensive medication) were included in this analysis.

At year 20, dietary intake was assessed by the interviewer-administered CARDIA Diet History, a validated dietary assessment tool querying 100 food questions, frequency, and portion size (including open-ended responses within each food question) to quantify daily nutrient and food intake.[13,14] Nutrient values were calculated based on frequency and portion size of food consumed and using the diet data entry software Nutrition Data System for Research (NDSR) developed at the University of Minnesota Nutrition Coordinating Center. Dietary sodium intake includes naturally occurring sodium in foods as well as that added during food processing. It does not include sodium from salt added at the table. Sodium values are in milligrams. Intake of isoflavones daidzein, genistein, and glycitein were summed for total isoflavone intake using NDSR methodology based on food table–derived isoflavone values in the United States Department of Agriculture Database for the Isoflavone Content of Selected Foods.[15] Quartiles of total isoflavone intake (mg/d) were created to evaluate for a possible dose-response relationship with BP. Total isoflavone intake quartiles were defined as: Q1: 0 mg/d to 0.33 mg/d, Q2: 0.34 mg/d to 0.73 mg/d, Q3: 0.74 mg/d to 2.50 mg/d, and Q4: 2.51 mg/d to 222.27 mg/d. Total energy (caloric) intake was calculated for each participant.

Statistical Analysis

Year 20 characteristics were computed as means (standard deviations) or frequencies (percentages) and differences tested using *t* tests or chi-square statistics, respectively, with the significance level set at $P<.05$. Characteristics of participants at each quartile of dietary isoflavone intake were compared using analysis of variance. Linear regression models for the overall cohort were fit to assess the association between SBP and daily total dietary isoflavone intake. A minimally adjusted linear regression model included only age and sex while our fully adjusted multivariable model included age, sex, BMI, smoking, physical activity, and intakes of alcohol, sodium, and total energy. Effect modification by race on the relationship between dietary isoflavone intake and SBP was tested by including the product total dietary isoflavone intake*race term in the model. In the presence of a significant interaction (*P* for interaction <.05), we performed a stratified analysis by race. We performed the following sensitivity analyses: (1) adjustment for education/income, (2) adjustment for animal protein or vegetable protein intake, (3) adjustment for potassium or fiber intake, (4) adjustment for dietary supplement use, and (5) adjustment for antihypertensive medication use. All analyses were performed using SAS version 9.3.4 (SAS Institute, Inc, Cary, NC).

RESULTS

The cohort was young to middle-aged, 56.9% were female, 46.6% were African American, and <20% had less than a high school education (Table I). Over a third of participants were either current or former smokers and over a third of the cohort was obese. Mean SBP for all participants was 115.5 mm Hg. One quarter of the cohort was hypertensive, with African American participants having twice the prevalence than Caucasians (36.5% vs 18.4%; $P<.0001$). Dietary isoflavone intake was significantly higher (by about 1.7 mg) among Caucasians ($P<.001$) vs African Americans and among those with higher education vs lower education ($P<.001$). Mean values for dietary intake of soy isoflavones in quartile 1, quartile 2, quartile 3, and quartile 4 were 0.2 mg/d, 0.5 mg/d, 1.3 mg/d, and 13.8 mg/d, respectively. In the highest quartile of dietary isoflavone intake compared with the lowest, there were fewer obese individuals, and adults tended to be more physically active (Table II).

An inverse, age-sex-energy intake–adjusted dose-response relationship was observed with dietary isoflavone intake and SBP, where each additional 10 mg of average dietary isoflavone consumption amounted to an average decrease of 1.0 mm Hg in SBP (Table III). Being in the highest quartile of dietary isoflavone intake compared with the lowest was associated with a 5.8 mm Hg lower SBP ($P<.0001$) (Table IV). In fully adjusted models, all relationships persisted, although attenuated, as being in the highest quartile of dietary isoflavone intake was associated with a 4.3 mm Hg lower SBP ($P<.0001$). Further adjustment in sensitivity

analysis for education, income, antihypertensive medication use, dietary supplement use, vegetable protein intake, animal protein intake, and fiber or potassium intake did not significantly affect the results (data not shown).

A statistically significant interaction was noted for dietary isoflavone intake and SBP by race (*P* for interaction <.001); therefore, we examined the dietary isoflavone-SBP relationship stratified by race. African American participants demonstrated significantly lower SBP values with higher dietary isoflavone intake compared with Caucasians. Each additional 10 mg of average dietary isoflavone consumption amounted to an average decrease of 1.0 mm Hg in SBP among African Americans (*P*=.02), whereas only an average decrease of 0.1 mm Hg was seen in SBP among Caucasians (*P*=0.76). Among African Americans there was a significant 4.4 mm Hg lower SBP comparing the highest quartile of dietary isoflavone intake with the lowest in age- and sex-adjusted models (*P*<.05) and a 3.7 mm Hg lower SBP in fully adjusted models (Table IV). Caucasians did not exhibit such a graded relationship between dietary isoflavone intake and SBP with a nonstatistically significant 1.6 mm Hg lower SBP in age- and sex-adjusted models comparing the highest quartile of dietary isoflavone intake with the lowest, which did not change appreciably in the fully adjusted models.

