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Dietary flavonoid intake is associated with weight modulation and obesity: The REasons for Geographic and Racial Differences in Stroke (REGARDS) study

By

Liang Ni

M.P.H., Emory University, 2019

Epidemiology

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Committee Chair

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Faculty Thesis Advisor: Terry Hartman, PhD, MPH, RD

An abstract of

A thesis submitted to the Faculty of the

Rollins School of Public Health of Emory University

in partial fulfillment of the requirements for the degree of

Master of Public Health

in The Epidemiology Department

2019

Abstract

Dietary flavonoid intake is associated with weight modulation and obesity: The REasons for Geographic and Racial Differences in Stroke (REGARDS) study

By Liang Ni

Background: Obesity is a major risk factor for many chronic diseases. Evidence suggests that intake of flavonoids, which are phenolic compounds with beneficial biochemical and antioxidant effects, might contribute to weight management. This study tests the hypothesis that intakes of total and subclasses of flavonoids are inversely associated with weight gain and incident obesity in older adults.

Methods: This study included 10,443 participants from the REGARDs study, a biracial cohort of community-dwelling adults aged 45 years and older. Baseline demographic and dietary information were collected at an in-home visit. Usual dietary intake was captured by the Block98 food frequency questionnaire and flavonoid intakes were estimated based on the USDA flavonoid databases. Weights of participants were measured at baseline and follow-up approximately 10 years later. The associations between flavonoid intakes and change in weight were assessed using marginal linear models controlling for potential confounders. The associations of flavonoid intakes with incident obesity were assessed in a subset of the cohort who were not obese at baseline (n=6,627) in multivariable logistical regression models.

Results: Weight change (mean ± SD) among the total population over 10 years was -1.7 ± 9.4 kg. Higher intakes of anthocyanins and flavanones were associated with more weight loss, with a significant linear trend for flavanone. A significant inverse association for anthocyanin intakes was observed in the obesity incidence analysis (OR for the second, third, fourth and fifth quintiles were 0.95 (95% CI: 0.74, 1.21), 0.86 (95% CI: 0.67, 1.1), 0.74 (95% CI: 0.58, 0.96), and 0.7 (95% CI: 0.54, 0.9), respectively, P for trend < 0.001). This association was significant among Caucasians, but not among African Americans, in stratified analysis. No significant results were found for total flavonoids or other flavonoid subclasses.

Conclusion: This study provides some evidence that flavonoid intake might be inversely associated with weight change.

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ACKNOWLEDGEMENTS

The Author would like to acknowledge Dr. Terry Hartman, Professor, Department of Epidemiology, Suzanne Judd, Associate Professor, Department of Biostatistics, University of Alabama at Birmingham, and Doratha Byrd, Postdoctoral Research Fellow, Metabolic Epidemiology Branch at The National Cancer Institute (NCI) for their continued inspiration, support, and encouragement.

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INTRODUCTION

More than two-thirds of U.S. adults are overweight or obese (body mass index [BMI] ≥25 and ≥30 kg/m^2, respectively) (1). Previous studies have reported that obesity is a risk factor for many common chronic diseases including cardiovascular disease, type 2 diabetes, certain forms of cancer, osteoarthritis and pulmonary disease (2). Weight gain in community-dwelling populations due to the cumulative effects of an imbalance between energy intake and expenditure can lead to an overall positive energy balance. Many dietary factors have been studied for their effects on weight change, including bioactive fatty acids, phenolic compounds, dietary fibers, plant sterols, and calcium (3).Some recent research has focused on flavonoids, bioactive polyphenols commonly found in fruits, vegetables, tea, herbs, and many other regularly consumed plant-based foods and beverages.

Previous studies have reported various beneficial biochemical and antioxidant effects of flavonoids and suggested that they might be associated with modulation of body weight (4, 5). Emerging evidence from both animal and human studies suggest that flavonoid intake may have a preventive effect on weight gain, although the specific mechanisms for the association remain unclear. A recent study in an animal model showed that body weight and body fat were lower when mice consumed high-fat diets supplemented with flavonoid extract (6). In a randomized clinical trial of 39 human participants who drank decaffeinated green tea (n=23) containing flavonoids or an herbal tea placebo (n=16) for 6 months, energy intakes of participants drinking

green tea was lower (-1096.5 ± 2059 (mean ± SD) kJ/d ~-262 kcal/d; P=0.02) than the placebo group (+37.7 ± 1934 (mean ± SD) kJ/d or ~+9 kcal/d; P=0.95) but the difference between groups failed to reach statistical significance (P=0.11) (7). This study also found weight loss among the green tea group while the placebo group experienced a slight weight gain, but again the difference between groups was not statistically significant (P=0.23). In a pooled analysis of three prospective cohorts including 124,086 US men and women, intakes of three flavonoid subclasses were inversely associated with weight gain (8). To standardize their results across flavonoids the investigators reported their results for each standard deviation increase in daily intake. Anthocyanins showed the strongest association (-0.23 (95% CI -0.30 to -0.15) lbs per 10 mg/d,), followed by total flavonoid polymers (-0.18 (95% CI -0.28 to -0.08) lbs per additional 138 mg/d), and flavanols (-0.16 (95% CI -0.26 to -0.06) lbs per additional7 mg/d)(8). Since all participants in the three cohorts were nurses and health professionals who were educated and primarily Caucasian, these results may not be widely generalizable. In addition, results were not reported for males and females separately.

