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Association of Dietary Flavonoid Intakes with End Stage Renal Disease: The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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Association of Dietary Flavonoid Intakes with End Stage Renal Disease: The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study

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2013

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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 Epidemiology

2018

Abstract

Background
Flavonoids are bioactive polyphenols that are widely distributed in fruits, vegetables, tea, herbs, and many other commonly consumed plant-based foods and beverages. Observational studies and randomized controlled trials suggest that higher flavonoid intake is associated with lower risk of type 2 diabetes and hypertension, two major risk factors of End Stage Renal Disease (ESRD). Research on flavonoid intake and ESRD in large population cohort is lacking.

Objective
We examined the associations of habitual dietary flavonoid intake with incident ESRD and kidney function decline in the large biracial cohort REasons for Geographic and Racial Differences in Stroke (REGARDS) study.

Methods
We included 19,666 ESRD-free participants from the REGARDS study for analysis of incident ESRD and 10,214 ESRD-free participants for the analysis of substantial kidney function decline. Flavonoid intake was estimated by the linkage of a Block98 food frequency questionnaire with the USDA's Provisional Flavonoid Addendum and Proanthocyanidin Database. Incident ESRD was verified by United State Renal Data System through June 3, 2014. Substantial decline in renal function was defined as a composite of ≥30% decline in estimated glomerular filtration rate from baseline or onset of ESRD. Associations between tertiles of flavonoid intake and incident ESRD were estimated by using multivariable Cox proportional hazards models. Unconditional multivariable logistic regression models were constructed to assess the association between tertiles of flavonoid intake and substantial decline in renal function.

Results
A total of 186 participants developed incident ESRD over 8.3 years. After adjustment for baseline renal measurements, socio-demographic, lifestyle, and dietary factors, isoflavone intake was inversely associated with incident ESRD ($HR_{T3\ vs.\ T1}$, 0.62; 95%CI, 0.40-0.95; $p_{trend} = 0.04$). Anthocyanidin intake was inversely but marginally significantly associated with incident ESRD ($HR_{T3\ vs.\ T1}$, 0.68; 95%CI, 0.43-1.06) and significantly associated with substantial decline in renal function (OR: 0.86; 95%CI: 0.76-0.98). Total flavonoid and other flavonoid subclass intakes were not associated with incident ESRD or substantial decline in renal function.

Conclusion
Higher reported intake of dietary isoflavone was associated with lower hazard of incident ESRD. There is some evidence that higher consumption of dietary anthocyanidins may be associated with slower kidney function decline.

(Word count: 348 words)

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BACKGROUND

Chronic kidney disease (CKD) affects about 11.5% of the United States population (1). Approximately 47% of people with CKD are 70 years of age or older (1). As CKD progresses to more severe stages, irreversible reduction in the number of nephrons, manifested by a decline in renal function, could lead to end stage renal disease (ESRD). ESRD requires dialysis and transplantation, which are accompanied by tremendous medical costs and poor survival (on average 3-5 years without kidney transplantation) (2).

A wide range of dietary interventions focused on macronutrients or dietary patterns have been investigated to slow kidney function decline. Generally, restricting protein improves outcomes among patients with established CKD (3, 4). A Mediterranean style diet, characterized by high fruit and vegetable and low red meat consumption, was associated with lower CKD incidence in the Northern Manhattan Study (aOR=0.50, 95%CI 0.31, 0.81) (5). An important question is whether interventions with other dietary bioactive components may also benefit renal function.

Flavonoids are bioactive polyphenols that are widely distributed in fruits, vegetables, tea, herbs, and many other commonly consumed plant-based foods and beverages. There is growing evidence of health benefits associated with higher habitual intake of dietary flavonoids (total or subclasses) including lower risk of type 2 diabetes (6) and hypertension (7), which are two major risk factors for ESRD (2). Type 2 diabetic rats treated with grape seed proanthocyanidin (a flavonoid subclass) extract (GSPE) experienced decreased fasting serum glucose and insulin, and lower systolic blood pressure. More importantly, GSPE improved renal function parameters and ameliorated

renal injury (8). In a 6-month randomized controlled trial (n = 78) of hypertensive adults between 20 and 50 years old, the addition of dietary flavonoids (425.8 ± 13.9 mg/day) via consumption of dark chocolate, dehydrated red apple, and green tea, concomitantly with usual anti-hypertensive treatment (AHT), resulted in an additional 5/4 mmHg reduction of systolic /diastolic blood pressure compared to AHT alone (9). The attenuation of elevated blood pressure by flavonoids may mitigate the potential vascular damage to the kidney caused by hypertension; and thus, slow the progression of renal function decline. To our knowledge, no previous studies have examined the association of dietary flavonoid intake with CKD in a large diverse prospective cohort. Using the REasons for Geographic and Racial Differences in Stroke (REGARDS) study, we tested the hypotheses that relatively high habitual intake of dietary flavonoids is associated with lower risk of ESRD and slower renal function decline after adjusting for potential confounders.

METHODS

Study design and data collection

The REasons for Geographic and Racial Differences in Stroke (REGARDS) Study is an ongoing biracial prospective cohort study designed to identify factors contributing to the excess stroke mortality in the Southeastern United States and among African-Americans. Between 2003 and 2007, the study recruited 30,239 English-speaking community-dwellers who were aged 45 years or older. Detailed recruitment and data collection methods have been described previously (10). Briefly, trained interviewers contacted potential participants by phone, collected sociodemographic information, and assessed their eligibility for the study. After verbal consent, eligible participants completed computer-assisted telephone interviews (CATI) to provide medical history and other health-related information. Later, trained health care professionals conducted in-home examinations to collect physical measurements (height, weight, and blood pressure) and fasting blood and urine samples. Electrocardiograms (ECG) were also taken during the in-home visit. Participants or their proxies were then contacted by phone every six months to verify vital status and collect information on recent hospitalizations and emergency room visits.

