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Obesity and synergistic risk factors for chronic kidney disease in African American adults: the Jackson Heart Study

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ABSTRACT

Background. African Americans are at high risk for chronic kidney disease (CKD). Obesity may increase the risk for CKD by exacerbating features of the metabolic syndrome and promoting glomerular hyperfiltration. Whether other factors also affecting these pathways may amplify or mitigate obesity–CKD associations has not been investigated.

Methods. We studied interactions between obesity and these candidate factors in 2043 African Americans without baseline kidney disease enrolled in the Jackson Heart Study. We quantified obesity as body mass index (BMI), sex-normalized waist circumference and visceral adipose volume measured by abdominal computed tomography at an interim study visit. Interactions were hypothesized with (i) metabolic risk factors (dietary quality and physical activity, both quantified by concordance with American Heart Association guidelines) and (ii) factors exacerbating or mitigating hyperfiltration (dietary protein intake, *APOL1* risk status and use of renin–angiotensin

system blocking medications). Using multivariable regression, we evaluated associations between obesity measures and incident CKD over the follow-up period, as well as interactions with metabolic and hyperfiltration factors.

Results. Assessed after a median of 8 years (range 6–11 years), baseline BMI and waist circumference were not associated with incident CKD. Higher visceral adipose volume was independently associated with incident CKD ($P = 0.008$) in a nonlinear fashion, but this effect was limited to those with lower dietary quality ($P = 0.001$; P-interaction $= 0.04$). In additional interaction models, higher waist circumference was associated with greater risk of incident CKD among those with the low-risk *APOL1* genotype ($P = 0.04$) but not those with a high-risk genotype (P-interaction $= 0.02$). Other proposed factors did not modify obesity–CKD associations.

Conclusions. Higher risks associated with metabolically active visceral adipose volume and interactions with dietary quality suggest that metabolic factors may be key determinants of obesity-associated CKD risk. Interactions between obesity and *APOL1* genotype should be considered in studies of African Americans.

Keywords: albuminuria, *APOL1*, CKD, metabolic syndrome, nutrition, obesity

INTRODUCTION

Obesity is a growing public health concern both in the USA and worldwide, affecting nearly 35% of the US adult population and with an even higher prevalence in African Americans [1–3]. It is increasingly recognized that obesity may contribute to the rising prevalence of chronic kidney disease (CKD) [4–7]. Specifically, obesity may promote CKD by exacerbating other features of the metabolic syndrome, such as insulin resistance and hypertension [8–10], or by inducing glomerular hyperfiltration [11–13]. Whether additional factors affecting metabolic syndrome and hyperfiltration alter the association of obesity with CKD is not well studied. Given the high prevalence of obesity and CKD in African Americans, understanding additional factors that may modify risk is important for public health and treatment strategies.

Based on the proposed pathophysiology, we hypothesized that additional risk factors affecting hypertension, insulin resistance and glomerular hyperfiltration may provide a 'second hit' that magnifies obesity-associated CKD risk. Specifically, adverse lifestyle factors, such as lower levels of physical activity and poor dietary quality, may exacerbate insulin resistance and hypertension [14, 15]. Multiple factors may also impact glomerular hyperfiltration. For instance, high dietary protein intake acutely increases glomerular filtration rate, whereas the use of renin–angiotensin–aldosterone system (RAAS) blocking agents mitigates hyperfiltration to preserve kidney function long term [16–20]. In African Americans specifically, high-risk variants in the *APOL1* gene may cause progressive nephron loss, compensatory hypertrophy of remaining glomeruli and hyperfiltration [21, 22]. Exploration of interactions between obesity and these proposed risk factors may identify opportunities to mitigate CKD in the context of obesity and provide insights about the pathophysiology of obesity-associated CKD.

In this study, we evaluate the association of obesity and other potentially synergistic risk factors with incident CKD in a prospective cohort of African Americans enrolled in the Jackson Heart Study (JHS). The JHS includes long-term follow-up; detailed phenotyping of key variables including diet, lifestyle habits and genetic risk for CKD; and complementary measures of obesity, including body mass index (BMI), waist circumference and directly quantified visceral adipose volume by computed tomography (CT). With these detailed measurements, the JHS provides an ideal opportunity to understand the possible interaction of the proposed risk factors in promoting CKD among African Americans.

MATERIALS AND METHODS

Study population

The JHS is a prospective cohort study designed to evaluate cardiovascular risk factors in African Americans. From 2000 to 2004, JHS enrolled 5301 African Americans 21–94 years of age from the Jackson, MS, USA, area and conducted two additional follow-up visits (Exam 2: 2005–2008, Exam 3: 2009–2013). The JHS included prior participants from the Atherosclerosis Risk in Communities Study, as well as family members of recruited JHS participants [23]. Our investigation includes JHS participants without prevalent CKD and with key data related to kidney function at baseline and at follow-up (Supplementary data, Figure S1). The study was approved by the institutional review board at the University of Mississippi Medical Center, Jackson State University and Tougaloo College. All participants provided written informed consent.