To our knowledge, no published studies have examined the influence of race on the association of flavonoid intake with weight change. The REGARDS (Reasons for Geographic and Racial Differences in Stroke) study is a biracial prospective cohort study of more than 30,000 community-dwelling US men and women designed to investigate regional and racial disparities in stroke (9). We hypothesized that habitual flavonoid intake is associated with better weight management over ten-years follow-

up and this association might be modified by sex, race and baseline BMI. We propose to evaluate the role of dietary flavonoid and flavonoid subclass intakes with weight and weight change over time in this unique population. In addition, in exploratory analyses we will consider whether there are possible differences in association by sex, race, physical activity level and baseline BMI.

METHODS

Study population

REGARDS participants were 45 years or older, English-speaking, non-Hispanic white and black adults living in the continental United States and recruited between 2003 and 2007. The study population, with self-reported sex and race balanced by design, was oversampled from the "Stroke Belt" which refers to the southeastern states including Alabama, Arkansas, Georgia, Louisiana, Mississippi, Tennessee, North Carolina, and South Carolina. The final cohort consisted of 56% residents from the southeastern United States, 42% of participants were black, and 55% were women. Our study has the approval of the institutional review boards of all participating universities and written informed consent was obtained from all participants.

Baseline data were collected by using computer-assisted telephone interviews to obtain participants' health status and medical history. Standardized, quality-controlled protocols were used by trained health care professions for conducting exanimations at participants' home. During the in-home visit, participants was asked to complete a medication inventory and their fasting blood, urine samples, electrocardiograms, blood pressure, height and weight measurements were obtained. Participants with history of all prevalent cancers except skin cancer were excluded from the study.

Assessment of flavonoid intake

This study was interested in the intake of total flavonoid and six flavonoid

subclasses including anthocyanidins, flavan-3-ols, flavanones, flavone, flavanols, and isoflavones. The flavonoid intake of each participant was estimated based on the intake of foods that were collected from 2003 to 2007 by use of the Block98 foodfrequency questionnaire (FFQ). Two USDA databases, the USDA Database for the Proanthocyanin Content of Selected Foods and the USDA Provisional Flavonoid Addendum to the USDA Food and Nutrient Database for Dietary Studies (FNDDS), were used complementarily to provide the estimates of flavonoid intake as described previously (9). The Provisional Flavonoid Addendum is the latest comprehensive food flavonoid database, with data for 29 flavonoids in 6 subclasses for 7147 foods and beverages in the FNDDS and is updated every 2 years.

Assessment of weight change

The weight (in kg) of the participants was measured at the first in-home visit (baseline) and follow-up weight measured approximately 10-years later. Measurements were conducted by trained health care professions with standardized protocols to ensure the quality of the measures. A subset of the population for analyzing the association between obesity incidence during follow-up was obtained by excluding people with baseline body mass index (BMI) equal to or higher than 30 kg/m^3. Obesity during follow-up was estimated by observing the number of people from this subset who became obese.

Assessment of covariates

The covariates considered for analysis included participants' age at baseline,

sample regions (“stroke belt”, “stroke buckle”, and “non stroke belt”), smoking status (“past”, “current”, “never”), income (“less than $20k”, “$20k-$34k”, “$35k-$74k”, “$75k and above”, “$75k and above”), education (years), physical activity level (“None”, “1 -3 time/week” , “≥4 times/ week”), blood pressure (mm/Hg), intake of selected foods/nutrients at baseline including, total energy intake, dietary fiber, and percentage of energy from total fat. Diseases developed during the ten years of follow-up that can cause weight change, including heart disease(self-reported MI, CABG, bypass, angioplasty, stenting or evidence of MI), diabetes (fasting glucose>=126/non-fasting glucose>=200 mg/dL or use of pills or insulin), kidney failure (self-reported), and dyslipidemia (TC>=240 or LDL>=160 or HDL<=40 mg/dL or on medication) were also considered.

Statistical analysis

In the present study, participants who reported a history of cancer or who completed <85% of the FFQ were excluded from the analyses. Total and subclasses of flavonoid intakes were summarized and reported in quintiles after energy-adjustment using the residual method (10). We investigated the baseline characteristics of the participants based on the total flavonoid intake quintiles. Differences in baseline characteristics across quintiles were assessed using analysis of variance (ANOVA) for continuous variables and chi-square statistics for categorical variables. Marginal linear models (MLM) controlling for potential confounders were used to estimate the association between change in weight from baseline to approximately 10 years later

with the baseline intakes of total flavonoid and each flavonoid subclass. Estimates of weight change over time for each intake quintile were obtained by including the product term of flavonoids quintiles and time. In model 1, we adjusted for age and sex, then added smoking status, education, physical activity level, total energy intake, and self-reported diagnosis of diseases developed during follow-up in model 2 as the fully adjusted marginal model. Logistic regression models were used to estimate the association of flavonoid intakes at baseline and the development of obesity during follow-up. Model 1 adjusted for sex and baseline age and model 2 controlled for the same confounders as in the fully adjusted marginal linear model. A number of other potential covariates did not appreciably contribute to model fit or interpretation; thus, were not included in final models. Tests of linear trend were conducted in final multivariable models by entering the respective flavonoid intake variables in each model as a continuous variable. We evaluated interactions by race, sex, physical activity level and baseline BMI by including each individual factor and its cross-product term with continuous flavonoid variables in separate multivariable models and by stratification by race, sex, physical activity levels, and BMI at baseline. Analyses were conducted by using R version 3.4.3 and SAS version 9.4.