By design, the study oversampled African-Americans and residents from eight southern states with high stroke mortality, often referred as to the Stroke Belt (Alabama, Arkansas, Georgia, Louisiana, Mississippi, Tennessee, North Carolina, and South Carolina). Within the Stroke Belt, the regions that experience a higher stroke mortality are referred as to the Stroke Buckle, and include the coastal plain regions of North Carolina, South Carolina, and Georgia. The final cohort was 42% African-American,

55% female, and 56% were residents of the Southeastern United States (10). The institutional review boards of all participating universities approved the REGARDS study protocol and all participants provided written consent.

Study population

We restricted the analysis to 21,636 participants who provided complete dietary data with total energy intake in the plausible range. We also excluded those with baseline ESRD defined as self-reported kidney failure from CATI (n = 316), or ESRD service started before date of first in-home visit (n = 13), or baseline estimated glomerular filtration rate (eGFR) <15 mL/min/1.73 m2 (n = 10). We further excluded those who were missing baseline renal measurements (urine albumin-creatinine ratio [ACR] (n = 904) or eGFR (n = 564)) or lost over follow-up (n = 153) or missing baseline in-home visit date (n = 10). The final analytic cohort included 19,666 participants.

Dietary assessment

During the first in-home visit, a self-administered 1998 Block Food Frequency Questionnaire (Block98 FFQ) was left with each participant and later returned by mail. The 107-item Block98 FFQ, developed by NutritionQuest, was used to assess usual dietary intake over the previous year. Although the nutrient database for the FFQ did not originally include flavonoids, the FFQ contained questions on flavonoid-rich foods, including fruits, vegetables, tea, and wine. The FFQ has been validated in different populations (11, 12) and previously used to examine the association of flavonoids with coronary heart disease (13) and ischemic stroke (14). Participants who completed <85% of the FFQ or with reported total energy intakes of <500 kcal or >3500 kcal/d for women and <800 kcal or >4500 kcal/d for men were excluded (15).

Assessment of flavonoid intake

The exposures of interest included dietary intakes of total flavonoids and seven flavonoid subclasses: anthocyanidins, flavan-3-ols, flavanones, flavones, flavonols, isoflavones, and proanthocyanidins. Food items in the FFQ were linked to the USDA Database for the Proanthocyanidin Content of Selected Foods and the USDA's Provisional Flavonoids Addendum to the USDA Food and Nutrient Database for Dietary Studies (FNDDS) 4.1 (16) to compute flavonoid intake. Detailed computation methods were described previously (13, 14).The intake of each flavonoid subclass was calculated by summing all measured flavonoid compounds of that subclass. Total flavonoid intake was calculated using two methods. Total flavonoid I was calculated by summing all flavonoid monomers (all subclasses except proanthocyanidins) while total flavonoid II was calculated by adding proanthocyanidins to total flavonoid I.

Assessment of outcomes

The primary outcome of interest was incident ESRD, which was identified via linkage to the US Renal Data System (USRDS) registry (17) through June 3, 2014. Follow-up time for each participant was calculated from the date of first in-home visit to the date of death, or last telephone follow-up, or first ESRD service, or June 3, 2014, whichever came first.

The secondary outcome of interest was substantial change in renal function. Trained health care professionals conducted another in-home examination at about 10-years of follow-up (between 2013 and 2016) and collected fasting blood and urine samples. The Chronic Kidney Disease Epidemiology Collaboration creatinine equation was used to calculate eGFR based on the serum creatinine measurement (1). The change

in eGFR from baseline to follow-up was computed for each participant with data for both time points. A significant change in renal function was defined as either developing incident ESRD or change in eGFR ≥30% (personal communication, Orlando Gutiérrez, MD) between the two in-home visits.

Measurement of covariates

Age at first in-home visit (continuous), sex (male/female), race (African-American/white), smoking status (current/past/never), marital status (married/no), physical activity, annual income, education, and regular use of medication (aspirin, non-steroidal anti-inflammatory drugs, antihypertensive/statin) were self-reported at baseline. Regions were classified as stroke belt, stroke buckle and other. Physical activity was categorized as none, 1-3 times per week, and ≥ 4 times per week. Annual income was divided into 5 categories: refused, <$20,000, $20,000-$34,999, $35,000-$74,999, and ≥$75,000. Education was classified as <high school, high school graduate, some college, and college graduate or higher.

Total energy (kcal) and protein (grams) intakes were treated as continuous variables. Body mass index (BMI) was calculated based on weight (kilograms - kg) and height (meters - m) measurements taken during the in-home visit and divided into 4 categories: underweight (<18.5 kg/m^2), normal (18.5 – 24.9 kg/m^2), overweight (25.0 – 29.9 kg/m^2), and obese (≥30.0 kg/m^2). Fasting serum low density lipoprotein (LDL) cholesterol (continuous) was measured in milligrams per deciliter (mg/dL). Systolic/ diastolic blood pressure (continuous) in millimeters of mercury (mmHg) was the average of 2 measurements taken during the in-home visit. Baseline eGFR was divided into 5 categories: <15 mL/min/1.73 m^2, 15 – 29.9 mL/min/1.73 m^2, 30 – 44.9 mL/min/1.73 m^2,

45 – 59.9 mL/min/1.73 m^2, and ≥ 60 mL/min/1.73 m^2. Urine ACR (mg/g) was log transformed and treated as a continuous variable.

History of coronary heart disease (CHD) at baseline was defined as self-reported myocardial infarction (MI) and/or self-reported coronary revascularization procedure and/or evidence of MI via ECG at first in-home visit. Hypertension was defined as self-reported use of anti-hypertensive medications and/or systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg measured during the home examination. Diabetes was defined as a fasting serum glucose concentration ≥126 mg/dL and/or a non-fasting serum glucose concentration ≥200 mg/dL and/or current use of insulin or oral hypoglycemic medication. CKD was defined using the joint distribution of the eGFR and ACR according to clinical practice guidelines (18) (eGFR <60 mL/min/1.73 m^2 and ACR >30 mg/g).