Exposure and outcome measurements

Obesity, the primary exposure, was measured using standard clinical measures, such as BMI and waist circumference, and using abdominal computed tomography (CT) to isolate visceral adipose volume [24]. BMI and waist circumference were measured using standard protocols at each study visit. As part of an ancillary study starting in 2006 (Exam 2), a noncontrast abdominal CT was performed in ∼54% of the JHS cohort. Adipose tissue was identified by radiographic tissue attenuation and the intraperitoneal adipose volume was calculated across 24 2-mm slices centered at L4–L5, as previously described [25]. JHS participants at Exam 2 were excluded from the CT scan for weight >350 lb, known pregnancy, unknown pregnancy status or age <40 years for women or <35 years for men [25].

The primary outcome was incident CKD at Exam 3. Incident CKD was defined as either (i) estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 accompanied by a >25% decline from baseline using the Chronic Kidney Disease Epidemiology Collaboration equation for serum creatinine or (ii) incident albuminuria, defined as a urine albumin:creatinine ratio (UACR) ≥30 mg/g. The UACR was calculated from a random spot urine collection or, if not available, a 24-h collection.

We hypothesized *a priori* that several factors may interact with obesity to modify CKD risk due to potentially synergistic

or antagonistic effects on metabolic risk factors or hyperfiltration. We considered physical activity, overall dietary quality, dietary protein intake, use of RAAS antagonists and *APOL1* genetic risk status. Physical activity was ascertained at Exam 1 by questionnaire and categorized by American Heart Association (AHA) recommendations [26]. Dietary intake was assessed at Exam 1 using the regionally appropriate and validated Delta Nutrition Intervention Research Initiative food frequency questionnaire [27, 28]. Dietary quality was scored based on compliance with five dietary goals proposed by the AHA's Life's Simple Seven recommendations [26]. Based on a 2000 kcal diet, 1 point was assigned for each: (i) ≥4.5 cups of fruits/vegetables daily; (ii) ≥2 servings (3.5 oz) of fish weekly; (iii) ≥3 servings (1 oz) of fiber-rich whole grains daily; (iv) <450 kcal (36 oz) from sugar-sweetened beverages per week and (v) <1500 mg of sodium daily. French fried potatoes and onion rings and fast food fried fish preparations did not contribute to (i) and (ii), respectively [29]. Dietary quality was scored as ideal (4–5 total), intermediate (2–3) or poor (0–1) [26], with ideal and intermediate diets combined in our analysis since few individuals consumed ideal diets. Dietary protein was quantified as absolute intake (g/day) and scaled intake (g/kg ideal body weight and percentage of total calories). The use of RAAS antagonists (angiotensin-converting enzyme inhibitors, angiotensin receptor blockers) was determined by reviewing medication lists and prescriptions at each study visit [30]. Variation in the *APOL1* gene locus was ascertained as previously described and individuals were classified as low risk (none or one risk allele) or high risk (two risk alleles) [31].

Additional covariates included demographics and medical history obtained by self-report and physical examination at baseline. Hypertension was defined as a clinical blood pressure of ≥140/90 mmHg, reported use of antihypertensive therapy or self-report. Diabetes mellitus was defined as fasting glucose ≥126 mg/dL or hemoglobin A1c ≥6.5%, reported use of insulin or hypoglycemic medications or self-report.

Statistical analysis

Obesity metrics were classified in clinically relevant categories (BMI) or using centiles (visceral adiposity and waist circumference), as well as continuously. Due to sex differences, waist circumference was first normalized to a gender-specific *z*-score before categorizing or analyzing continuously.

Because we only had two discrete measures of kidney function, we modeled the odds of incident CKD over ∼8 years of follow-up between Exams 1 and 3 using logistic regression. Based on exploratory data analysis, we incorporated quadratic terms in models as needed to account for nonlinear relationships between obesity and outcomes. We used likelihood ratio tests to evaluate fit compared with linear models. Models were adjusted for age, gender, income level, systolic blood pressure, diabetes, baseline eGFR and baseline log UACR. We assessed the fit of the final logistic models by comparing the model-predicted probabilities with observed frequencies of incident CKD within fine categories of exposure.

To test our hypothesis that the association of obesity with CKD would be modified by other clinical factors related to metabolic risk factors (dietary quality, physical activity) and renal hyperfiltration (dietary protein intake, high-risk *APOL1* status, RAAS antagonist use), we fit logistic models and tested interaction terms. Because models of visceral adiposity and incident CKD incorporated quadratic terms, in this instance interactions were evaluated using likelihood ratio tests of nested models. The adjusted prevalence of CKD was determined and graphed from these models by predicting prevalence from the model for an average JHS participant in the affluent category with all other covariates centered at their respective means.

We evaluated our sensitivity to several key factors. A key limitation of our study was measurement of visceral adipose volume at Exam 2 and not at baseline when BMI, waist circumference and baseline CKD status were determined. To better compare results from visceral adipose, BMI and waist circumference models, we fit additional models of BMI and waist circumference utilizing Exam 2 values and restricting analyses to those with an available abdominal CT. Additionally, we reasoned that if body anthropometrics were stable between Exams 1 and 2, visceral adiposity, which was only measured at Exam 2, was likely to be a reliable estimate of its value at baseline. With this in mind, we conducted sensitivity analyses of visceral adiposity and incident CKD limited to those individuals with a <3% increase in waist circumference between Exams 1 and 2. Another key limitation of the study was missing data and infrequent assessments of kidney function. For instance, missing data on kidney function at Exam 3 could be due to death or loss to follow-up, which are potentially informative. To evaluate the possible impact of this on our results, we built additional sensitivity models under the two extreme assumptions that all missing outcomes were unobserved incident CKD events or, alternatively, all were unobserved nonevents. Finally, to ensure results were not entirely driven by changes in microalbuminuria, we fit models using a purely eGFR-based definition of incident CKD (i.e. eGFR <60 mL/min/1.73 m^2 with a >25% decline) as well as models using >300 mg/g to define incident albuminuria. Statistical analyses were performed using R (R Core Team, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC, USA) and the 2016 Jackson Heart Study Vanguard Center data package.