RESULTS

Overall, 10,443 participants were included in our analysis. Median (IQR) total flavonoid intakes were 244 mg/d (289 mg/d) for women and 249 mg/d (279 mg/d) for men. Median (IQR) total flavonoid intakes for Caucasian individuals were 267 mg/d (322 mg/d) and were 209 mg/d (225 mg/d) for individuals who were African Americans. Baseline population characteristics are summarized by quintiles of absolute total flavonoid intake in **Table 1**. Compared to those consuming diets lower in total flavonoids, those who consumed more flavonoids were more likely to be white and reported being more physically active and consuming higher total energy and fiber intakes, among other things. Baseline weight had a slightly decreasing trend across increasing quintiles of total flavonoid intake (83 kg quintile 5 vs. 84 kg quintile 1, $P < 0.001$). Prevalence of obesity at baseline also exhibited a decreasing trend across increasing quintiles of total flavonoid intake (33.7% quintile 5 vs. 41.8% quintile 1, $P<0.001$).

Figure 1. illustrates baseline and follow-up weight among our total study population, and among race and gender groups, respectively. During the ten years follow-up, mean body weight was reduced by 1.66 kg, while 814 participants became obese (12%). Less weight loss was observed among whites (-1.40 kg compared with -2.19 kg for blacks), and among men -1.27 kg (compared with -1.93 kg for women), respectively. The unadjusted differences in mean weight from baseline to follow-up and the differences in mean weight change between race and gender groups are all statistically significant ($P<0.05$).

The associations between weight change and flavonoid intakes are presented in **Table 2.** To show the influence of potential confounders, two marginal linear models were used with adjustment for age, sex and energy intake in model 1. Important confounders including lifestyle and self-reported disease development during follow-up were added in model 2. Results are presented by quintiles of intake for weight change from baseline to 10-year follow-up. The results from both model 1 and model 2 showed that people in the second, third, fourth and fifth quintiles of anthocyanin and flavanone intakes experienced significantly more weight loss compared to people in the lowest quintiles, but of these, a significant trend was observed only for flavanone in the fully adjusted model. People with the highest intakes of anthocyanin and flavanone experienced greater weight loss (differences in mean weight loss $Q_{5v.1}$=0.26 kg and 0.79 kg, respectively) compared to those with the lowest intake. Higher intakes of flavone and flavonol were associated with less weight loss, with significant linear trends. No associations were found between weight change and intakes of total flavonoids or other flavonoid subclasses.

The total flavonoid, anthocyanin, flavanone, flavan-3-ol and flavanone intakes had statistically significant interactions with race in the model (P-interaction all < 0.05); the results of the analysis on the association between weight change and these flavonoid intakes stratified by race are showed in **Table 3.** Generally, weight loss across quintiles of flavonoids was higher among African American than among Caucasians. After controlling for age, sex, baseline energy intake, and other identified confounders, higher intakes of anthocyanin and flavanone were associated with

weight loss among both Caucasians and African Americans; however, significant linear trends were only observed among Caucasians. We did not observe differences in association between weight change and total and flavonoid subclass intakes by sex, physical activity level or baseline BMI.

The associations of intakes of total and flavonoid subclasses with incident obesity over 10 years are presented in **Table 4.** There was an inverse association, with a significant linear trend between anthocyanin and obesity incidence after controlling for age, sex and baseline energy intake in model 1 which remained significant when further controlling for additional confounders in model 2. Inverse associations were also observed for flavanone and flavone with incident obesity models, although without significant trends. No associations were found between total flavonoids or other flavonoids subclasses and incident obesity.

We observed statistically significant interactions by race only for anthocyanin (P-interaction = 0.007) in the incident obesity analyses; the results for the associations between anthocyanin and incidence of obesity stratified by race are presented in **Table 5**. Overall, the results showed that compared to the lowest quintile of anthocyanin intakes, the odds of becoming obese decreased in the second, third, fourth and fifth quintiles among Caucasians with a significant linear trend, but not among African Americans. We did not observe differences in association between the development of obesity and total and flavonoid subclass intakes by sex, physical activity level or baseline BMI.

DISCUSSION

Our results suggest that intakes of anthocyanin and flavanone may be associated with weight loss during 10-years of follow-up; however, the magnitude of these associations may be small. Further, in stratified analyses, the association of flavanone intake with weight loss was significant in Caucasians, but not in African Americans, and the stratified results for anthocyanidin were not significant in either race. Consistent with the weight change results, we also observed a significant inverse association between anthocyanin intake and incident obesity. After stratification by race, this inverse association was only significant among Caucasians.