Statistical analysis

All data analysis was performed using SAS 9.4 (SAS Institute). Baseline characteristics of the participants were reported across categories of total flavonoid I intake. Differences in baseline characteristics across tertiles were tested using the Kruskal-Wallis test for continuous variables and chi-square statistics for categorical variables. Several Cox proportional hazard models were created to estimate the associations of total and each flavonoid subclass intakes with incident ESRD. The proportional hazard assumption was satisfied for all exposures and covariates except for income, eGFR, and diabetes. Model 1 included only flavonoid intake. Model 2 also included age, sex, and race. Model 3 adjusted for covariates in model 2, socioeconomic factors (education, income, and marital status), baseline renal measurements (log (ACR)

and eGFR), total energy and protein intake, history of CHD, and lifestyle factors (smoking, exercise, regular use of medications). Model 4 adjusted for covariates in model 3 plus CKD risk factors (BMI categories, diabetes, hypertension, and LDL cholesterol). We also examined whether the association of flavonoid intake with incident ESRD differed by race. Tests for trend were calculated by treating exposure as a continuous variable and by using median intake of each flavonoid tertile as a continuous variable. Unconditional logistic regression models were constructed to examine the association between flavonoid intake and substantial decline in kidney function using the aforementioned hierarchical approach described for ESRD.

RESULTS

A total of 21,297 ESRD-free participants provided usable FFQ data. Of these, 19,666 participants (~92%) remained in the analytic cohort after exclusions. Overall, older African American females with lower social economic status were more likely to have missing baseline renal measurements whereas younger African American females with lower social economic status were more likely to be lost over follow-up.

Table 1 presents the selected baseline characteristics of the analytic cohort by total flavonoid intake. In general, participants were 65 years of age at enrollment and 55% female. Those with higher flavonoid intakes were more likely to be white, to have better socioeconomic status (education and income), and to have adopted a healthier lifestyle (never smoking and physically active). Participants with highest total flavonoid intakes on average had lower serum LDL concentrations and higher reported total energy and protein intakes compared to those with the lowest intakes. Median and range of each flavonoid subclass and total flavonoid intake tertiles are illustrated in Supplemental Table 2. Flavan_3_ol and proanthocyanidin were the two subclasses that contributed the most to total flavonoid intake.

A total of 186 participants developed incident ESRD over a median follow-up of 8.3 years. The crude rate of ESRD in the analytic cohort was 1.2 per 1,000 person-years. The crude rate of ESRD was lower at higher intakes compared to lower intakes for most flavonoid subclasses except flavonone (Supplemental Table 1). The associations of each flavonoid subclass and total flavonoid intake with incident ESRD are summarized in Table 2. Higher habitual intake of isoflavone was consistently associated with lower hazards of ESRD across all models. Compared with those in the lowest tertile (T1) of

isoflavone intake, the hazards of ESRD were 30% and 38% lower for those in the middle (T2) and highest (T3) tertiles, respectively, after adjusting for baseline renal measurements, social-demographic, lifestyle, and dietary factors ($T_{2\ v.1}$: [HR, 0.70; 95%CI, 0.47-1.03]; $T_{3\ v.1}$: [HR, 0.62; 95%CI, 0.40-0.95]; p for trend: 0.04). The associations became stronger after additional adjustment for potential mediators (BMI, diabetes, hypertension, and LDL), suggesting that the association between isoflavone and ESRD might be independent of these common risk factors. Anthocyanidin intake was also inversely associated with ESRD but the associations were not statistically significant ($T_{2\ v.1}$: [HR, 0.94; 95%CI, 0.65-1.36]; $T_{3\ v.1}$: [HR, 0.68; 95%CI, 0.43-1.06]; p for trend: 0.08). Total flavonoid and other flavonoid subclass intakes were not associated with incident ESRD.

In the analytic cohort, the isoflavone intake on average was higher among African Americans than whites. We observed effect modification by race for the association between isoflavone intake and incident ESRD (p=0.02) (Table 3). But with smaller numbers with ESRD within isoflavone categories after stratification, the race specific hazard ratios should be interpreted cautiously.

The associations of each flavonoid subclass and total flavonoid intake with substantial decline in renal function by second in-home visit are summarized in Table 4. Those who did not have a second in-home visit were more likely to be older, African American, of lower socioeconomic status, to have other comorbidities, and to report lower consumption of flavonoids. Of 10,214 participants who had second in-home visits or developed ESRD before their second in-home visit, 2,659 (26%) experienced substantial decline in renal function. Anthocyanidin intake was inversely associated with

substantial decline in renal function. Compared to those in the lowest tertile, those in the highest tertile were at 14% lower odds of having ≥30% decline in eGFR or onset of ESRD after adjusting for confounders ($T_{3\ v.1}$: [OR, 0.86; 95%CI: 0.76-0.98]; p for trend: 0.02). Total and other flavonoid subclass intakes were not associated with substantial decline in renal function by second in-home visit.

DISCUSSION

To our knowledge, our study is the first large and diverse prospective cohort study to examine the association of total flavonoid and flavonoid subclass intakes with incident ESRD and kidney function decline. In this biracial community-based cohort, we observed an inverse, statistically significant association of dietary isoflavone intake with incident ESRD. We also found that higher intake of dietary anthocyanidin was associated with lower odds of having substantial decline in eGFR.

