ORIGINAL RESEARCH

Cigarette Smoking and Chronic Kidney Disease in African Americans in the Jackson Heart Study

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***Background*—**Controversy exists regarding the association of cigarette smoking and renal dysfunction, particularly among African Americans, who are disproportionately affected by chronic kidney disease; therefore, we evaluated the relationship between cigarette smoking and rapid renal function (RRF) decline in the Jackson Heart Study.

***Methods and Results*—**Rates of RRF decline were determined among 3648 African American participants enrolled at baseline in the Jackson Heart Study. RRF decline was defined as an absolute decline of estimated glomerular filtration rate of 30% from visit 1 to visit 3. There were 422 current, 659 past, and 2567 never smokers identified at visit 1. After adjustment for age, sex, body mass index, diabetes, hypertension, cholesterol, physical activity, education, alcohol consumption, and prevalent cardiovascular disease, current smokers demonstrated a significantly higher incidence of RRF decline compared with never smokers (incidence rate ratio 1.83, 95% CI 1.31–2.56). Current smokers using 1 to 19 and ≥20 cigarettes daily had an increased incidence of RRF decline (incidence rate ratios of 1.75 [95% CI 1.18–2.59] and 1.97 [95% CI 1.17–3.31], respectively). There was a significant, progressive reduction in estimated glomerular filtration rate from visit 1 to visit 3 in current and past smokers compared with never smokers. Finally, current smokers had a 1.38-fold increase in C-reactive protein compared with never smokers, after controlling for covariates.

***Conclusions*—**In a large African American cohort, current cigarette smoking was independently associated with RRF decline in a dose-dependent manner. There was also evidence of increased inflammation (C-reactive protein) in current smokers, suggesting a potential mechanism for these relationships. **(*J Am Heart Assoc*. 2016;5:e003280 doi: 10.1161/JAHA.116.003280)**

Key Words: African Americans • chronic kidney disease • cigarette smoking

End-stage renal disease disproportionately affects African Americans, who have 4 times greater risk compared with white Americans.[1] The disparity has been largely attributed to higher rates of hypertension, obesity, and diabetes.[2] Cigarette smoking may also be an independent risk factor for chronic kidney disease (CKD).[3] Cardiovascular and renal diseases are closely linked, and there is abundant evidence that smoking accelerates adverse effects on the cardiovascular system.[4,5]

Although recent evidence suggests cigarette smoking may have detrimental effects on renal function,[6] this has not been adequately studied, especially in African American populations. Because African Americans are more likely to develop advanced renal dysfunction and known risk factors such as hypertension and diabetes[7] than their white counterparts, they may be more susceptible to the potential adverse renal effects of cigarette smoking. Nevertheless, few data are available on the effects of cigarette smoking on renal function in African Americans. The objective of this study was to evaluate the relationship of cigarette smoking and renal function in participants of the Jackson Heart Study, a large African American cohort.

Methods

Study Population

The Jackson Heart Study is the largest single-site prospective cohort study of cardiovascular disease in African Americans

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and includes 5301 participants aged 21 to 84 years. Participants were recruited from the tricounty area surrounding Jackson, Mississippi, and were evaluated at baseline from 2000 to 2004. Data were collected for 3 participant examinations and were completed by visit 3 (V3), from 2009 to 2012. The present analysis includes participants (n=3648) with serum creatinine measurements at visit 1 (V1) and V3 to assess renal function and excludes participants with dialysis reported at either V1 or V3 (n=32).

The study was approved by the institutional review board at the University of Mississippi Medical Center. Each participant provided written informed consent. The baseline examination (V1) included a home interview, self-administered questionnaires, and a clinic visit that included blood and urine collection. Each participant was asked to fast overnight before the clinic visit at which blood pressure and anthropometric measurements were obtained. Blood and urine samples were collected according to the National Committee for Clinical Laboratory standards, as reported previously.[8]

Study Variables

Estimated glomerular filtration rate (GFR) was assessed using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[9] in which the serum creatinine measurements at V1 were optimally calibrated using a Deming regression model, as described previously.[10] Rapid renal function (RRF) decline was defined as an absolute decrease of ≥30% in estimated GFR from V1 to V3.[11,12]

Cigarette smoking status was obtained via questionnaire. Participants who smoked >400 cigarettes in their lifetime were defined as *ever* smokers. Participants who gave a positive response to the question, "Do you now smoke cigarettes?" were classified as current smokers. Those who responded negatively to these questions were classified as *never* smokers. Participants who were classified as ever smokers who no longer smoked at the time of the examination were classified as past smokers. Further information related to number of cigarettes smoked daily was also collected.