Relatively few prospective observational studies have evaluated the association of anthocyanin intake with obesity incidence or weight modulation. In a study including three large U.S. cohorts of health professionals with over 124,000 participants followed for four years, the authors observed that among seven flavonoid subclasses, the strongest association was observed for anthocyanins (-0.23 lbs per additional SD/d, 95% CI: -0.3 to -0.15) (8). Compared with our study, this pooled cohort study has a larger, relatively younger population (43.9 y v.63.1 y) and lower average intake of anthocyanins (8.3 mg/d v.13.0 mg/d) at baseline. Although the findings for anthocyanin in our study were not as strong as the pooled cohort study, we considered the potential effects of race. Another observational study based on the REGARDs cohort assessed the association between flavonoid intakes and incident coronary heart disease (CHD) and found a significant inverse association between anthocyanidin and proanthocyanin intakes and incident CHD (HRs for quintile 5 compared with quintile

1: 0.71; 95% CI: 0.52, 0.98; P-trend = 0.04; proanthocyanins: 0.63; 95% CI: 0.47, 0.84; P-trend = 0.02)(9). Increased BMI has been associated with higher risk of CHD across different populations of both sexes (11). Our finding of an inverse association of anthocyanin with weight gain and incident obesity could in part explain the protective association observed for anthocyanin intakes with incident CHD.

The results from clinical trials also provide some support for our findings. In a randomized clinical trial, 48 subjects who had metabolic syndrome and an average BMI of 37.8±2.3 kg/m^2, consumed a blueberry beverage containing 742 mg of total anthocyanidin daily. After 8 weeks, weight loss (-0.4 kg v. 0.5 kg for the control group) was observed in participants consuming the blueberry beverage, although the difference was not significant (12). In another randomized clinical trial, obese and insulin resistant participants who received a blueberry smoothie containing 668 mg anthocyanin daily had improved insulin sensitivity and increased plasma satiety hormones concentrations, compared to the placebo group (13). Improved insulin sensitivity could enhance the metabolism of blood sugar potentially avoiding body fat deposition. Increased satiety could modulate appetite preventing weight gain (14).

Our finding of a significant inverse association between anthocyanin and incident obesity among Caucasians, but not in African Americans, is a novel finding. In our study population, there were more Caucasian than African American participants in the higher quintiles of anthocyanin intake. For example, in the highest quintile of total flavonoid intake 75.2 % of participants were Caucasian, compared with 24.8% African Americans. Higher intakes among Caucasians may be contributing to the

differential association we observed.

The relationship of higher flavanone intakes with both weight change and incident obesity in our study is interesting. In our population, orange juice, oranges and grapefruit contributed most to flavanone intakes. Flavanones showed no preventive effect on weight change in the U.S. pooled cohort study (8). The mean intake of flavanone at baseline in our population was 25.8 mg/d which is lower than the flavanone intakes in the pooled cohort study (33.7 mg/d). Despite limited evidence in the literature suggesting a direct association between flavanone and weight modulation or obesity, evidence indicates that flavanone might have protective effects on oxidative stress, systemic inflammation (15), and hyperlipidemia (16). The association between flavanones and weight-related outcomes should be explored in future studies.

In contrast to our study, which found no association of flavonol intakes with weight change over time, previous studies have reported that flavanol may have favorable effects on weight modulation. The Netherlands Cohort Study investigators assessed the association between three flavonoid subgroups and BMI over a 14-year period in 4280 men and women. Women in the highest flavonoid intake group experienced significantly lower increases in BMI (BMI increased by 0.40 for total flavanols/flavones) compared with women in the lowest intake group (BMI increased by 0.95 for total flavanols/flavones, $P<0.05$ for the comparison between groups)(17). Although a meta-analysis on the anti-obesity effect of different flavonoids studied in controlled clinical trials concluded that flavanols have protective effects on weight

change in the overall population, of 24 studies included, only one study reported a significant favorable result (18). In addition, the flavonoids and flavonoid subclasses studied in the meta-analysis were mostly in the form of supplements. Therefore, further research regarding the association between flavanol and body weight is of interest.

A strength of this study is the large, biracial, geographically diverse cohort with a prospective design followed for 10 years. The flavonoid intakes were estimated comprehensively using a USDA databases with updated data for the U.S. population. Weights were measured by experienced health professions.

Our study also had some limitations. Since the The Block98 FFQ was not specifically desgined for the measurement of flavonoid intakes it may not have included all major food sources of flavonoids, leading to measurement errors. Another limitation of our study was that we only had weight data measured at two timepoints. As a result, we could not assess the role of flavonoid intakes on the rate of weight change. Marginal linear models were used to model the correlation between two timepoints, which assumes the rate of weight change across time is the same for each individual. Unfortunately, we were not able to analyse the covariance between multiple timepoints.

In conclusion, we found higher intakes of anthocyanin were modestly associated with more weight loss and inversely associated with the development of obesity among Caucasians. We also found that higer intakes of flavanone were assiciated with more weight loss, with a significant linear trend; but also only among Cacasians.

Further studies which are racially diverse and including multiple timepoints are needed to evaluate athe association between flavonoid intakes and weight modulation.

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TABLES AND FIGURE

Table 1.