In a prospective cohort study of 948 elderly women in West Australia, high proanthocyanidin consumers were at 50% lower odds of developing renal failure in 5 years (T3 v.1: [OR, 0.40; 95%CI, 0.18-0.89]; p for trend: 0.048) (19). However, in our study, we did not observe associations of dietary proanthocyanidins with incident ESRD or substantial kidney function decline. The difference in results between the two studies could in part be attributable to the different population characteristics, dietary contributors or in the measurement of proanthocyanidins or the covariates controlled for in the models. Compared to the REGARDS study participants, the study participants in the West Australia cohort (all Caucasian) were, on average, 10 years older, less likely to have diabetes (5% vs 17% in REGARDS) and had higher intake of proanthocyanidins. The models used in West Australia cohort did not adjust for socioeconomic factors, which appeared to be important risk factors for ESRD in our study.

Soy and legumes are the major sources of dietary isoflavone in the US. Administration of genistein, a type of isoflavone abundant in soybeans, lowered blood pressure, improved renal lipid profiles, and attenuated the pathological renal structural change in fructose-fed hypertensive rats (20). The protection of renal structure might be a

potential mechanism behind the lower rate of incident ESRD among those with higher isoflavone consumption. While animal research supports the inverse association of dietary isoflavone with incident ESRD, human studies are limited. A six-month randomized double-blinded placebo-controlled trial of 270 Chinese women found no association of soy flour (40 g/day) or purified daidzein (isoflavone, 63 mg/day) with improvement in renal parameters but reported modest improvement in renal function in a subgroup with diminished baseline renal function (21). The relatively short duration of the trial may have contributed to the findings. Also, compared to our study, both the study design and the trial participants (baseline renal function, race, and diet) are very different.

The major food sources of dietary anthocyanidins in the REGARDS study are wine, non-orange fruit juice, and berries. In a hypertensive rat model, a blueberry-enriched diet preserved renal hemodynamics, improved redox status in kidneys, and attenuated nephropathy (22). In large prospective cohorts, higher consumption of anthocyanidins has been associated with lower risk of non-fatal myocardial infarction (23) and hypertension (7, 24). A 24-week randomized double-blinded controlled trial of 58 type 2 diabetes patients also found that supplementation of 160mg of anthocyanins (anthocyanidin glycoside) twice a day improved lipid profiles, enhanced antioxidant capacity, and prevented insulin resistance (25). The improvement of endothelial function (26) and the anti-oxidant activity of anthocyanidins might explain the potential slower decline in renal function observed among the participants with higher anthocyanidin consumption in our study.

Strengths and limitations

Our study results should be interpreted with caution due to the limitations to be considered. The assessment of dietary flavonoids was based on linkage with the USDA database to provide relatively accurate estimates of intake but the FFQ used to collect dietary information was not specifically designed for flavonoids. Therefore, there could be measurement error but using ranked instead of absolute intake values should reduce the potential effect of measurement errors. Another limitation is that the FFQ only assessed the diet over past year and was collected at baseline. Our analysis was based on the assumption that participants in this cohort did not change their diet dramatically during the study. Only about 70% of participants returned their FFQ. Those who did not return their FFQ were more likely to be older African Americans with lower social economic status, less healthy, and had a higher proportion of incident ESRD. It is conceivable that those who did not return their FFQ would have lower consumption of fruit and vegetables, thus, lower intake of flavonoids. In addition, the measurement of eGFR was based on one single measurement and we cannot exclude the possibility of sample mishandling or acute kidney injury. Lastly, although we adjusted for several potential confounders, we cannot exclude the possibility of residual confounding. However, the strength of association on the risk ratio scale that the unknown confounder have with both flavonoid intake and ESRD would have to be as strong as 2.61 and 2.3 to attenuate the observed associations of isoflavone and anthocyanidin intake with incident ESRD, respectively (27). For substantial decline in renal function, the minimum strength of association with the unknown confounder on the risk ratio scale would need to be at least 1.37 to attenuate the observed association (27).

Our study maintains several strengths including the large sample size and the diverse population. Also, we have both ACR and eGFR measurements to objectively assess renal function. In addition, ESRD cases were ascertained by linkage through USRDS, ensuring good specificity and minimizing bias.

Conclusion and future directions

In conclusion, in multivariable adjusted models, we found that higher reported intake of dietary isoflavone was associated with lower hazard of incident ESRD. Our study also suggests that higher consumption of dietary anthocyanidins might be associated with slower kidney function decline. Additional research in large diverse cohorts is warranted to confirm our findings before planning any intervention trials to assess the renal benefits of dietary flavonoids.

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TABLES

(See next page)

Table 1 Selected baseline characteristics for 19,666 participants in the REGARDS study 2003-2007 by tertiles of total flavonoid intake[1]

	Total flavonoid intake			
	T1 (*n* = 6,555)	T2 (*n* = 6,556)	T3 (*n* = 6,555)	*p*[2]
Median (range) intake, *mg/d*	51.7 (≤ 85.6)	132.4 (85.6 - 228.0)	429.5 (228.0 - 1720.7)	
Age, *y*	64.4 ± 9.2	65.3 ± 9.3	65.0 ± 9.1	<0.001
Female, %	55.5	54.7	55.7	0.48
White, %	61.4	64.2	76.4	<0.001
BMI, *kg/m²*	29.2 ± 6.2	28.9 ± 5.9	28.9 ± 6.0	0.01
Energy intake, *kcal/d*	1,498.2 ± 618.5	1,766.9 ± 695.5	1,869.9 ± 755.5	<0.001
Protein intake, *g/d*	55.1 ± 25.9	64.9 ± 29.9	67.3 ± 30.8	<0.001
Diabetes[3], %	18.5	17.3	17.4	0.25
Hypertension[4], %	56.2	56.9	55.5	0.63
CHD history[5], %	16.6	16.0	17.6	0.19
Region[6], %				<0.001
Stroke Belt	33.6	33.0	37.2	
Stroke Buckle	19.1	19.8	26.3	
Non-Belt	47.3	47.2	36.5	
Missing	-	-	0.0	
Education, %				<0.001
<High school	11.4	8.4	8.1	
High school graduate	27.9	22.6	25.9	
Some college	27.4	26.5	28.2	
College graduate	33.3	42.4	37.7	
Missing	0.1	0.0	0.0	
Annual income, %				<0.001
Refused	11.8	11.5	11.7	
<$20,000	17.2	14.1	14.2	
$20,000-$34,999	25.0	22.1	25.0	
$35,000-$74,999	30.6	33.0	31.5	
≥$75,000	15.4	19.4	17.7	
Married, %	60.2	61.7	65.0	<0.001
Physical activity, %				<0.001
None	35.5	28.7	30.7	
1-3 times/wk	35.5	38.0	36.5	
≥4 times/wk	27.5	31.9	31.5	
Missing	1.6	1.2	1.4	