Age, sex, and anthropometric data such as body mass index were recorded at the baseline examination of the Jackson Heart Study. Hypertension was defined as blood pressure ≥140/90 mm Hg or use of blood pressure–lowering medication, and diabetes was defined as fasting glucose ≥126 mg/dL or hemoglobin A1c ≥6.5% or use of diabetic mediation within 2 weeks prior to the clinic visit.[8] In addition, total cholesterol was measured from plasma with the use of a cholesterol oxidase method (Roche Diagnostics) on a Roche COBAS FARA centrifugal analyzer, and serum C-reactive protein (CRP) was measured by the latex particle immunoturbidimetric assay (Roche Diagnostics).

Statistical Analysis

All statistical analyses were performed using SAS 9.4 software (SAS Institute). All *P* values were 2-tailed, and a *P* value <0.05 was considered statistically significant. Baseline characteristics were compared with chi-square tests or 1-way ANOVA for the differences among never, past, and current smokers. Poisson regression models were performed for univariate and multivariate analyses to estimate the association between smoking status at V1 and RRF decline from V1 to V3 and to yield incidence rate ratios (IRRs) and 95% CIs. CRP values were transformed using natural logarithms to approximate normal distributions. Univariate and multivariate linear regression were used to model smoking status-log-CRP relations in Jackson Heart Study participants.

Results

Overall, 3648 of 5301 participants had creatinine measures at V1 and V3 and were included in our analyses. There were 422 participants identified as current smokers and 659 participants identified as past smokers; 2567 participants were identified as never smokers. Baseline characteristics subdivided by smoking status are listed in Table 1. Current smokers were more likely to be male (*P*<0.001) compared with never smokers and were likely to be younger (*P*<0.001) than past smokers. Body mass index was lower in current smokers (*P*<0.001), who had lower rates of hypertension (*P*<0.001) and diabetes (*P*<0.001) than past smokers and higher prevalent cardiovascular disease at V1 (*P*<0.001) than never smokers. Current smoking was also associated with more alcohol consumption (*P*<0.001) and less physical activity (*P*=0.007).

Current Cigarette Smoking Is Associated With More RRF Decline

After adjustment for age, sex, body mass index, diabetes, hypertension, and total cholesterol, current smokers demonstrated a significantly higher incidence of RRF (IRR 1.86, 95% CI 1.35–2.56) decline compared with never smokers (Table 2). Further analyses (Model 4) were performed with the addition of physical activity, education, alcohol consumption in the past 12 months, and prevalent cardiovascular disease at V1 in the models, and a similar increased IRR was observed for RRF decline in current smokers compared with never smokers (IRR 1.83, 95% CI 1.31–2.56). There was a significant progressive reduction in estimated GFR from V1 to V3 in current, past, and never smokers (Figure).

Table 1. Baseline Characteristics of Jackson Heart Study Participants by Smoking Status

Variable	Never Smokers (n=2567)	Past Smokers (n=659)	Current Smokers (n=422)	*P* Value*
Age, y	53.4±12.5	59.3±10.4	52.2±10.2	<0.001
Sex, male (%)	30.6	49.8	51.2	<0.001
Body mass index	32.2±7.3	31.5±6.4	29.5±6.8	<0.001
Ideal health indicator via physical activity†, %	20.5	23.5	15.6	0.007
Alcohol consumption in the past 12 months, %	42.3	52.1	73.4	<0.001
Education, less than high school, %	14.1	22.5	22.3	<0.001
Prevalent cardiovascular disease at visit 1, %	6.2	13.8	10.9	<0.001
Hypertension, %	55.4	66.6	53.1	<0.001
Diabetes, %	17.7	24.3	15.0	<0.001
Total cholesterol, mg/dL	199.1±38.9	201.2±39.2	195.8±40.9	0.105
High-sensitivity C-reactive protein, mg/L	4.9±7.2	4.9±8.0	5.1±7.7	0.862

Continuous values are presented as mean±SD, and all other values are percentages.
*Chi-square test or ANOVA was used to compare baseline characteristics of participants by smoking status.
†≥150 min/week moderate intensity or ≥75 min/week vigorous intensity or combination based on American Heart Association physical activity classification.