RESULTS

Study population

At baseline, our study population ($n = 2043$) had a mean (± SD) age of 52.8 ± 11.9 years and eGFR of 98.8 ± 17.5 mL/min/1.73 m^2. Overall, 61.9% of participants were female, 15.7% had diabetes and 54.3% had hypertension. The median BMI was 30.3 kg/m^2 [interquartile range (IQR) 26.7–34.9], with 85.8% overweight or obese (≥25 kg/m^2). Waist circumference was elevated in 73.4% of women and 42.4% of men [32]. The median visceral adipose volume at Exam 2 was 745 cm^3 (IQR 525–1010). Overall characteristics of the eligible study population at Exams 1 and 2, as well as the subset with visceral adiposity from abdominal CT at Exam 2 ($n = 1477$) are presented in Table 1. Baseline characteristics in the JHS participants excluded from our visceral adiposity analyses ($n = 3824$) are shown in Supplementary data, Table S1.

Table 1. Characteristics of participants at each stage of analysis

Variable	Eligible cohort at Exam 1 ($n = 2043$)	Eligible cohort at Exam 2 ($n = 1907$)	Eligible cohort with visceral adipose volume ($n = 1477$)
Demographics			
Age, years	52.8 ± 11.9	53.2 ± 11.7	54.0 ± 10.6
Female, *n* (%)	1264 (61.9)	1191 (62.5)	931 (63.0)
Income, *n* (%)			
Poor	183 (9.0)	164 (8.6)	108 (7.3)
Lower middle	337 (16.5)	314 (16.5)	231 (15.6)
Upper middle	542 (26.5)	505 (26.5)	397 (26.9)
Affluent	652 (31.9)	619 (32.5)	509 (34.5)
Missing	329 (16.1)	305 (16.0)	232 (15.7)
Smoking status[a], *n* (%)			
Never	1485 (72.7)	1392 (73.0)	1080 (73.1)
Former	350 (17.1)	331 (17.4)	260 (17.6)
Current	206 (10.1)	183 (9.6)	137 (9.3)
Comorbidities			
Systolic BP (mmHg)	123.7 ± 16.1	123.7 ± 15.9	123.9 ± 15.7
Diastolic BP (mmHg)	79.3 ± 10.0	79.2 ± 10.0	79.4 ± 9.9
Hypertension, *n* (%)	1110 (54.3)	1048 (55.0)	835 (56.5)
Diabetes, *n* (%)	321 (15.7)	302 (15.8)	226 (15.3)
Kidney function			
eGFR (mL/min/1.73 m^2)	98.8 ± 17.5	98.5 ± 17.5	97.7 ± 16.8
Hyperfiltration[b], *n* (%)	222 (10.9)	205 (10.7)	137 (9.3)
Albumin:creatinine ratio[c] (mg/g)	5 (4–9)	5 (4–9)	5 (4–8)
Obesity measures			
Body mass index (kg/m^2)	31.5 ± 6.9	31.5 ± 6.9	31.3 ± 6.4
Obese (≥30 kg/m^2), *n* (%)	1065 (52.1)	995 (52.2)	754 (51.1)
Overweight (25–29.9 kg/m^2), *n* (%)	688 (33.7)	643 (33.7)	521 (35.3)
Normal/underweight (<25 kg/m^2), *n* (%)	290 (14.2)	269 (14.1)	202 (13.7)
Waist circumference[d], *n* (%)			
Normal	785 (38.4)	727 (38.1)	573 (38.8)
Overweight/obese	1258 (61.6)	1180 (61.9)	904 (61.2)
Exam 2 visceral adipose volume (cm^3)	NA	NA	792.3 ± 364.3
Proposed effect modifiers			
AHA dietary quality categorization[a,e], *n* (%)			
Poor health (0–1)	1010 (49.4)	936 (49.1)	725 (49.1)
Intermediate health (2–3)	793 (38.8)	753 (39.4)	593 (40.2)
Ideal health (4–5)	23 (1.1)	20 (1.1)	17 (1.2)
AHA physical activity category, *n* (%)			
Poor health	910 (44.5)	846 (44.4)	642 (43.5)
Intermediate health	681 (33.3)	640 (33.6)	489 (33.1)
Ideal health	452 (22.1)	421 (22.1)	346 (23.4)
Dietary protein intake			
Total protein intake (g/day)	80.0 ± 35.2	79.6 ± 35.0	78.8 ± 34.3
Protein/IBW (g/kg/day)	1.32 ± 0.58	1.31 ± 0.58	1.30 ± 0.58
Protein/total calories (%)	14.6 ± 3.1	14.6 ± 3.1	14.6 ± 3.1
APOL1 status[a], *n* (%)			
High-risk	162 (7.9)	154 (8.1)	122 (8.3)
Low-risk	1120 (54.8)	1045 (54.8)	814 (55.1)
Use of ACE-i and/or ARB[a], *n* (%)			
No	1398 (68.4)	1317 (69.1)	1041 (70.5)
Yes	250 (12.2)	235 (12.3)	180 (12.2)

Mean±SD shown for continuous variables (unless otherwise indicated) and proportions shown for categorical variables. ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; IBW, ideal body weight.