Smoking status, %				<0.001
Never	40.7	46.9	47.3	
Former	41.7	41.5	40.3	
Current	17.3	11.1	12.0	
Missing	0.4	0.4	0.4	
Regular use of medications[7], %	61.7	63.4	64.6	0.003
SBP, *mmHg*	126.8 ± 16.5	126.7 ± 16.1	126.6 ± 16.1	0.82
DBP, *mmHg*	76.3 ± 9.6	76.1 ± 9.5	76.0 ± 9.3	0.26
CKD[6], %	10.1	9.2	9.6	0.25
eGFR, *mL/min/1.73 m^2*	86.1 ± 19.3	85.7 ± 18.3	84.6 ± 18.0	<0.001
ln(ACR)	2.3 ± 1.2	2.2 ± 1.1	2.2 ± 1.1	0.41
Serum albumin, *g/dL*	4.2 ± 0.3	4.2 ± 0.3	4.2 ± 0.3	<0.001
Total cholesterol, *mg/dL*	193.2 ± 39.9	192.3 ± 39.0	191.5 ± 39.6	0.09
HDL cholesterol, *mg/dL*	52.2 ± 16.2	53.1 ± 16.6	51.4 ± 16.1	<0.001
LDL cholesterol, *mg/dL*	114.8 ± 34.9	113.5 ± 33.7	112.8 ± 34.4	0.01

Note: values are mean ± SDs unless specified.

Abbreviations: ACR, albumin-creatinine ratio; BMI, body mass index; CHD, coronary heart disease; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; REGARDS, REasons for Geographic and Racial Differences in Stroke; SBP, systolic blood pressure; T, tertile.

[1] Total flavonoids intake is the sum of anthocyanidin, flavan-3-ol, flavanone, flavone, flavonol, and isoflavone intakes.

[2] p values calculated based on Kruskal-Wallis tests for continuous variables and chi-square tests for categorical variables.

[3] Diabetes at baseline: a fasting serum glucose ≥126 mg/dL, or a non-fasting glucose serum glucose ≥200 mg/dL, or current use of insulin or oral hypoglycemic pills. 38, 30, and 34 participants were missing diabetes status in T1, T2, and T3, respectively.

[4] Hypertension at baseline: systolic blood pressure ≥140 mmHg, or diastolic blood pressure ≥90 mmHg, or self-reported use of antihypertensive. 16, 15, and 14 participants were missing hypertension status in T1, T2, and T3, respectively.

[5] History of coronary heart disease: self-reported or electrocardiogram-diagnosed at baseline. 108, 108, and 104 participants were missing history of coronary heart disease information in T1, T2, and T3, respectively.

[6] Stroke Belt includes Alabama, Arkansas, Georgia, Louisiana, Mississippi, North Carolina, South Carolina, and Tennessee. Stroke Buckle includes coastal plains of Georgia, North Carolina, and South Carolina. Non-belt includes remaining area in lower 48 contiguous states. Regions are mutually exclusive.

[7] Medications include statin, aspirin, and non-steroidal anti-inflammatory drugs. 49, 34, and 51 participants were missing self-reported use of medications in T1, T2, and T3, respectively.

[8] CKD at baseline was defined as eGFR < 60mL/min/1.73 m^2 or ACR ≥ 30 mg/g.

Table 2 Hazard ratios and 95% confidence intervals for incident ESRD by tertiles of flavonoid intake in the REGARDS study (*N = 19,666*)