TABLE I. Demographic and Clinical Characteristics at Year 20: CARDIA

Variable (N=3142)	Mean (SD) or Percentage (No.)
Age at year 20 examination, y	45.2 (3.63)
Female	56.9% (1788)
African American	46.6% (1466)
Highest degree (high school, bachelors/masters, doctorate) (n=3140)	80.7% (2521)
Total isoflavone intake, mg/d	4.0 (11.3)
Physical activity (total intensity score) (n=3132)	335.2 (274.78)
Ever smoked (n=3119)	38.5% (1201)
Alcohol consumption, mL/d (n=3080)	10.5 (21.72)
BMI, kg/m^2 (n=3129)	29.4 (7.24)
Underweight (BMI<18.5 kg/m^2)	0.9% (28)
Normal (18.5 kg/m^2≤BMI<25 kg/m^2)	27.6% (863)
Overweight (25 kg/m^2≤BMI<30 kg/m^2)	33.3% (1041)
Obese (BMI ≥30 kg/m^2)	38.3% (1197)
Systolic blood pressure	115.5 (14.6)
Hypertensive	26.8% (843)

Abbreviations: BMI, body mass index; SD, standard deviation.

DISCUSSION

This is the first study to examine the effect of dietary isoflavone intake in a community-based cohort and separately among Caucasians and African Americans. Our findings show that SBP was 4.3 mm Hg lower among patients consuming the highest amount of isoflavones. The association was independent of age, sex, BMI, smoking, physical activity, and intakes of alcohol, sodium, and total energy intake. The results were modified by race, with a stronger benefit in African Americans. This is a potentially important finding since African Americans are at higher risk for hypertension with an earlier onset that is associated with more severe end-organ damage, including left ventricular hypertrophy, renal failure, and stroke, compared with Caucasians.[10,11] Our results have major implications for BP lowering on a population basis since isoflavones are readily available in several soy products. Dietary modalities to lower BP are important because they are less costly than medications and adherence may be better.

TABLE II. Participant Characteristics According to Dietary Isoflavone Intake at Year 20: CARDIA

Variable	Isoflavone Quartile 1 (n=764)	Isoflavone Quartile 2 (n=801)	Isoflavone Quartile 3 (n=789)	Isoflavone Quartile 4 (n=788)
Age at year 20 examination, y	44.8 (3.8)	45.2 (3.7)	45.2 (3.6)	45.6 (3.3)
Female, %	64.8	53.8	47.4	61.9
African American, %	67.4	49.3	39.2	31.4
Education, y	14.4 (2.5)	14.7 (2.6)	15.0 (2.6)	15.9 (2.5)
Physical activity (total intensity score)	266.4 (241.3)	311.0 (265.2)	346.5 (269.0)	414.8 (299.0)
Ever smoked, %	32.9	39.5	43.9	37.6
Alcohol consumption, mL/d	8.7 (23.1)	9.9 (15.5)	13.5 (28.3)	10.0 (17.6)
Total energy, kcal/d	1948.6 (965.6)	2386.1 (1067.1)	2718.1 (1604.5)	2547.7 (1444.6)
BMI, kg/m^2	31.1 (7.5)	29.9 (7.3)	29.10 (6.5)	27.7 (6.2)
BMI (n=3129), %				
Underweight (BMI <18.5 kg/m^2)	0.9	0.9	0.6	1.2
Normal (18.5 kg/m^2≤BMI<25 kg/m^2)	21.1	24.6	26.7	37.9
Overweight (25 kg/m^2≤BMI<30 kg/m^2)	27.4	34.6	37.9	33.0
Obese (BMI ≥30 kg/m^2)	50.7	39.9	34.8	28.0

Values are expressed as mean (standard deviation) or frequency (percentage).