Dose-Dependent Relationship Between Cigarette Smoking and Incidence of RRF Decline

After subdividing current smokers into those who smoked 1 to 19 and ≥20 cigarettes daily, there was an increased rate of RRF decline in both groups. The rate was higher as daily cigarette use increased (Table 2) (IRR 1.75, 95% CI 1.18–2.59 and IRR 1.97, 95% CI 1.17–3.31 for 1–19 and ≥20 cigarettes daily, respectively).

Current Smoking Is Associated With Increased Systemic Inflammation

High-sensitivity CRP was assessed at V1 for all participants. After adjustment for covariates, natural log–transformed CRP values were analyzed with the linear regression model to determine the effect of current and past smoking on CRP levels. Current smokers had 1.38-fold higher CRP levels compared with never smokers, and past smokers had 1.10-fold higher CRP levels after controlling for covariates (Table 3). This relationship was also dose dependent because number of cigarettes smoked daily was associated with higher CRP levels after controlling for covariates.

Discussion

Findings of this study from a large African American cohort show that current cigarette smoking is associated with an increased incidence of RRF decline compared with never smoking. Furthermore, daily cigarette exposure was dose-dependently associated with an increased incidence of RRF decline. Current smoking was also associated with elevated CRP levels, suggesting that inflammation may contribute to renal dysfunction.

In a cross-sectional analysis of 7476 participants from the PREVEND (Prevention of REnal and Vascular ENd stage Disease) study, investigators found that current smokers had more albuminuria than nonsmokers. In participants who smoked >20 cigarettes daily, there were dose-dependent associations between smoking and high normal albuminuria (relative risk 1.33), elevated GFR (relative risk 1.82), and decreased GFR (relative risk 1.53).[13] In a study of >65 000 Norwegians followed for a median of 10.3 years, former and current smoking were significantly associated with the risk of kidney failure compared with never smoking (hazard ratios of 3.32 and 4.01, respectively).[14] In a retrospective case–control study of 4142 nondiabetic participants (aged >65 years) of the Cardiovascular Health Study Cohort, there was an increased risk of serum creatinine rise (0.3 mg/dL) with increased tobacco usage, suggesting a dose-dependent effect of cigarette smoking; however, only ≈3% of the studied population experienced an increase in serum creatinine over the 3-year time period.[15] In a large prospective study of 23 534 men and women from Washington County, Maryland, followed for 20 years, current smoking was significantly associated with risk of CKD in both men and women (hazard ratio of 2.6 for the total population) and accounted for 31% of the attributable risk of CKD in this population.[16] A major drawback of this study is that 99% of participants were white.

Our findings corroborate the association between current cigarette smoking and an increased risk of CKD observed in other populations. To our knowledge, this analysis is the first

Table 2. Association Between Smoking and Rapid Decline in Renal Function >30% From Visit 1 to Visit 3

Model	Smoking Status, Incidence Rate Ratio (95% CI); *P* Value			
	Past vs Never Smokers	Current vs Never Smokers	Current (1–19 Cigarettes per Day) vs Never Smokers	Current (≥20 Cigarettes per Day) vs Never Smokers
Model 1, unadjusted	1.53 (1.21–1.94); <0.001	1.51 (1.14–1.99); 0.004	1.35 (0.95–1.91); 0.095	1.82 (1.21–2.75); 0.004
Model 2, adjusted for age, sex and body mass index	1.26 (0.99–1.61); 0.059	1.90 (1.43–2.54); <0.001	1.67 (1.17–2.39); 0.005	2.31 (1.50–3.53); <0.001
Model 3, includes model 2 plus diabetes, hypertension, total cholesterol	1.21 (0.94–1.57); 0.147	1.86 (1.35–2.56); <0.001	1.73 (1.18–2.54); 0.005	2.03 (1.23–3.35); 0.005
Model 4, includes model 3 plus education, physical activity, prevalent cardiovascular disease, and alcohol consumption in the past 12 months	1.20 (0.92–1.56); 0.172	1.83 (1.31–2.56); <0.001	1.75 (1.18–2.59); 0.006	1.97 (1.17–3.31); 0.011

n=3648, 400 incident rapid decline cases.