		Crude			Model 2[3]			Model 3[4]			Model 4[5]		
	No. of ESRD	HR	95% CI		HR	95% CI		HR	95% CI		HR	95% CI	
Flavonol													
T1	75	1.00			1.00			1.00			1.00		
T2	62	0.79	0.56	1.10	0.91	0.65	1.27	1.18	0.81	1.74	1.04	0.69	1.58
T3	49	0.62	0.44	0.89	0.91	0.63	1.32	1.16	0.75	1.79	1.08	0.67	1.72
P-trend[6]			*0.01*			*0.64*			*0.52*			*0.76*	
Flavone													
T1	80	1.00			1.00			1.00			1.00		
T2	63	0.77	0.55	1.06	0.92	0.66	1.29	0.94	0.64	1.36	0.91	0.61	1.37
T3	43	0.51	0.36	0.75	0.71	0.49	1.04	1.02	0.65	1.61	0.95	0.58	1.54
P-trend[6]			*<0.01*			*0.08*			*0.90*			*0.86*	
Flavanone													
T1	55	1.00			1.00			1.00			1.00		
T2	59	1.06	0.74	1.53	0.89	0.62	1.29	1.19	0.78	1.81	1.12	0.72	1.73
T3	72	1.28	0.90	1.81	0.95	0.66	1.35	1.34	0.90	2.01	1.18	0.77	1.80
P-trend[6]			*0.15*			*0.91*			*0.18*			*0.48*	
Flavan-3-ol													
T1	68	1.00			1.00			1.00			1.00		
T2	56	0.80	0.56	1.14	0.88	0.62	1.25	1.33	0.90	1.97	1.11	0.73	1.70
T3	62	0.89	0.63	1.25	1.23	0.86	1.74	1.21	0.81	1.81	1.11	0.73	1.71
P-trend[6]			*0.83*			*0.11*			*0.65*			*0.74*	
Isoflavone													
T1	92	1.00			1.00			1.00			1.00		
T2	50	0.53	0.38	0.75	0.61	0.43	0.86	0.70	0.47	1.03	0.59	0.39	0.89
T3	44	0.46	0.32	0.66	0.54	0.37	0.77	0.62	0.40	0.95	0.57	0.36	0.91
P-trend[6]			*<0.01*			*<0.01*			*0.04*			*0.04*	
Anthocyanidin													
T1	83	1.00			1.00			1.00			1.00		
T2	63	0.74	0.54	1.03	0.75	0.54	1.04	0.94	0.65	1.36	0.80	0.53	1.21
T3	40	0.47	0.32	0.68	0.50	0.34	0.73	0.68	0.43	1.06	0.67	0.41	1.07
P-trend[6]			*<0.01*			*<0.01*			*0.08*			*0.10*	
Proanthocyanidin													
T1	81	1.00			1.00			1.00			1.00		
T2	61	0.73	0.53	1.02	0.85	0.61	1.19	1.07	0.73	1.56	1.13	0.76	1.68
T3	44	0.52	0.36	0.76	0.61	0.42	0.88	0.87	0.55	1.39	0.78	0.47	1.27
P-trend[6]			*<0.01*			*<0.01*			*0.57*			*0.32*	

Total Flavonoid I[1]													
T1	71	1.00			1.00			1.00			1.00		
T2	52	0.70	0.49	1.00	0.71	0.50	1.02	1.30	0.87	1.92	1.04	0.68	1.58
T3	63	0.86	0.61	1.20	1.12	0.79	1.58	1.29	0.87	1.90	1.09	0.72	1.66
P-trend[6]			*0.75*			*0.20*			*0.31*			*0.69*	
Total Flavonoid II[2]													
T1	72	1.00			1.00			1.00			1.00		
T2	59	0.78	0.56	1.11	0.85	0.60	1.19	1.28	0.86	1.89	1.09	0.71	1.67
T3	55	0.74	0.52	1.05	0.94	0.66	1.34	1.16	0.77	1.75	1.04	0.67	1.62
P-trend[6]			*0.13*			*0.87*			*0.60*			*0.91*	

Abbreviations: BMI, body mass index; CI, confidence interval; ESRD, end stage renal disease; HR, hazard ratio; REGARDS, REasons for Geographic and Racial Differences in Stroke; T, tertile.

[1] Total flavonoid I intake is the sum of anthocyanidin, flavan-3-ol, flavanone, flavone, flavonol, and isoflavone intakes.

[2] Total flavonoid II intake is the sum of total flavonoid I and proanthocyanidin intakes.

[3] Model 2 adjusted for age, race, and sex.

[4] Model 3 adjusted for variables of model 2, social economic factors (education, income, marital status), renal measurements at baseline (log (ACR), eGFR), energy and protein intake, history of coronary heart disease, and lifestyle factors (smoking, exercise, regular use of medications).

[5] Model 4 adjusted for variables in model 3 plus BMI categories, diabetes, hypertension, and LDL.

[6] Test for trend by using median of each tertile, modeled as a continuous variable.

Table 3 Hazard ratios and 95% confidence intervals for incident ESRD by tertiles of flavonoid intake in the REGARDS study, stratified by race (*N = 19,666*)

	White (*n = 13,243*)							Black (*n = 6,423*)						
		Model 3[3]			Model 4[4]				Model 3[3]			Model 4[4]		
	No. of ESRD	HR	95% CI		HR	95% CI		No. of ESRD	HR	95% CI		HR	95% CI	
Flavonol														
T1	18	1.00			1.00			57	1.00			1.00		
T2	25	1.54	0.79	3.01	1.35	0.67	2.71	37	1.02	0.64	1.63	0.90	0.54	1.48
T3	16	0.93	0.44	1.95	0.86	0.40	1.87	33	1.36	0.81	2.27	1.24	0.71	2.17
P-trend[5]			*0.33*			*0.32*				*0.34*			*0.47*	
Flavone														
T1	21	1.00			1.00			59	1.00			1.00		
T2	24	1.11	0.58	2.13	1.15	0.58	2.30	39	0.85	0.54	1.35	0.81	0.49	1.33
T3	14	0.76	0.36	1.60	0.71	0.33	1.54	29	1.24	0.72	2.13	1.15	0.65	2.03
P-trend[5]			*0.22*			*0.16*				*0.64*			*0.70*	
Flavanone														
T1	26	1.00			1.00			29	1.00			1.00		
T2	16	0.92	0.46	1.84	0.76	0.37	1.58	43	1.41	0.83	2.39	1.43	0.82	2.51
T3	17	0.98	0.51	1.89	0.86	0.43	1.72	55	1.62	0.98	2.70	1.45	0.85	2.49
P-trend[5]			*0.91*			*0.88*				*0.04*			*0.12*	
Flavan-3-ol														
T1	17	1.00			1.00			51	1.00			1.00		
T2	19	1.36	0.68	2.71	1.06	0.51	2.21	37	1.31	0.81	2.10	1.14	0.68	1.90
T3	23	1.06	0.53	2.11	1.07	0.53	2.17	39	1.31	0.81	2.12	1.14	0.67	1.93
P-trend[5]			*0.49*			*0.75*				*0.42*			*0.67*	
Isoflavone*														
T1	22	1.00			1.00			70	1.00			1.00		
T2	22	1.06	0.56	2.00	1.20	0.61	2.34	28	0.54	0.32	0.89	0.37	0.21	0.65
T3	15	0.59	0.29	1.21	0.65	0.30	1.41	29	0.65	0.39	1.07	0.55	0.32	0.94
P-trend[5]			*0.21*			*0.27*				*0.20*			*0.13*	
Anthocyanidin														
T1	29	1.00			1.00			54	1.00			1.00		
T2	18	0.63	0.33	1.20	0.64	0.32	1.28	45	1.14	0.73	1.79	0.90	0.55	1.47
T3	12	0.54	0.25	1.13	0.61	0.28	1.32	28	0.75	0.44	1.29	0.70	0.40	1.23
P-trend[5]			*0.21*			*0.44*				*0.59*			*0.46*	
Proanthocyanidin														
T1	20	1.00			1.00			61	1.00			1.00		
T2	28	1.22	0.66	2.25	1.33	0.69	2.56	33	0.97	0.60	1.58	1.00	0.60	1.67
T3	11	0.79	0.35	1.75	0.69	0.29	1.62	33	0.91	0.54	1.54	0.81	0.46	1.43
P-trend[5]			*0.39*			*0.17*				*0.98*			*0.82*	