Baseline characteristics for 10,443 participants without CHD at baseline in the REGARDS study 2006–2016, by quintile of total flavonoid intake1

	Quintile of total flavonoid intake					
	1	2`	3	4	5	P[2]
Total Flavonoids, mg/d, median	90.6	161.8	245.5	376.4	719.1	
n	2088 (19.99)	2089 (20)	2089 (20)	2089 (20)	2088 (19.99)	
Age, y	62.4 ± 8.21[3]	63.1 ± 8.55	63.2 ± 8.43	63.6 ± 8.45	63.1 ± 8.21	0.001
Energy intake, kcal	1332.9 ± 520.32	1590.1 ± 588.71	1791.3 ± 652.98	1912.3 ± 728.9	1976 ± 774.62	<0.001
BMI, kg/m^2	29.7 ± 6.34	29.1 ± 5.94	29 ± 5.86	29 ± 6.03	28.8 ± 5.8	<0.001
Weight, kg	85.5 ± 20.33	83.7 ± 18.62	83.8 ± 19.17	83.8 ± 18.34	83 ± 19	<0.001
Male, n (%)	881 (42.2)	858 (41.1)	893 (42.7)	900 (43.1)	850 (40.7)	0.451
White, n (%)	1257 (60.2)	1347 (64.5)	1403 (67.2)	1459 (69.8)	1681 (80.5)	<0.001
Diabetes, n (%)	389 (18.6)	332 (15.9)	329 (15.7)	336 (16.1)	322 (15.4)	0.122
Obesity[4], n (%)	873 (41.8)	750 (31.9)	724 (34.7)	765 (26.6)	704 (33.7)	<0.001
Education, n (%)						
Less than high school	182 (8.7)	117 (5.6)	115 (5.5)	118 (5.6)	126 (6)	<0.001
High school graduate	568 (27.2)	482 (23.1)	430 (20.6)	469 (22.5)	504 (24.1)	
Some college	580 (27.8)	556 (26.6)	549 (26.3)	545 (26.1)	579 (27.7)	
College graduate and above	757 (36.3)	934 (44.7)	994 (47.6)	957 (45.8)	879 (42.1)	
Physical activity, n (%)[5]						<0.001
None	737 (35.3)	612 (29.3)	560 (26.8)	528 (25.3)	554 (26.5)	
1 to 3 times per week	790 (37.8)	838 (40.1)	813 (38.9)	856 (41)	810 (38.8)	
4 or more per week	533 (25.5)	617 (29.5)	700 (33.5)	688 (32.9)	706 (33.8)	
Smoking status, n (%)						<0.001
Never	932 (44.6)	1012 (48.4)	1053 (50.4)	1044 (50)	1059 (50.7)	
Past	814 (39)	836 (40)	836 (40)	862 (41.3)	826 (39.6)	
Current	335 (16)	238 (11.4)	193 (9.2)	174 (8.3)	195 (9.3)	
Annual income, n (%)						<0.001
less than $20k	299 (14.3)	227 (10.9)	238 (11.4)	220 (10.5)	247 (11.8)	
$20k-$34k	494 (23.7)	481 (23)	408 (19.5)	494 (23.6)	427 (20.5)	
$35k-$74k	670 (32.1)	688 (32.9)	767 (36.7)	696 (33.3)	720 (34.5)	
$75k and above	379 (18.2)	461 (22.1)	478 (22.9)	462 (22.1)	458 (21.9)	
Refused	246 (11.8)	232 (11.1)	198 (9.5)	217 (10.4)	236 (11.3)	
Dietary fiber, g/1000 kcal/ d	8.5 ± 3.16	9.7 ± 3.68	10.3 ± 3.83	10.3 ± 3.87	10 ± 3.83	<0.001
Protein, %kcal	14.9 ± 3.46	15 ± 3.03	14.8 ± 2.93	14.6 ± 2.88	14.5 ± 3.06	<0.001

Fat, %kcal	39 ± 8.28	38 ± 7.57	37.1 ± 7.4	36.9 ± 7.47	37.3 ± 7.58	<0.001
Added sugars %kcal	15.7 ± 10.82	14.2 ± 9.02	13.6 ± 8.9	14.5 ± 8.85	16.2 ± 10	0.057
Saturated fat, g/1000 kcal/ d	12.8 ± 3.22	12 ± 2.8	11.6 ± 2.72	11.4 ± 2.68	11.7 ± 2.85	<0.001

1. Sum of absolute intake of anthocyanidin, flavan3-ol, flavanone, flavone, and flavonol intakes. a-TE, a-tocopherol equivalent; CHD, coronary heart disease; REGARDS, REasons for Geographic and Racial Differences in Stroke.

2 Data were analyzed by using ANOVA and chi-square tests for continuous and categorical variables, respectively.

3 Mean ± SD (all such values).

4 Obesity was defined as BMI≥30 kg/m^2

5 Answer to “How many times per week do you engage in intense physical activity, enough to work up a sweat

Table 2. Change in Weight (kg) from baseline to follow-up by quintile of energy-adjusted flavonoid intake for 10,443 participants in the REGARDS study[1]