[a]The sum of frequencies for these categorical variables may not add up to 100% due to missing participant values.

[b]Hyperfiltration is defined as an eGFR >120 mL/min/1.73 m^2.

[c]Values shown for median (interquartile range).

[d]Waist circumference categorization determined by 2005 National Cholesterol Education Program ATP III Guidelines, which defined overweight/obese as a waist circumference ≥102 cm for males and ≥88 cm for females [15].

[e]Numbers in parentheses represent the Healthy Diet Score, based on the number of components met in the AHA optimal diet recommendations.

Complementary measures of obesity were moderately to strongly correlated, particularly when measured at the same visit. Visceral adipose volume at Exam 2 correlated modestly with Exam 2 BMI ($r = 0.49$) and strongly with Exam 2 waist circumference *z*-scores ($r = 0.66$ for women, 0.62 for men). The change in weight and waist circumference between Exams 1

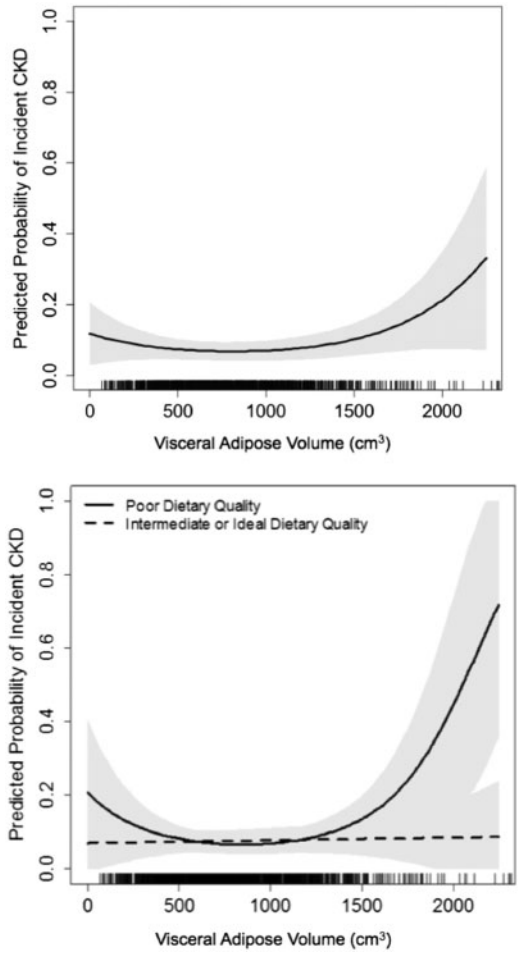

FIGURE 1: Predicted probability of incident CKD by visceral adipose volume in those with visceral adipose volume data ($n = 1477$) overall (176 events; top figure) and stratified by dietary quality ($n = 1335$; 157 events; bottom figure). Dietary quality modified the association of visceral adipose volume and incident CKD (P-interaction = 0.04) such that greater visceral adiposity was associated with a greater risk of incident CKD among those with a poor diet (solid line; $n = 723$; P = 0.001) but not an intermediate or ideal diet (dashed line; $n = 610$; P = 0.96). Light gray regions represent 95% CIs. Probabilities are derived from logistic regression models adjusted for age, gender, income level, systolic blood pressure, diabetes, eGFR and albuminuria and incorporating quadratic terms for visceral adipose volume due to the nonlinear association with risk (P = 0.02). Displayed probabilities represent the modeled probability of CKD in an average JHS participant in the affluent category when all other covariates are centered at their respective means.

and 2 was modest overall, with a median weight change of 1.1 kg (IQR −2.5 – 4.6) and a median change in absolute waist circumference of 2.4 cm (IQR −2.3 – 6.7). Visceral adipose volume was not available at Exam 1.

Overall association of obesity with CKD

Incident CKD was assessed over the period between Exams 1 and 3, spanning a median of 8 years (range 6–11). By Exam 3, 12.4% of the study population had developed incident CKD ($n = 254$), including 93 participants by eGFR criteria alone, 136 with incident albuminuria alone and 25 meeting both eGFR and UACR criteria at Exam 3. The number of incident CKD cases was higher with greater BMI, waist circumference *z*-score and visceral adipose volume (Supplementary data, Figure 2). BMI and waist circumference *z*-score were not associated with incident CKD when modeled continuously (P = 0.1 for each). However, higher visceral adipose volume was associated with an increased risk of incident CKD overall (P = 0.008), but was nonlinear (Figure 1; P = 0.02). The highest quartile of waist circumference *z*-score was associated with a greater risk of incident CKD compared with the lowest; however, there was no linear trend across quartiles (Table 2).