Total Flavonoid I[1]															
T1	21	1.00			1.00			50	1.00			1.00			
T2	15	0.85	0.42	1.72	0.76	0.36	1.58	37	1.56	0.97	2.50	1.21	0.72	2.03	
T3	23	0.99	0.52	1.89	0.93	0.47	1.81	40	1.45	0.90	2.34	1.20	0.71	2.03	
P-trend[5]			*0.60*			*0.65*				*0.22*			*0.49*		
Total Flavonoid II[2]															
T1	19	1.00			1.00			53	1.00			1.00			
T2	21	1.21	0.62	2.38	1.05	0.51	2.15	38	1.29	0.81	2.06	1.10	0.66	1.84	
T3	19	1.01	0.50	2.01	0.94	0.46	1.92	36	1.25	0.76	2.06	1.11	0.64	1.92	
P-trend[5]			*0.50*			*0.48*				*0.38*			*0.49*		

Abbreviations: BMI, body mass index; CI, confidence interval; ESRD, end stage renal disease; HR, hazard ratio; REGARDS, REasons for Geographic and Racial Differences in Stroke; T, tertile.

[1] Total flavonoid I intake is the sum of anthocyanidin, flavan-3-ol, flavanone, flavone, flavonol, and isoflavone intakes.

[2] Total flavonoid II intake is the sum of total flavonoid I and proanthocyanidin intakes.

[3] Model 3 adjusted for demographic (age, race, sex), social economic factors (education, income, marital status), renal measurements at baseline (log (ACR), eGFR), energy and protein intake, history of coronary heart disease, lifestyle factors (smoking, exercise, regular use of medications).

[4] Model 4 adjusted for variables in model 3 plus BMI categories, diabetes, hypertension, and LDL.

[5] Test for trend by using median of each tertile, modeled as a continuous variable.

* In Model 4, isoflavone tertile X race interaction term, p=0.0248.

Table 4 Odds ratios and 95% confidence intervals for substantial decline in renal function[1] by tertiles of flavonoid intake in the REGARDS study (*N = 10,214*)

		Crude			Model 2[4]			Model 3[5]		
	No. of event	OR	95% CI		OR	95% CI		OR	95% CI	
Flavonol										
T1	860	1.00			1.00			1.00		
T2	903	0.93	0.84	1.04	1.01	0.89	1.13	1.02	0.90	1.15
T3	896	0.88	0.79	0.99	1.00	0.88	1.13	1.01	0.89	1.15
P-trend[6]			*0.03*			*0.94*			*0.93*	
Flavone										
T1	831	1.00			1.00			1.00		
T2	896	0.94	0.84	1.05	1.02	0.90	1.15	1.02	0.90	1.15
T3	932	0.91	0.82	1.02	1.07	0.94	1.22	1.07	0.94	1.22
P-trend[6]			*0.13*			*0.25*			*0.25*	
Flavanone										
T1	904	1.00			1.00			1.00		
T2	862	0.91	0.82	1.01	0.92	0.82	1.03	0.93	0.83	1.04
T3	893	1.02	0.91	1.13	1.00	0.89	1.13	1.01	0.90	1.14
P-trend[6]			*0.43*			*0.70*			*0.55*	
Flavan_3_ol										
T1	897	1.00			1.00			1.00		
T2	869	0.88	0.79	0.98	0.90	0.80	1.01	0.90	0.80	1.01
T3	893	0.92	0.83	1.03	0.93	0.83	1.04	0.94	0.83	1.06
P-trend[6]			*0.60*			*0.57*			*0.73*	
Isoflavone										
T1	894	1.00			1.00			1.00		
T2	897	0.89	0.79	0.99	1.02	0.91	1.15	1.03	0.91	1.16
T3	868	0.74	0.67	0.83	0.92	0.81	1.04	0.95	0.83	1.08
P-trend[6]			*<0.01*			*0.10*			*0.27*	
Anthocyanin										
T1	881	1.00			1.00			1.00		
T2	924	0.91	0.82	1.02	0.95	0.84	1.07	0.94	0.84	1.06
T3	854	0.78	0.70	0.87	0.86	0.76	0.98	0.86	0.76	0.98
P-trend[6]			*<0.01*			*0.02*			*0.02*	
Proanthocyanidin										
T1	848	1.00			1.00			1.00		
T2	954	0.99	0.89	1.11	1.11	0.98	1.25	1.13	1.00	1.27
T3	857	0.85	0.76	0.95	0.93	0.82	1.07	0.94	0.82	1.08
P-trend[6]			*<0.01*			*0.15*			*0.18*	

