Obesity, metabolic health, and the risk of end-stage renal disease

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Abstract

Obesity is associated with chronic kidney disease progression. Whether metabolic risk factors modify this association is unclear. Here we examined associations of body mass index (BMI) and metabolic health with risk of end-stage renal disease (ESRD) in the Reason for Geographic and Racial Differences in Stroke (REGARDS) study. Among 21,840 participants eligible for analysis, 247 developed ESRD (mean follow-up of 6.3 years). Metabolic health significantly modified the association of BMI with ESRD. In models stratified by presence or absence of metabolic syndrome and adjusted for demographic, lifestyle and clinical factors, higher BMI was associated with lower risk of ESRD in those without (hazard ratio per 5 kg/m^2 increase in BMI 0.70, 95%CI 0.52,0.95), but not those with (hazard ratio, 1.06) metabolic syndrome. In models stratified by weight and metabolic health, compared to normal weight (BMI 18.5–24.9 kg/m2) participants without metabolic syndrome the overweight individuals (BMI 25–29.9) and obese individuals (BMI of 30 or more) with metabolic syndrome had greater risk of ESRD (hazard ratios of 2.03 and 2.29, respectively), whereas obesity without the metabolic syndrome was associated with lower risk of ESRD (hazard ratio 0.47). Thus, higher BMI is associated with lower ESRD risk in those without but not those with metabolic syndrome.

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Keywords

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INTRODUCTION

In the general population, obesity (defined as a body mass index [BMI] 30 kg/m^2) has been associated with adverse cardiovascular outcomes and increased mortality [1, 2]. Obesity has also been implicated in the development and progression of chronic kidney disease (CKD) [3-9]. However, there is accumulating evidence that obesity may confer protective benefits in individuals with chronic disease conditions, including coronary artery disease and CKD [10-18]. The reasons for why obesity is associated with a protective effect in certain subgroups is unclear, but may be related to the presence or absence of concurrent metabolic risk factors, such as insulin resistance, lipid disorders and visceral adiposity. Studies have shown that individuals who are obese based upon BMI criteria but have a metabolically healthy profile have better outcomes than those who have a metabolically unhealthy profile [18, 19]. For example, in a population of black and white adults with CKD, we recently showed that overweight and obese individuals who were metabolically healthy had a lower risk for mortality as compared to normal weight individuals who were metabolically healthy [19]. In contrast, we observed no differences in mortality when comparing metabolically unhealthy overweight and obese individuals to metabolically healthy normal weight individuals [19]. Whether metabolic health similarly modifies the association of BMI with the incidence of end-stage renal disease (ESRD) is unclear. The primary focus of this analysis was to examine the independent and joint associations of BMI and metabolic health with risk of ESRD within the Reason for Geographic and Racial Differences in Stroke (REGARDS) study, a large prospective cohort of 30,239 black and white adults from across the United States.

RESULTS

After excluding 4,143 individuals missing data on any of the parameters used to define metabolic syndrome, 318 individuals who had a BMI < 18.5 kg/m^2, 3,536 individuals who did not fast or had missing data on fasting status prior to collection of the blood samples, 319 individuals lost to follow-up, and 83 individuals who were receiving hemodialysis at the time of study enrollment, 21,840 participants were included in the final analyzed sample.

Table 1 depicts the baseline characteristics of the study sample by categories of BMI and metabolic health. As compared to individuals with normal weight, individuals in the overweight and obese categories were more likely to be younger, black, have a history of hypertension, diabetes, coronary heart disease (CHD) and stroke, have lower socioeconomic status, have albuminuria (urine albumin to creatinine ratio [ACR] 30 mg/g) and have lower estimated glomerular filtration rate (eGFR) at baseline. Participants with metabolic syndrome were more likely to be female, black, have lower socioeconomic status and have a history of hypertension, diabetes, CHD and stroke at baseline as compared to individuals

without metabolic syndrome. Those with metabolic syndrome were also more likely to have albuminuria and lower eGFR than those without metabolic syndrome.

Associations of BMI and metabolic health with ESRD

A total of 247 participants developed ESRD over a mean 6.3 ± 1.3 years of follow-up. Metabolic health modified the association of BMI with ESRD in a Cox regression model adjusted for age, race, sex, geographic region of residence, socio-demographic status, lifestyle factors and co-morbidities ($P_{interaction}= 0.01$); therefore, we stratified all subsequent analyses by presence or absence of metabolic syndrome. The association of BMI and ESRD was not modified by age, gender, or race (P for interaction > 0.10 for all). When stratified by the presence or absence of the metabolic syndrome, among participants without the metabolic syndrome, higher BMI was associated with lower risk of ESRD in models adjusted for age, race, sex, and geographic region of residence (HR per 5 kg/m^2 increase in BMI 0.67, 95% confidence interval [CI] 0.49, 0.91), and in models further adjusted for education, income, physical activity, cigarette smoking, systolic blood pressure and a history of CHD and stroke (HR per 5 kg/m^2 increase in BMI 0.70, 95% CI 0.52, 0.95). Among participants with the metabolic syndrome, there were no statistically significant associations of increasing BMI with risk of incident ESRD (HR per 5 kg/m^2 increase in BMI 1.06, 95%CI 0.93, 1.21).