Obesity and metabolic syndrome risk factors

A high prevalence of poor dietary quality was observed across all levels of adiposity, ranging from 45.9 to 55.0% by tertile of visceral adipose volume. Associations of BMI and waist circumference with incident CKD did not differ by dietary quality (P-interaction = 0.2 for each; Table 2). However, dietary quality modified the association of visceral adiposity with incident CKD (P-interaction = 0.04) such that greater visceral adiposity was associated with a higher incident CKD risk in those with poor diet (P = 0.001) but not intermediate or ideal diet (P = 0.96; Figure 1). The relative odds of incident CKD associated with poor versus intermediate or ideal dietary intake at different levels of adiposity are presented in Supplementary data, Table S2. Physical activity did not modify the association of any obesity measure with CKD (Table 3).

Similar to the primary result, we observed no interaction between dietary quality and BMI (P-interaction = 0.3) or waist circumference (P-interaction = 0.2) when measured at Exam 2 among those with CT available. In those with a <3% waist circumference increase between Exams 1 and 2 ($n = 728$), we found similar relationships between visceral adipose volume and incident CKD (P = 0.04) and interaction between visceral adiposity and dietary quality (P-interaction = 0.003). When classifying those with missing outcome data ($n = 704$) as either all events or nonevents, there were no changes in the associations between obesity measures and incident CKD risk or in the observed interactions (data not shown). With incident CKD defined by eGFR criteria alone, we obtained similar results (P-interaction = 0.004 for visceral adiposity and dietary quality). Our findings were also similar when defining incident albuminuria as >300 mg/g, with a higher incident CKD risk in participants with poor diet (P = 0.002) but not intermediate or ideal diet (P = 0.5).

Obesity and hyperfiltration risk factors

We observed no interactions between any obesity measure and dietary protein intake or the use of RAAS blocking agents at Exam 1 (Table 3). *APOL1* risk status (13% with high-risk status among those tested; Table 1) interacted with waist circumference *z*-score (P-interaction = 0.02; Figure 2) but not baseline BMI (P-interaction = 0.3) or visceral adiposity (P-interaction = 0.1). When stratified by *APOL1* risk status, a higher waist circumference *z*-score was significantly associated with a higher incident CKD risk in those with low-risk *APOL1* status {P = 0.04; odds ratio [OR] 2.16 for Q4 versus Q1 [95% confidence interval (CI) 1.18–3.96]} but not in those in the high-risk *APOL1* group (P = 0.08). Although interactions were not

Table 2. Comparison of adjusted[a] ORs of incident CKD for the overall cohort, for poor dietary quality and for more optimal dietary quality by obesity metrics

Exposure	Overall		Intermediate/ideal dietary quality		Poor dietary quality		
	OR (95% CI)	P-value[b]	OR (95% CI)	P-value[b]	OR (95% CI)	P-value[b]	P-interaction
Exam 1, BMI (kg/m^2)							
Q1 (<26.7)	1.0		1.0		1.0		
Q2 (26.7–30.3)	1.03 (0.65–1.64)		1.19 (0.61–2.32)		0.91 (0.48–1.71)		
Q3 (30.3–34.9)	1.17 (0.74–1.85)		1.09 (0.55–2.17)		1.22 (0.66–2.24)		
Q4 (>34.9)	1.30 (0.81–2.08)		1.64 (0.84–3.21)		1.04 (0.55–1.97)		0.2
		0.1		0.05		0.9	
Exam 1, waist circumference *z*-score							
Q1 (< −0.69)	1.0		1.0		1.0		
Q2 (−0.69 to −0.12)	1.43 (0.88–2.31)		1.67 (0.82–3.38)		1.24 (0.64–2.39)		
Q3 (−0.12 – 0.54)	1.00 (0.61–1.64)		1.05 (0.50–2.21)		0.96 (0.50–1.84)		
Q4 (> 0.54)	1.71 (1.06–2.74)		2.36 (1.18–4.73)		1.29 (0.68–2.43)		0.2
		0.1		0.04		0.9	
Visceral adipose volume[c,d] (cm^3)							
Q1 (<525)	1.28 (0.73–2.24)		0.72 (0.33–1.54)		2.61 (1.12–6.09)		
Q2 (525–745)	1.0		1.0		1.0		
Q3 (745–1010)	1.02 (0.60–1.75)		0.89 (0.43–1.84)		1.32 (0.58–3.01)		
Q4 (>1010)	1.46 (0.89–2.41)		0.80 (0.39–1.62)		2.71 (1.28–5.75)		0.04

[a]Models were adjusted for age, gender, income level, systolic blood pressure, diabetes, eGFR and albuminuria. Overall result is additionally adjusted for the main effect of dietary quality.
[b]P-value for linear trend.
[c]Linear trend was not tested for visceral adiposity due to nonlinear relationships in continuous analyses.
[d]For visceral adipose volume, the second quartile (Q2) serves as the reference category given the U-shaped association (P = 0.02) of visceral adiposity and incident CKD risk in continuous analyses.

significant, both higher visceral adiposity [OR 2.18 for Q4 versus Q2 (95% CI 1.08–4.41)] and higher BMI [OR 1.90 for Q4 versus Q1 (95% CI 1.08–3.33)] were associated with an increased risk of incident CKD among those with low-risk, but not high-risk, *APOL1* status (Table 3).