Total Flavonoid I[2]										
T1	884	1.00			1.00			1.00		
T2	879	0.91	0.82	1.02	0.97	0.86	1.09	0.98	0.87	1.10
T3	896	0.95	0.85	1.06	0.97	0.86	1.09	1.00	0.88	1.12
P-trend[6]			*0.67*			*0.76*			*0.90*	
Total Flavonoid II[3]										
T1	892	1.00			1.00			1.00		
T2	878	0.89	0.80	0.99	0.96	0.85	1.07	0.96	0.85	1.08
T3	889	0.91	0.82	1.01	0.94	0.84	1.07	0.96	0.85	1.09
P-trend[6]			*0.19*			*0.43*			*0.96*	

Abbreviations: BMI, body mass index; CI, confidence interval; ESRD, end stage renal disease; OR, odds ratio; REGARDS, REasons for Geographic and Racial Differences in Stroke; T, tertile.

[1] Substantial decline in renal function is defined as either developing ESRD or estimated glomerular filtration rate dropping greater or equal to 30% between two in-home examinations.

[2] Total flavonoid I intake is the sum of anthocyanidin, flavan-3-ol, flavanone, flavone, flavonol, and isoflavone intakes.

[3] Total flavonoid II intake is the sum of total flavonoid I and proanthocyanidin intakes.

[4] Model 2 adjusted for demographic factors (age, sex, race), social economic factors (education, income, marital status), renal measurements at baseline (log (ACR), eGFR), energy and protein intake, history of coronary heart disease, BMI category, and lifestyle factors (smoking, exercise, regular use of medications).

[5] Model 3 adjusted for variables in model 2 plus diabetes, hypertension, and LDL.

[6] Test for trend by using median of each tertile, modeled as a continuous variable.

Supplemental Table 1 Crude ESRD rate[1] for 19,666 participants in the REGARDS study 2003-2007 by tertile of flavonoids intake

	T1 (*n = 6,555*)	T2 (*n = 6,556*)	T3 (*n = 6,555*)
Flavonol			
Incident ESRD	75	62	49
Total person-years	49,186	50,916	51,090
Rate (per 1000 person-years)	1.52	1.22	0.96
Flavone			
Incident ESRD	80	63	43
Total person-years	49,340	50,531	51,321
Rate (per 1000 person-years)	1.62	1.25	0.84
Flavanone			
Incident ESRD	55	59	72
Total person-years	50,007	50,310	50,875
Rate (per 1000 person-years)	1.10	1.17	1.42
Flavan_3_ol			
Incident ESRD	68	56	62
Total person-years	49,711	50,741	50,740
Rate (per 1000 person-years)	1.37	1.10	1.22
Isoflavone			
Incident ESRD	92	50	44
Total person-years	49,528	50,510	51,154
Rate (per 1000 person-years)	1.86	0.99	0.86
Anthocyanidin			
Incident ESRD	83	63	40
Total person-years	49,516	50,579	51,097
Rate (per 1000 person-years)	1.68	1.25	0.78
Proanthocyanidin			
Incident ESRD	81	61	44
Total person-years	49,487	50,688	51,018
Rate (per 1000 person-years)	1.64	1.20	0.86
Total Flavonoid I[2]			
Incident ESRD	71	52	63
Total person-years	49,400	51,035	50,757
Rate (per 1000 person-years)	1.44	1.02	1.24
Total Flavonoid II[3]			
Incident ESRD	72	59	55
Total person-years	49,370	51,008	50,815
Rate (per 1000 person-years)	1.46	1.16	1.08

Abbreviations: ESRD, end stage renal disease; REGARDS, REasons for Geographic and Racial Differences in Stroke; T, tertile.

[1] Incident ESRD till 06/03/2014.

[2] Total flavonoid I intake is the sum of anthocyanidin, flavan-3-ol, flavanone, flavone, flavonol, and isoflavone intakes.

[3] Total flavonoid II intake is the sum of total flavonoid I and proanthocyanidin intakes.

Supplemental Table 2 Tertiles of flavonoid intake for 19,666 participants in the REGARDS study 2003-2007

	Median	Range	
Flavonol, *mg/d*			
T1	8.3	0.6	12.0
T2	16.0	12.0	21.4
T3	29.6	21.4	137.7
Flavone, *mg/d*			
T1	0.4	0.0	0.6
T2	0.8	0.6	1.0
T3	1.6	1.0	13.8
Flavanone, *mg/d*			
T1	3.2	0.0	7.7
T2	16.5	7.7	30.1
T3	50.7	30.1	356.9
Flavan_3_ol, *mg/d*			
T1	13.3	0.3	26.3
T2	56.1	26.3	154.7
T3	379.1	154.8	1,327.0
Isoflavone, *mg/d*			
T1	0.2	0.0	0.3
T2	0.4	0.3	0.7
T3	1.2	0.7	109.3
Anthocyanidin, mg/d			
T1	4.4	0.0	6.8
T2	9.6	6.8	13.5
T3	20.1	13.5	98.1
Proanthocyanidin, *mg/d*			
T1	43.0	0.9	62.7
T2	83.9	62.7	110.0
T3	151.9	110.1	883.6
Total Flavonoid I[1], *mg/d*			
T1	51.7	2.7	85.6
T2	132.4	85.6	228.0
T3	429.5	228.0	1,720.7
Total Flavonoid II[2], *mg/d*			
T1	109.4	4.4	169.8
T2	241.7	169.9	348.0
T3	571.4	348.1	1,988.0

Abbreviations: REGARDS, REasons for Geographic and Racial Differences in Stroke; T, tertile.
1 Total flavonoid I intake is the sum of anthocyanidin, flavan-3-ol, flavanone, flavone, flavonol, and isoflavone intakes.
[2] Total flavonoid II intake is the sum of total flavonoid I and proanthocyanidin intakes.