reported from a prospective study of African American participants to evaluate this dose-response relationship. African Americans are disproportionately affected by CKD.[1] This disparity has been attributed to higher rates of hypertension and diabetes in African Americans compared with white Americans, but it appears that other unexplained factors may play a role. Because African Americans may be predisposed to develop renal dysfunction and have higher incidence of known CKD risk factors such as hypertension and diabetes, they may be more susceptible to the adverse effects of cigarette smoking, especially if smoking interacts synergistically with these known risk factors.

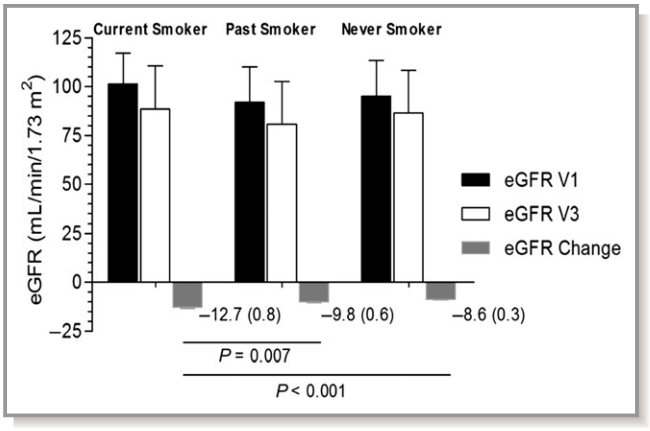

Figure. There is a significant, progressive reduction in eGFR from V1 to V3 in current, past, and never smokers. V1 and V3 eGFRs are presented as the summary statistics mean (SD), and the eGFR changes for 3 groups are presented as least squares means with corresponding standard errors from the multivariate linear regression model adjusting for age, sex, body mass index, diabetes, hypertension, total cholesterol, education, physical activity, prevalent cardiovascular disease, and alcohol consumption in the past 12 months. eGFR indicates estimated glomerular filtration rate; V, visit.

We assessed the relationship between cigarette smoking and a commonly measured inflammatory marker, CRP, to determine possible mechanisms by which smoking may cause renal dysfunction. Both current and past smoking were associated with higher CRP levels. Several large cohort studies including the Chronic Renal Insufficiency Cohort (CRIC), the Framingham Offspring cohort, and the Multi-Ethnic Study of Atherosclerosis (MESA) have demonstrated a negative association between CRP and renal function.[17–19] Our findings build on these studies by demonstrating a positive relationship between cigarette smoking exposure and levels of CRP. Inflammation may mediate the effect of smoking to cause renal dysfunction. Some of the potential mechanisms by which inflammation may contribute to renal dysfunction include increased oxidative stress, endothelial dysfunction, and atherogenesis.[20–22] Further studies are needed to determine whether inflammatory markers such as CRP are helpful in predicting which patients who smoke are at increased risk of kidney damage and should be considered for therapies such as statin drugs in addition to recommending smoking cessation.