TABLE III. Total Dietary Isoflavone Intake Relative to Systolic Blood Pressure at Year 20: CARDIA

	Regression Coefficient	SE	*P* Value		Regression Coefficient	SE	*P* Value		Regression Coefficient	SE	*P* Value
Soy intake (per 10 mg)	−1.1	0.2	<.0001	Soy intake (per 10 mg)	−1.0	0.2	<.0001	Soy intake (per 10 mg)	−0.6	0.22	.007
				Age	0.4	0.1	<.0001	Age	0.3	0.07	<.0001
				Female	−5.2	0.5	<.0001	Female	−5.6	0.55	<.0001
				Total energy intake, kcal	0.0003	0.0002	.09	BMI, kg/m^2	0.5	0.04	<.0001
								Smoking	1.6	0.53	.003
								Physical activity intensity score	−0.00038	0.00096	.69
								Alcohol, mL/d	0.04	0.01	.0008
								Total energy intake, kcal	0.001	0.0005	.008
								Sodium intake, mg	−0.0008	0.0003	.007

Abbreviations: BMI, body mass index; SE, standard error.

TABLE IV. Systolic Blood Pressure According to Quartile of Dietary Isoflavone Intake at Year 20: CARDIA (N=3142)

	Beta Estimate (Standard Error)					
	Overall		African Americans		Caucasians	
	Minimally Adjusted (N=3142)	Fully Adjusted (N=3038)	Minimally Adjusted (n=1465)	Fully Adjusted (n=1403)	Minimally Adjusted (n=1676)	Fully Adjusted (n=1635)
Average isoflavone intake, mg/d						
Quartile 1 (0–0.33)	–	–	–	–	–	–
Quartile 2 (0.34–0.73)	−3.2 (0.7)[a]	−3.0 (0.7)[a]	−2.7 (1.0)[b]	−2.8 (1.1)[b]	−0.7 (1.0)	−0.5 (0.9)
Quartile 3 (0.74–2.50)	−4.6 (0.7)[a]	−4.1 (0.7)[a]	−2.6 (1.1)[b]	−2.2 (1.2)	−2.0 (0.9)[b]	−2.1 (0.9)[b]
Quartile 4 (2.51–222.27)	−5.8 (0.7)[a]	−4.3 (0.9)[a]	−4.4 (1.2)[b]	−3.7 (1.3)[b]	−1.6 (0.9)	−0.8 (0.9)

[a]*P*<.0001. [b]*P*<.05. Fully adjusted model controlled for age, sex, body mass index, smoking, alcohol intake, physical activity, total energy, and sodium intake.

The consumption of soy protein is currently encouraged by the Food and Drug Administration, who support the claim that 25 g/d of soy protein, included in a diet low in saturated fat and cholesterol, may reduce the risk of coronary heart disease.[16] This recommendation is based on a meta-analysis of studies that found an association between increased soy intake and more favorable lipid profiles, specifically lower serum low-density lipoprotein and triglyceride and higher serum high-density lipoprotein levels.[17] Our data suggest that intake of isoflavones (organic compounds found primarily in soy) is associated with a significant BP-lowering effect. This association was independent of age, sex, weight, smoking, alcohol, physical activity, sodium contained in food, and total energy intake. SBP was, on average, 4.3 mm Hg lower among those who consumed the highest amount of dietary isoflavones compared with those who consumed the least amount, indicating a potentially significant additional cardiovascular benefit from dietary soy intake.

The effect of soy protein on BP has been previously evaluated in randomized controlled trials. In a study of 300 prehypertensive and untreated hypertensive Chinese adults, participants randomized to 40 g/d of isolated soybean protein supplement in the form of cookies showed a greater decrease in SBP than controls who received 40 g of complex carbohydrate.[5] The effect was particularly prominent among hypertensives where the SBP in the intervention group was 7.9 mm Hg lower compared with 2.3 mm Hg among those without hypertension. In another study, 60 healthy, postmenopausal women were randomized to 8 weeks of either a Therapeutic Lifestyle Changes diet (consisting of 30% energy from total fat, 15% energy from protein, and 55% energy from carbohydrate, plus 1200 mg calcium per day and two fatty fish meals per week) alone or one in which soy nuts (containing 25 g of soy protein and 101 mg of aglycone isoflavones) replaced 25 g of non-soy protein.[6] The soy protein diet lowered SBP by 9.9% in hypertensive and 5.2% in normotensive patients compared with baseline SBP values. In a double-blind randomized trial of 40 hypertensive men and women, soymilk (500 mL twice a day for 3 months) in place of cow's milk was associated with

an SBP decrease of 17 mm Hg.[7] In a recent meta-analysis of 14 randomized controlled trials with a total of 789 normotensive participants ingesting 25 mg to 375 mg of soy isoflavones for 2 to 24 weeks, SBP decreased on average by 1.9 mm Hg.[8] A separate meta-analysis by Liu and colleagues[9] of 11 trials with a daily intake of isoflavones of 65 mg to 153 mg showed a significant, larger effect of soy on SBP lowering among hypertensives (5.9 mm Hg).