	Quintiles of flavonoid intake					
	Q1	Q2	Q3	Q4	Q5	P-trend[2]
Total Flavonoids[3], mg/d	109.1 (-221.6, 148.9)[4]	178.9 (148.9, 210)	248.6 (210.1, 298.8)	367.7 (298.8, 481)	722.8 (481.1, 1899.5)	
Model1[1]	-1.43 ± 0.21	-2 ± 0.21	-1.7 ± 0.21	-1.7 ± 0.21	-1.44 ± 0.21	0.6682
Model2[2]	-1.8 ± 0.22	-2.21 ± 0.22	-1.79 ± 0.22	-1.79 ± 0.22	-1.72 ± 0.21	0.3989
Isoflavone, mg/d	0.4 (-0.5, 0.5)	0.6 (0.5, 0.7)	0.8 (0.7, 1)	1.2 (1, 1.5)	2.2 (1.5, 13.9)	
Model1	-1.84 ± 0.21	-1.82 ± 0.21	-1.76 ± 0.21	-1.66 ± 0.21	-1.19 ± 0.21	0.0253
Model2	-2.14 ± 0.21	-1.98 ± 0.22	-1.98 ± 0.22	-1.84 ± 0.22	-1.37 ± 0.22	0.0133
Anthocyanin, mg/d	4.1 (-8.5, 5.9)	7.3 (5.9, 8.8)	10.5 (8.8, 12.5)	15 (12.5, 18.7)	25.2 (18.7, 96.1)	
Model1	-1.14 ± 0.21	-2.12 ± 0.21	-1.67 ± 0.21	-1.7 ± 0.21	-1.66 ± 0.21	0.3434
Model2	-1.5 ± 0.22	-2.41 ± 0.22	-1.73 ± 0.22	-1.88 ± 0.22	-1.76 ± 0.22	0.9730
Flavan_3_ol, mg/d	5.3 (-116.6, 22.3)	34.6 (22.4, 46.6)	65.5 (46.6, 110.1)	191.5 (110.1, 277.3)	530.1 (277.3, 1338)	
Model1	-1.74 ± 0.21	-1.77 ± 0.21	-1.57 ± 0.21	-1.91 ± 0.21	-1.28 ± 0.21	0.2259
Model2	-2.02 ± 0.22	-1.88 ± 0.22	-1.77 ± 0.22	-2.07 ± 0.22	-1.57 ± 0.21	0.2967
Flavanone, mg/d	1.8 (-24.2, 5.6)	8.4 (5.6, 11.5)	16.5 (11.5, 23.6)	32.8 (23.6, 46.2)	57.1 (46.2, 341.6)	
Model1	-0.79 ± 0.21	-1.82 ± 0.21	-1.46 ± 0.21	-1.96 ± 0.21	-2.25 ± 0.21	<.0001
Model2	-1.24 ± 0.22	-2.06 ± 0.21	-1.56 ± 0.22	-2.15 ± 0.22	-2.29 ± 0.22	0.0014
Flavone, mg/d	0.4 (-0.5, 0.5)	0.6 (0.5, 0.7)	0.8 (0.7, 1)	1.2 (1, 1.5)	2.2 (1.5, 13.9)	
Model1	-1.59 ± 0.21	-2.02 ± 0.21	-2.08 ± 0.21	-1.39 ± 0.21	-1.2 ± 0.21	0.0307
Model2	-1.93 ± 0.22	-2.3 ± 0.22	-2.2 ± 0.22	-1.4 ± 0.22	-1.47 ± 0.22	0.0076
Flavonol, mg/d	8.4 (-9.8, 10.7)	12.6 (10.7, 14.5)	16.8 (14.5, 19.5)	22.7 (19.5, 27.4)	35.2 (27.4, 120)	
Model1	-2.03 ± 0.21	-1.9 ± 0.21	-1.89 ± 0.21	-1.38 ± 0.21	-1.1 ± 0.21	0.0003
Model2	-2.38 ± 0.22	-2.15 ± 0.22	-1.89 ± 0.22	-1.53 ± 0.22	-1.38 ± 0.21	0.0001

1 All values are Mean± SE. Results of Model 1 were derived from a marginal linear model adjusted baseline total energy intake, age and sex. Results of model 2 were derived from a marginal linear model adjusted for age, sex, race, exercise, education, smoking status, baseline total energy intake disease developed during follow-up.

2 P-trend values were derived from type 3 tests

3 Sum of anthocyanidin, flavan3-ol, flavanone, flavone, and flavonol intakes.

4 Median (range) (all such values).

Table 3. Change in Weight (kg) from baseline to follow-up by quintile of energy-adjusted flavonoid intake for 10,443 participants in the REGARDS study, stratified by race[1]

		Quintiles of flavonoid intake					
		Q1	Q2	Q3	Q4	Q5	P trend
Total Flavonoids, mg/d		109.1 (-221.6, 148.9)[2]	178.9 (148.9, 210)	248.6 (210.1, 298.8)	367.7 (298.8, 481)	722.8 (481.1, 1899.5)	
	Black	-1.99 ± 0.4	-3.09 ± 0.39	-2.47 ± 0.4	-2.45 ± 0.42	-1.95 ± 0.56	0.80
	White	-1.7 ± 0.26	-1.69 ± 0.26	-1.44 ± 0.26	-1.51 ± 0.25	-1.67 ± 0.23	0.81
Anthocyanin, mg/d		4.1 (-8.5, 5.9)	7.3 (5.9, 8.8)	10.5 (8.8, 12.5)	15 (12.5, 18.7)	25.2 (18.7, 96.1)	
	Black	-2.21 ± 0.44	-2.52 ± 0.39	-2.33 ± 0.41	-2.46 ± 0.42	-2.75 ± 0.48	0.51
	White	-1.19 ± 0.25	-2.35 ± 0.26	-1.45 ± 0.25	-1.62 ± 0.25	-1.45 ± 0.24	0.84
Flavan_3_ol, mg/d		0.1 (-1.2, 0.3)	0.4 (0.3, 0.5)	0.6 (0.5, 0.7)	0.8 (0.7, 1)	1.6 (1, 108.8)	
	Black	-2.42 ± 0.42	-2.61 ± 0.39	-2.5 ± 0.38	-2.53 ± 0.44	-1.88 ± 0.56	0.56
	White	-1.83 ± 0.25	-1.45 ± 0.26	-1.32 ± 0.26	-1.89 ± 0.24	-1.5 ± 0.23	0.75
Flavanone, mg/d		1.8 (-24.2, 5.6)	8.4 (5.6, 11.5)	16.5 (11.5, 23.6)	32.8 (23.6, 46.2)	57.1 (46.2, 341.6)	
	Black	-1.62 ± 0.51	-2.68 ± 0.46	-2.27 ± 0.41	-2.42 ± 0.4	-2.91 ± 0.38	0.12
	White	-1.14 ± 0.23	-1.84 ± 0.24	-1.2 ± 0.25	-2 ± 0.26	-1.93 ± 0.26	0.03