DISCUSSION

In our prospective study of obesity and synergistic risk factors for CKD in African Americans, we found that greater visceral adiposity, assessed by abdominal CT, was associated with an increased risk of incident CKD. However, this elevated risk was evident only among those with poor dietary quality. Although we did not directly evaluate insulin resistance or inflammatory markers, prior studies note that visceral adipose tissue contributes to higher circulating levels of free fatty acids and inflammatory molecules that may promote the development of insulin resistance, endothelial dysfunction and kidney disease [33–37]. Relevant to our cohort of adult African Americans with a high prevalence of obesity, we propose that components of a poor-quality diet, such as large quantities of fat and simple sugars, may synergize with the metabolic and inflammatory derangements found in metabolic syndrome and induced by increased visceral adipose tissue, contributing to CKD risk [38, 39].

The low prevalence of ideal diet quality (1.1%) in our study mirrors the low prevalence seen nationally [40]. It is unknown from our analysis which specific features of dietary quality account for the interaction with obesity. However, in the JHS, differences in dietary quality were driven primarily by variations in the intake of fruits and vegetables, fish and sugar-sweetened beverages [29]. Increased consumption of fruits, vegetables and fish may preserve kidney function through improved blood pressure and anti-inflammatory effects [41, 42]. In animal models, high intake of fructose, found in sugar-sweetened beverages, has been associated with the development of obesity, hypertension, insulin resistance and acceleration of CKD progression [43, 44]. Thus the confluence of increased visceral adiposity with features of a poor quality diet, including low intake of fruits, vegetables and fish and high intake of refined sugars, could lead to magnified risks of the metabolic syndrome and kidney disease.

Although higher visceral adiposity was associated with increased incident CKD risk in our study, more conventional measures of obesity, such as BMI and waist circumference, did not. Another recent investigation of JHS participants similarly found no relationship between BMI or waist circumference and risk of rapid renal function decline over time [45]. BMI does not distinguish between lean and nonlean body mass, and higher lean mass is associated with better outcomes in CKD [46–48]. While waist circumference may more accurately capture central adiposity, it too may not fully reflect the metabolic risk associated with visceral adipose [49]. Therefore we hypothesize that misclassification of the more metabolically active visceral adipose by BMI and waist circumference is the main reason we did not observe associations between these parameters and incident CKD overall. Thus the stronger association of visceral adiposity with incident CKD observed here suggests that the metabolic consequences of obesity, as opposed to body size *per se*, are paramount in promoting CKD.

Interestingly, we only observed associations between higher obesity metrics and higher risk of incident CKD in low-risk *APOL1* individuals but not in those with a high-risk genotype. Our results concur with a prior report in African Americans with presumed hypertensive CKD [50]. Persistent inflammation, in the form of elevated interferon levels, may result in a wasting

Table 3. Comparison of adjusted[a] ORs (95% CI) of incident CKD by obesity metrics within strata

Exposure	Intermediate/ ideal physical activity	Poor physical activity	P-interaction[c]	Low dietary protein (≤14.2% total kcal)	High dietary protein (>14.2% total kcal)	P-interaction[c]
Exam 1, BMI (kg/m^2)						
Q1 (<26.7)	1.0	1.0		1.0	1.0	
Q2 (26.7–30.3)	1.30 (0.72–2.33)	0.75 (0.40–1.43)		0.98 (0.53–1.81)	1.07 (0.53–2.15)	
Q3 (30.3–34.9)	0.90 (0.48–1.69)	1.33 (0.73–2.42)		1.38 (0.73–2.61)	1.01 (0.51–2.01)	
Q4 (>34.9)	1.16 (0.61–2.19)	1.37 (0.76–2.45)	0.1	1.34 (0.72–2.51)	1.25 (0.62–2.52)	0.9
Exam 1, waist circumference *z*-score						
Q1 (< −0.69)	1.0	1.0		1.0	1.0	
Q2 (−0.69 to −0.12)	1.56 (0.83–2.90)	1.23 (0.65–2.35)		1.33 (0.70–2.52)	1.48 (0.71–3.08)	
Q3 (−0.12 – 0.54)	1.01 (0.53–1.93)	0.80 (0.41–1.55)		1.28 (0.66–2.48)	0.78 (0.37–1.65)	
Q4 (> 0.54)	1.68 (0.89–3.19)	1.69 (0.93–3.06)	0.4	1.77 (0.93–3.39)	1.61 (0.80–3.25)	0.7
Visceral adipose volume[b] (cm^3)						
Q1 (<525)	0.73 (0.35–1.52)	2.11 (0.95–4.67)		1.26 (0.58–2.71)	1.35 (0.59–3.12)	
Q2 (525–745)	1.0	1.0		1.0	1.0	
Q3 (745–1010)	0.64 (0.32–1.30)	1.75 (0.83–3.70)		1.19 (0.55–2.58)	0.90 (0.43–1.89)	
Q4 (>1010)	1.21 (0.64–2.31)	2.02 (0.99–4.09)	0.5	1.69 (0.81–3.53)	1.32 (0.67–2.59)	0.5