Figure 1 depicts the association of BMI with ESRD risk in the full study sample and stratified by absence or presence of metabolic syndrome. Increasing BMI was associated with increased risk of developing ESRD in the full study sample (Figure 1A). However, when stratified by the absence or presence of metabolic syndrome, increasing BMI was associated with a lower risk of developing ESRD in individuals without the metabolic syndrome (Figure 1B), whereas no association of BMI with risk of ESRD was observed in individuals with the metabolic syndrome (Figure 1C).

Table 2 depicts the incidence rates for ESRD per 1,000 person-years of follow-up by categories of weight and metabolic syndrome status. ESRD incidence rates were higher in those with the metabolic syndrome as compared to those without the metabolic syndrome within each weight category. **Figure 2** reports the HRs for ESRD as a function of weight and metabolic syndrome categories, with individuals who were normal weight and without the metabolic syndrome serving as the referent group. In models adjusted for age, race, sex, geographic region of residence, educational achievement, annual family income, physical activity, cigarette smoking, and history of CHD and stroke, the HR for ESRD was higher in overweight and obese participants with the metabolic syndrome than in normal weight participants without the metabolic syndrome (HR 2.03 95%CI, 1.26, 3.17 and HR 2.29 95%CI 1.51, 3.48, respectively). Among all the individual metabolic risk factors, higher triglycerides, higher blood pressure and higher fasting glucose were significantly associated with higher risk of ESRD, with the magnitude of the association being the greatest for higher blood pressure and higher fasting glucose (data not shown). In contrast, when comparing overweight or obese without the metabolic syndrome to normal weight participants without the metabolic syndrome, the HRs for ESRD were 0.65 (95%CI 0.39, 1.11) and 0.47 (95%CI 0.23, 0.95), respectively.

DISCUSSION

In this prospective study of 21,840 black and white community-living adults, we found that metabolic health modified the association of BMI with risk of incident ESRD, such that higher BMI was associated with lower risk of incident ESRD among those without metabolic syndrome, but not those with metabolic syndrome. Further, as compared to normal weight individuals without the metabolic syndrome, individuals with the metabolic syndrome had an approximately 2-fold greater risk of developing ESRD irrespective of weight status, whereas among those without the metabolic syndrome, obesity was associated with lower risk of ESRD. These findings suggest that the magnitude and direction of the association of BMI with risk of incident ESRD depends on an individual's concurrent metabolic health. Additionally, these results suggest BMI alone is an inadequate marker of future risk of ESRD.

Our findings provide important context to the results of several prior studies examining the association of BMI with risk of ESRD. Vivante and colleagues showed that higher BMI was associated with higher risk of developing ESRD in 1.2 million adolescents over a 25 year follow-up period [20]. Other reports including a study of over 300,000 subjects by Hsu et al. showed a higher risk of ESRD associated with higher BMI in the general population [21-25]. These results are consistent with the findings depicted in Figure 1A of the current manuscript in which higher BMI was associated with greater risk of ESRD in the full study sample. Importantly, however, none of the prior studies stratified the analysis by absence or presence of the metabolic syndrome. This is critical in that higher BMI was associated with lower risk of ESRD in those without the metabolic syndrome, whereas no association of BMI with ESRD risk was observed in those with the metabolic syndrome in the current study. When coupled with our finding that the metabolic syndrome was a powerful risk factor for ESRD, this suggests that the link between higher BMI and greater risk of ESRD reported in prior studies was primarily driven by the association of metabolic syndrome with ESRD risk and not necessarily by a direct association of BMI with ESRD. If so, it is possible that the magnitude of the association of higher BMI with risk of ESRD was underestimated in these prior studies by combining both individuals with minimal to no metabolic risk factors—who had an inverse association between BMI and ESRD risk in the current study—with individuals with metabolic syndrome, who were likely driving the association of higher BMI with higher risk of ESRD. Future collaborative studies with larger sample sizes are needed to clarify this issue.