According to the Centers for Disease Control and Prevention, 17.5% of African Americans smoke cigarettes.[23] Although African Americans are less likely to smoke compared with white Americans, metabolism of substances in cigarettes differs in African Americans compared with other ethnic groups.[24] Specifically, differences in CYP2A6 enzyme activity, nicotine and cotinine glucuronidation, and cotinine clearance have been reported in African Americans compared with white Americans.[25,26] Cotinine clearance significantly influences the metabolism of nicotine to cotinine, and Benowitz et al reported that it is 25% lower in African Americans. In addition, the flavoring additive menthol moderately inhibits CYP2A6-mediated nicotine metabolism,[27] and

Table 3. Association Between Smoking Status and C-Reactive Protein at Visit 1 Among Jackson Heart Study Participants

Model	Smoking Status, Fold Change (95% CI); *P* Value			
	Past vs Never Smokers	Current vs Never Smokers	Current (1–19 Cigarettes per Day) vs Never Smokers	Current (≥20 Cigarettes per Day) vs Never Smokers
Model 1, unadjusted	1.02 (0.92–1.13); 0.733	1.07 (0.94–1.22); 0.306	1.09 (0.94–1.28); 0.261	1.04 (0.84–1.28); 0.743
Model 2, adjusted for age, sex, and body mass index	1.13 (1.03–1.25); 0.012	1.46 (1.30–1.63); <0.001	1.39 (1.21–1.59); <0.001	1.63 (1.35–1.97); <0.001
Model 3, includes model 2 plus diabetes, hypertension, and total cholesterol	1.12 (1.01–1.23); 0.034	1.45 (1.28–1.63); <0.001	1.38 (1.20–1.59); <0.001	1.64 (1.34–1.99); <0.001
Model 4, includes model 3 plus education, physical activity, prevalent cardiovascular disease, and alcohol consumption in the past 12 months	1.10 (1.00–1.22); 0.054	1.38 (1.22–1.57); <0.001	1.33 (1.15–1.53); <0.001	1.55 (1.26–1.90); <0.001

menthol cigarettes are popular with African American cigarette smokers.[28,29] Menthol cigarette use has been associated with increased concentrations of blood cadmium, and exposure to low levels of cadmium has been associated with renal tubular damage.[30,31]

Our study has several key strengths. To our knowledge, this is the first prospective study to demonstrate a dose relationship between cigarette smoking and renal function decline in a large African American cohort. As discussed, this is important because of the prevalence of smoking among African Americans and their higher rates of CKD and end-stage renal disease. Renal function was assessed using the CKD-EPI equation instead of the Modification of Diet in Renal Disease equation. The CKD-EPI equation has been shown to be a better predictor of renal disease risk compared with the Modification of Diet in Renal Disease equation and appears to be more accurate for African Americans.[32] We also demonstrated a potential mechanism by which cigarette smoke may contribute to renal dysfunction.

Our study has a few limitations. The type of cigarettes that the participants smoked was not available for analysis. We currently do not have levels of cotinine available to directly measure cigarette smoking exposure. In addition, GFR was estimated based on serum creatinine levels instead of direct measurements such as iothalamate clearance; however, this is an inherent limitation of most large prospective studies. Nicotine has also been associated with hyperfiltration, which makes interpretation of renal function more difficult. We observed higher baseline estimated GFR in current smokers, consistent with previous observations.[13,33] Given this confounding observation, we used the rate of renal decline as a marker of cigarette smoking–induced renal dysfunction. Pinto-Sietsma and colleagues observed both decreased and increased estimated GFR in smokers.[13] They hypothesized this may be related to smoking-induced renal hypoperfusion and glomerular damage with compensatory glomerular hypertrophy and hyperfiltration. Others have suggested that smoking-induced renal injury may follow a pattern similar to obesity-induced renal dysfunction, which is often initially associated with glomerular hyperfiltration.[33] Finally, our data were obtained from an African American cohort and may not be generalizable to other ethnic groups.

Cigarette smoking is a widely recognized risk factor for cardiovascular disease, and aggressive antismoking campaigns have been successful in increasing awareness of this relationship. The detrimental effects of cigarette smoking on kidney disease are less well established, and there is subsequently less emphasis placed on tobacco cessation for renal patients without overt cardiovascular disease. Our data show that current cigarette smoking is independently associated with RRF decline in a large African American cohort, and this relationship is dose dependent. There was also evidence of increased inflammation (CRP) in current smokers, suggesting a potential mechanism for these relationships. Based on these observations, cigarette smoking should be considered as a strong risk factor for renal dysfunction and CKD, and smoking cessation should be recommended for current cigarette smokers, particularly those with risk factors for CKD.

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Disclosures

None.

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