Exposure	*APOL1* low-risk	*APOL1* high-risk	P-interaction[c]	No RAAS blockade	Plus RAAS blocking medication use	P-interaction[c]
Exam 1, BMI (kg/m^2)						
Q1 (<26.7)	1.0	1.0		1.0	1.0	
Q2 (26.7–30.3)	0.97 (0.54–1.75)	0.96 (0.21–4.30)		1.20 (0.72–1.99)	1.03 (0.31–3.45)	
Q3 (30.3–34.9)	0.93 (0.51–1.71)	0.85 (0.21–3.48)		0.98 (0.57–1.69)	1.58 (0.52–4.78)	
Q4 (>34.9)	1.90 (1.08–3.33)	0.87 (0.19–4.05)	0.3	1.21 (0.72–2.06)	2.20 (0.74–6.54)	0.3
Exam 1, waist circumference *z*-score						
Q1 (< −0.69)	1.0	1.0		1.0	1.0	
Q2 (−0.69 to −0.12)	1.56 (0.84–2.92)	1.38 (0.36–5.29)		1.45 (0.84–2.52)	2.22 (0.65–7.67)	
Q3 (−0.12 – 0.54)	1.04 (0.54–1.98)	0.66 (0.16–2.62)		0.96 (0.54–1.72)	0.78 (0.22–2.69)	
Q4 (> 0.54)	2.16 (1.18–3.96)	0.59 (0.15–2.38)	0.02	1.79 (1.04–3.08)	2.87 (0.93–8.84)	0.8
Visceral adipose volume[b] (cm^3)						
Q1 (<525)	1.43 (0.64–3.17)	0.62 (0.13–3.03)		0.92 (0.47–1.82)	0.77 (0.19–3.16)	
Q2 (525 – 745)	1.0	1.0		1.0	1.0	
Q3 (745 – 1010)	2.12 (1.01–4.43)	0.94 (0.23–3.83)		1.15 (0.63–2.10)	0.83 (0.25–2.72)	
Q4 (>1010)	2.18 (1.08–4.41)	0.60 (0.15–2.43)	0.1	1.91 (1.09–3.34)	0.85 (0.28–2.64)	0.5

[a]Models were adjusted for age, gender, income level, systolic blood pressure, diabetes, eGFR and albuminuria.
[b]For visceral adipose volume, the second quartile (Q2) serves as the reference category given the U-shaped association (P = 0.02) of visceral adiposity and incident CKD risk in continuous analyses.
[c]P-interaction between obesity measures and the proposed synergistic risk factor from the continuous linear model for BMI and waist circumference and from the quadratic model for visceral adipose volume.

syndrome associated with *APOL1*-related disease [51]. In fact, African American women with high-risk *APOL1* have been found to have lower BMIs than their lower-risk counterparts [21]. Because *APOL1*-associated kidney disease is incompletely penetrant and most individuals with a high-risk genotype will not exhibit kidney disease [22], we hypothesize that the seemingly paradoxical relationship between *APOL1* genotype and obesity may merely be a marker of individuals with penetrant *APOL1*-associated disease. Alternatively, a high-risk *APOL1* genotype may overpower the impact of adiposity in promoting CKD. We cannot exclude the possibility that survival bias may also affect our results, such that individuals with typical *APOL1*-associated kidney disease may have developed baseline CKD and were largely excluded from our analysis. In light of similarly paradoxical interactions between *APOL1* risk status and obesity measures in other African American cohorts [50], our finding warrants deeper investigation.

A key strength of our investigation was the use of a large, prospective, high-risk study population with long-term follow-up. Relative to other racial groups, African Americans exhibit higher rates of obesity and greater risk for advanced and progressive CKD [1, 52], and our study participants reside in the Southeastern USA, a region with a high prevalence of overweight, obesity and metabolic disease [53]. Also, though connections between better dietary quality and more optimal renal outcomes have been reported [54–58], to our knowledge our study is the first to report on the synergy between dietary quality and adiposity in CKD risk. Our study also has some limitations. First, with visceral adiposity measured at Exam 2 and only two available measurements of kidney function (Exams 1 and 3), it is possible that some renal function decline had already occurred before CT measurement of visceral adiposity. Thus reverse causation cannot be fully excluded. As reassurance, BMI and waist circumference at Exam 2 correlated well with visceral adipose volume, there was minimal weight change between Exams 1 and 2 on average and associations between visceral adiposity, dietary quality and incident CKD remained robust when limiting the analyses to those without clinically relevant increase in waist circumference between visits, a surrogate measure of central adiposity. Second, data on physical activity and dietary intake are subject to recall bias and were only available at baseline, not accounting for individual changes that occurred over time. Third, there was the potential for informative missing data on incident