1 Listed flavonoid had significant interaction with race (P-interaction < 0.05) All values are Mean± SE. Results were derived from a marginal linear model adjusted for age, sex, race, exercise, education, smoking status, and disease developed during follow-up.

2 Median (range) (all such values).

Table 4. OR (95% CIs) for incidence of obesity by quintile of energy-adjusted flavonoid intake for 6,627 participants in the REGARDS study[1]

	Quintiles of flavonoids intake					
	Q1	Q2	Q3	Q4	Q5	P-trend[2]
Total Flavonoid, mg/d	111 (-118.1, 148.9)[3]	179.6 (149.2, 210)	249.8 (210.1, 298.8)	366.1 (298.8, 481)	729 (481.1, 1899.5)	
Cases	186 (15.31)	161 (12.02)	159 (11.65)	147 (11.1)	161 (11.63)	
Model 1	1	0.85 (0.67, 1.07)	0.83 (0.65, 1.05)	0.8 (0.63, 1.02)	0.82 (0.65, 1.04)	0.1044
Model 2	1	0.89 (0.69, 1.15)	0.88 (0.69, 1.14)	0.88 (0.69, 1.14)	0.9 (0.7, 1.15)	0.4364
Isoflavone, mg/d	0.1 (-1.2, 0.3)	0.4 (0.3, 0.5)	0.6 (0.5, 0.7)	0.8 (0.7, 1)	1.6 (1, 108.8)	
Cases	155 (12.75)	177 (13.76)	155 (11.78)	170 (12.54)	157 (10.81)	
Model 1	1	1.16 (0.92, 1.47)	0.98 (0.77, 1.26)	1.06 (0.83, 1.34)	0.83 (0.65, 1.05)	0.064
Model 2	1	1.31 (1.01, 1.69)	1.05 (0.79, 1.39)	1.2 (0.92, 1.58)	0.94 (0.72, 1.22)	0.3336
Anthocyanin, mg/d	4.1 (-8, 5.9)	7.3 (5.9, 8.8)	10.5 (8.8, 12.5)	15.1 (12.5, 18.7)	25.4 (18.7, 96.1)	
Cases	195 (15.92)	172 (13.86)	162 (12.44)	143 (10.62)	142 (9.39)	
Model 1	1	0.97 (0.77, 1.22)	0.84 (0.67, 1.06)	0.72 (0.56, 0.91)	0.62 (0.49, 0.78)	<.0001
Model 2	1	0.95 (0.74, 1.21)	0.86 (0.67, 1.1)	0.74 (0.58, 0.96)	0.7 (0.54, 0.9)	0.0012
Flavan_3_ol, mg/d	6.5 (-106.1, 22.3)	34.6 (22.4, 46.6)	65.9 (46.6, 110.1)	190.6 (110.1, 277.2)	532.2 (277.3, 1338)	
Cases	168 (12.68)	161 (11.88)	165 (12.77)	147 (11.29)	173 (12.79)	
Model 1	1	1 (0.79, 1.27)	1.13 (0.89, 1.43)	0.97 (0.76, 1.24)	1.12 (0.89, 1.41)	0.4711
Model 2	1	1.09 (0.83, 1.42)	1.25 (0.95, 1.63)	1.06 (0.81, 1.38)	1.22 (0.95, 1.58)	0.1908
Flavanone, mg/d	2.1 (-22.2, 5.6)	8.5 (5.6, 11.5)	16.6 (11.5, 23.6)	33.1 (23.6, 46.2)	56.6 (46.2, 312)	
Cases	177 (13.72)	165 (13.03)	156 (11.84)	159 (11.57)	157 (11.39)	
Model 1	1	0.83 (0.66, 1.05)	0.86 (0.68, 1.08)	0.76 (0.6, 0.96)	0.81 (0.64, 1.03)	0.0562
Model 2	1	0.91 (0.71, 1.17)	0.91 (0.71, 1.17)	0.76 (0.59, 0.99)	0.88 (0.68, 1.13)	0.1379
flavone, mg/d	0.4 (-0.4, 0.5)	0.6 (0.5, 0.7)	0.8 (0.7, 1)	1.2 (1, 1.5)	2.2 (1.5, 13.9)	
Cases	173 (14)	165 (12.61)	151 (11.4)	160 (11.71)	165 (11.85)	
Model 1	1	0.97 (0.77, 1.23)	0.9 (0.71, 1.14)	0.87 (0.69, 1.1)	0.83 (0.65, 1.05)	0.0706
Model 2	1	0.96 (0.74, 1.23)	0.93 (0.72, 1.2)	0.93 (0.72, 1.2)	0.9 (0.69, 1.16)	0.3902
Flavonol, mg/d	8.5 (-7.3, 10.7)	12.5 (10.7, 14.5)	16.7 (14.5, 19.5)	22.8 (19.5, 27.4)	35.4 (27.4, 120)	
Cases	186 (15.31)	161 (12.02)	159 (11.65)	147 (11.1)	161 (11.63)	
Model 1	1	0.93 (0.73, 1.17)	0.84 (0.67, 1.07)	0.88 (0.7, 1.11)	0.86 (0.68, 1.09)	0.1937
Model 2	1	0.96 (0.75, 1.23)	0.89 (0.69, 1.15)	0.97 (0.75, 1.24)	0.95 (0.74, 1.22)	0.7439