Isoflavones, the suspected active ingredients in soy, are found in green tea, peanuts, tofu, and other plant foods. The mechanism behind the BP-lowering effect seen here that might be attributed to isoflavones could be through the activation of endothelial nitric oxide (NO) synthase (eNOS) and stimulation of NO production. Endothelial cells generate the potent vasodilator NO from L-arginine using NO synthases. Genistein, one of the primary isoflavones found in soy, has been demonstrated to have direct nongenomic effects on eNOS activity in human aortic endothelial cells, leading to eNOS activation and NO synthesis.[18] In healthy Caucasian postmenopausal women, increased soy consumption has been associated with higher plasma concentrations of NO.[19]

What may support NO as a possible mechanism for our findings is our finding of a stronger correlation between increased dietary isoflavone intake and lower SBP among African Americans. Most prior studies do not mention, and probably did not assess, racial makeup. It is unlikely that prior studies did not have a 46% African American constituency as we did. The inclusion of African Americans in our cohort likely drives the larger effects size seen for isoflavone intake on SBP lowering. Among hypertensives and normotensives, African Americans have been shown to exhibit relative endothelial dysfunction compared with Caucasians, which is marked by decreased endothelium-derived NO production and bioavailability.[20–22] Total eNOS protein appears to be increased in African Americans, but there is a lack of biologically active NO production.[23] It is possible that increased dietary isoflavone intake may indeed replete NO in this group, possibly altering the NO balance to help reverse the relative NO deficiency present in African Americans.

The importance of BP, especially SBP, as an independent risk factor for coronary events, stroke, heart failure, and chronic kidney disease is well-known.[24] Observational studies document a progressive and continuous increase in risk as SBP rises above 115 mm Hg.[25] There are several lifestyle interventions that have consistently been shown to lower SBP. Moderate dietary salt restriction results in a fall in SBP in hypertensive and normotensive individuals by 5.0 mm Hg and 2.0 mm Hg, respectively.[26] Weight loss of about 5.1 kg was shown in a meta-analysis of 25 trials to be associated with a mean drop in SBP of 4.4 mm Hg, where BP reductions were similar in hypertensive and normotensive patients.[27] Meta-analysis of SBP reductions with increased potassium intake showed reductions of 4.4 mm Hg and 1.8 mm Hg in hypertensive and normotensive patients, respectively.[28] Meta-analysis of 15 randomized controlled trials demonstrated that decreased consumption of alcohol reduced SBP by 3.3 mm Hg.[29]

In our study, high total dietary isoflavone intake was associated with 4.3 mm Hg lower SBP compared with low dietary isoflavone intake. This magnitude of effect, if supported by larger randomized controlled trials, would make increased dietary isoflavone intake similarly efficacious as dietary salt restriction or weight loss for controlling BP. Additionally, the high isoflavone content of soy products makes dietary supplementation a relatively effortless recommendation. An 8 oz glass of soy milk contains 6 g of soy protein and 22 mg of total isoflavones, and 100 g of roasted soybeans have as much as 35 g of soy protein and 130 mg of total isoflavones. Of course, although diets rich in soy or soy-containing products appear safe and potentially beneficial, the long-term safety of high doses of soy isoflavones is not yet known.[30]

STUDY STRENGTHS AND LIMITATIONS

The strengths of our study include the large biracial population, standardized BP measurements, and assessment of dietary intake using the CARDIA Diet History. To our knowledge, this is the first study to assess the relationship of dietary isoflavone intake and BP in a community-based cohort and separately among Caucasians and African Americans. We feel this difference is a significant part of what makes our findings interesting and noteworthy. The comprehensive population-based nature of our study increases the generalizability over prior smaller studies in select groups. There are, however, several limitations of our study. Cross-sectional studies do not establish a cause and effect relationship. One must take into account that there is no way to separate soy intake from living a healthier lifestyle. There are possible unmeasured confounders that we could not control for; however, the dose-response relationship on SBP as isoflavone intake increases and the consistent results seen in several multivariable models argue against our results being due solely to confounding. Although genistein and daidzein are major phytonutrients found in soy food products, it is possible that other components found in soy or unidentified non-soy factors that covary with isoflavone exposure could explain the observed decrease in BP. One cannot separate the chemical constituent from the whole food in this observational study, although our assessment of total isoflavone intake was food table–derived. Lastly, measurement error associated with nutrient estimates from the diet history could potentially underestimate any true association.

CONCLUSIONS

Our results suggest a possible BP benefit of moderate dietary intake of isoflavone-rich foods, including soy and soy products. There may be an increased benefit for

dietary intake of isoflavone-rich foods in African Americans. Our results have potential implications for BP lowering on a population basis and deserve further investigation. Because our finding was more pronounced in African Americans than in Caucasians, underrepresented minority participants should be included in future studies to better understand the association between isoflavone-rich food intake and BP.

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