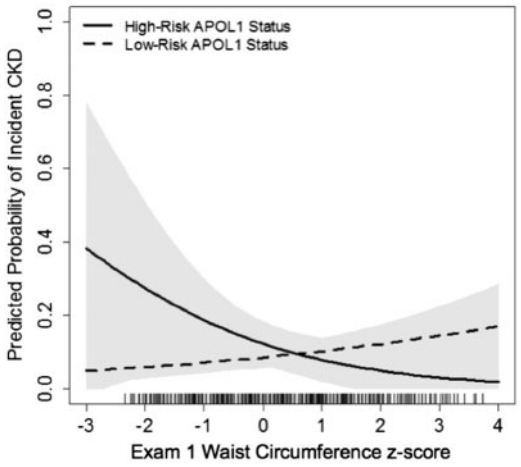

FIGURE 2: Predicted probability of incident CKD (167 events) by gender-specific waist circumference *z*-score with high-risk *APOL1* status (solid line; $n = 161$) and low-risk *APOL1* status (dashed line; $n = 1{,}119$). Light gray regions represent 95% CIs. There was significant interaction between waist circumference and *APOL1* risk status (P-interaction = 0.02). With low-risk *APOL1* status, a higher waist circumference *z*-score was significantly associated with higher incident CKD risk (P = 0.04), but this relationship was reversed, but not significant (P = 0.08), in participants with high-risk *APOL1* status. Probabilities are derived from logistic regression models adjusted for age, gender, income level, systolic blood pressure, diabetes, eGFR and albuminuria. Displayed probabilities represent the modeled probability of CKD in an average JHS participant in the affluent category when all other covariates are centered at their respective means. In our cohort of 2043 JHS participants at Exam 1, 162 (8%) had high-risk *APOL1* genetic status, 1120 (55%) had low-risk *APOL1* status and 761 (37%) had no *APOL1* genotyping data.

CKD events as well as misclassification of CKD status with only one UACR and eGFR measurement each at Exams 1 and 3. Nonetheless, our results were robust in a number of sensitivity analyses considering alternative definitions of CKD and albuminuria and imputing missing cases as either all events or nonevents. Finally, though there might be an inflammatory pathway linking poor dietary quality and visceral adiposity with CKD risk, we did not study any inflammatory biomarkers, such as C-reactive protein, in our analyses.

In summary, we observed an association between higher visceral adiposity and an increased risk for new-onset CKD in African American adults that was only present among those with poor diet quality. Both this diet–obesity interaction and the stronger overall association between visceral adiposity and CKD compared with other obesity metrics suggest that metabolic factors promoted by dietary intake and greater visceral adipose volume are major pathways promoting CKD. Future studies should investigate possible mechanisms directly and evaluate interventions that focus on optimizing dietary quality in African Americans with obesity.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

AUTHORS' CONTRIBUTIONS

The authors' contributions to this manuscript include concept and study design (R.E.O., C.J.D., N.A.B., L.E.B., J.J.S.); analysis and interpretation of data (all authors); providing intellectual content of critical importance (all authors) and drafting, revision and final approval of the manuscript (all authors).

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CONFLICT OF INTEREST STATEMENT

None declared. The results presented in this article have not been published in whole or part, except in abstract form.

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ORIGINAL ARTICLE

White blood cell fractions correlate with lesions of diabetic kidney disease and predict loss of kidney function in Type 2 diabetes

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ABSTRACT

Background. Inflammation linked to diabetic kidney disease (DKD) may affect white blood cell (WBC) counts and differentials. We examined the cross-sectional associations of total WBC count and WBC fractions with structural lesions of DKD in 108 Pima Indians with Type 2 diabetes who underwent research kidney biopsies. We also examined the longitudinal association of these WBC variables with renal function loss (RFL) in 941 Europeans with Type 2 diabetes from the SURDIAGENE study.

Methods. Associations of WBC variables with morphometric parameters were assessed by linear regression. RFL was defined as≥40% loss of estimated glomerular filtration rate from baseline. Associations with RFL were evaluated by Cox regression. Hazard ratios (HRs) were reported per standard deviation increment of each WBC variable.

Results. After multivariable adjustment, lymphocyte ($r = -0.20$, $P = 0.043$) and eosinophil ($r = 0.21$, $P = 0.032$) fractions in the Pima Indians correlated with glomerular basement membrane width. Eosinophil fraction also correlated with glomerular filtration surface density ($r = -0.21$, $P = 0.031$). Lymphocyte fraction ($r = 0.25$, $P = 0.013$), neutrophil fraction ($r = -0.23$, $P = 0.021$) and the neutrophil:lymphocyte ratio ($r = -0.22$, $P = 0.024$) correlated with percentage of normally fenestrated endothelial cells. During median follow-up of 4.5 years, 321 SURDIAGENE participants developed RFL. Lower lymphocyte fraction [HR = 0.67, 95% confidence interval (95% CI) 0.60–0.76] and higher neutrophil fraction (HR = 1.35, 95% CI 1.20–1.52), total WBC count (HR = 1.20, 95% CI 1.08–1.35) and neutrophil:lymphocyte ratio (HR = 1.44, 95% CI 1.28–1.62) each predicted RFL in this cohort.

Conclusions. WBC fractions associate with morphometric lesions of DKD and predict RFL in individuals with Type 2 diabetes.

Keywords: biomarkers, CKD, diabetic kidney disease, inflammation, kidney biopsy

INTRODUCTION

Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease (ESRD) worldwide, and carries large human and societal costs [1]. The growing list of inflammatory markers associated with progressive kidney disease [2–6] suggests that inflammation plays a key role in DKD development and progression. A complete white blood cell (WBC) count is a low cost and widely available clinical test that reflects inflammation, and WBC counts and fractions have been linked to diabetes