1 ORs (95% CIs) were calculated with the use of logistic regression models. Model 1: Odds Ratio (OR) derived from logistic regression model adjusting for age and sex. Model 2: Odds Ratio (OR) derived from logistic regression model adjusted for age, sex, race, exercise, education, smoking status, and disease developed during follow-up. The

2 P-trend values were calculated with the use of the Wald test.

3 Median (range) (all such values).

Table 5. OR (95% CIs) for incidence of obesity by quintile of energy-adjusted flavonoid intake for 6,627 participants in the REGARDS study, stratified by race[1]

	Quintiles of flavonoids intake					
	Q1	Q2	Q3	Q4	Q5	P-trend[2]
Anthocyanin, mg/d	4.1 (-8, 5.9)[3]	7.3 (5.9, 8.8)	10.5 (8.8, 12.5)	15.1 (12.5, 18.7)	25.4 (18.7, 96.1)	
White	1	0.88 (0.66, 1.17)	0.75 (0.56, 1)	0.63 (0.47, 0.85)	0.59 (0.44, 0.79)	<.0001
Cases (%)	313 (0.26)	362 (0.29)	348 (0.27)	334 (0.25)	264 (0.17)	
Black	1	1.2 (0.75, 1.92)	1.26 (0.79, 2.01)	1.17 (0.72, 1.89)	1.2 (0.72, 2)	0.55
Cases (%)	912 (0.74)	879 (0.71)	954 (0.73)	1012 (0.75)	1249 (0.83)	

1 ORs (95% CIs) were calculated with the use of a logistic regression model adjusted for age, sex, race, exercise, education, smoking status, total energy intakes, and disease developed during follow-up. Only anthocyanin interacted with race (P-interaction=0.007)

2 P-trend values were calculated with the use of the Wald test.

3 Median (range) (all such values).

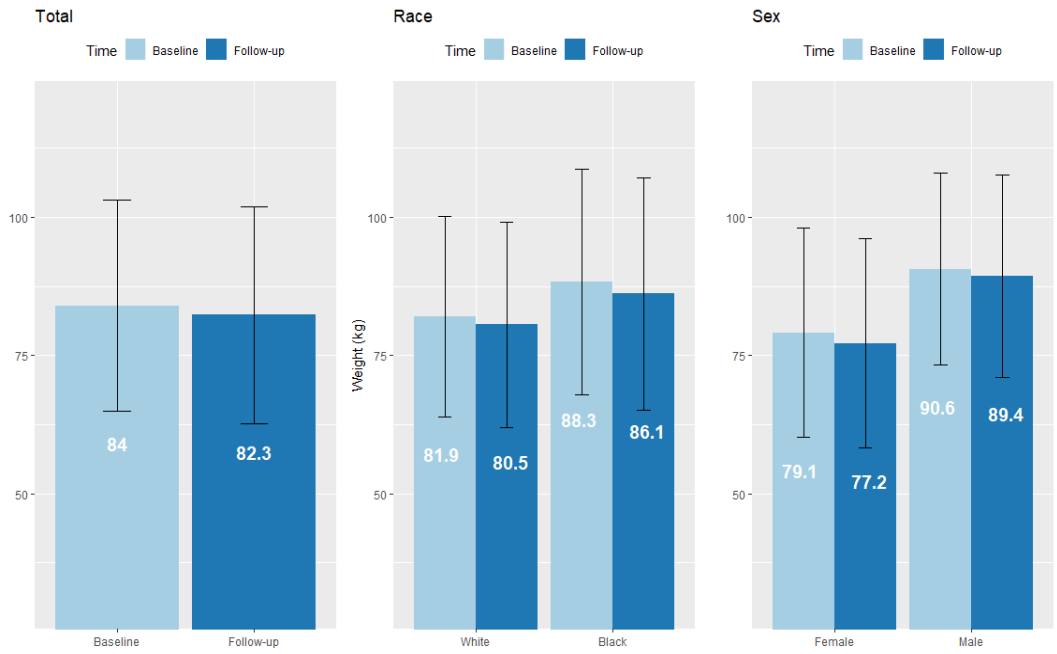

Figure 1

Weight in kg at baseline and follow-up. The average weight change (kg) for the total population was -1.65 (95% CI: -2.2 to -1.1), for whites was -1.40 (95% CI: -2.0 to -0.8) v. blacks -2.19 (95% CI: -3.2 to -1.2), and for females -1.93 (95% CI: -2.6 to -1.3) v. males -1.27 (95% CI: -2.0 to -0.5).