The reasons for our finding of an association of higher BMI with lower risk of ESRD among individuals without the metabolic syndrome is unclear. However, this is in line with several prior studies showing that higher BMI is associated with improved survival in individuals with CKD [10-17]. The physiological mechanisms underlying this "obesity paradox" are not well understood. Poor nutritional status or protein-energy wasting are strong predictors of worse outcomes in the CKD population.[26] Recent evidence suggests that protein energy wasting can be induced by inflammation, an effect that is potentially mediated by suppression of appetite and lowering of albumin due to systemic effects of interleukin-6 or tumor necrosis factor alpha [27-29]. Protein energy wasting and increased inflammation are thought to be major underlying mechanisms responsible for increased mortality in this

population. Moreover, adipose tissue is now recognized as an active endocrine organ secreting bioactive molecules such as leptin, tumor necrosis factor alpha and interleukin-6 which are thought to be potential mediators of insulin resistance, diabetes, hyperlipidemia, endothelial dysfunction, and atherosclerosis [30]. It is also possible that in the advanced CKD and ESRD population, improved nutritional status, elevated adiponectin levels, and increased energy reserves associated with elevated BMI may not only negate but rise above the deleterious pro-inflammatory and atherogenic effects of increased fat mass, potentially explaining why we observed a protective association of obesity with ESRD risk among individuals who did not meet criteria for the metabolic syndrome [31].

The results of our study also support and strengthen the important role metabolic syndrome plays in the development of ESRD. Across all BMI categories, the subgroups with metabolic syndrome were found to have a 2-fold higher risk of developing ESRD as compared to normal weight individuals without metabolic syndrome. This finding is consistent with prior studies showing an association between the presence of metabolic syndrome and development and progression of CKD [32-39]. It is also interesting to note that among all the factors contributing towards metabolic syndrome, higher blood pressure, higher triglycerides and higher fasting glucose were the individual metabolic risk factors most strongly associated with increased risk of development of ESRD. Focusing on these factors in clinical practice might prove to be most efficacious way not only to measure the risk of poor renal outcomes related to higher BMI but also reducing the risk of ESRD by specifically targeting these factors.

Strengths of our study include a large cohort, using standardized criteria for defining the metabolic syndrome, robust data collection and utilizing USRDS data which captures more than 95% of the incident ESRD events across the Unites States. Also, unlike many prior studies that used a composite outcome of all-cause mortality and ESRD, we focused on ESRD as our primary outcome. Our study also had a number of limitations. As with any other observational study, causal relationships cannot be inferred from our observations. Next, we could not establish differential contributions of fat mass or lean mass towards BMI, precluding us from determining the associations of body composition with incident ESRD in this population. It is not clear whether loss of adipose tissue or muscle mass or both leads to worse outcomes in this population. At least one study found that reducing either muscle mass or fat mass was associated with increased mortality [12]. Results from our study may not be applicable to other ethnic groups such as Asians, Hispanics and other minorities. Also, due to low event numbers in some categories, we may have been underpowered to detect statistically significant associations. Finally, we only had a single measurement of BMI, limiting our ability to establish the impact of weight loss or gain during the follow-up period.

Multiple studies in the past have shown that elevated BMI is associated with increased risk for developing CKD and ESRD. However, none of these studies assessed the effects of metabolic health on this association. Our study shows that a clustering of metabolic risk factors may modify the association of BMI with the risk of incident ESRD, suggesting that BMI alone is a poor marker of future risk of ESRD. Our study highlights the importance of assessing metabolic health status along with BMI and understanding their joint effect on the

risk for developing ESRD. Further research to study the effects of elevated BMI among metabolically healthy individuals on incidence of ESRD is needed.

METHODS

Study Participants

The REGARDS study is a population-based investigation of stroke incidence in black and white US adults 45 years of age. Details of the study design have been reviewed elsewhere [40]. Briefly, participants were recruited from the 48 contiguous US states and the District of Columbia. The study was designed to provide approximately equal representation of men and women, and oversampled black individuals and persons living in the stroke belt/ buckle of the US. Overall, 30,239 black and white adults were enrolled between January 2003 and October 2007 (42% black, 55% women). The REGARDS study protocol was approved by the Institutional Review Boards governing research in human subjects at the participating centers and all participants provided informed consent.

Primary Exposures

The exposures of interest were BMI and metabolic health status defined in accordance with the harmonized criteria for metabolic syndrome [41]. Specifically, individuals who had evidence of 3 of the following metabolic risk factors were categorized as having the metabolic syndrome: elevated waist circumference (> 102 cm for men; > 88 cm for women), elevated fasting triglycerides (150 mg/dL), reduced fasting high-density lipoprotein [HDL] (< 40 mg/dL in men; < 50 mg/dL in women), elevated blood pressure (systolic 130 and/or diastolic 85 mm Hg or current treatment with anti-hypertensive therapy), and elevated fasting glucose (100 mg/dL or known history of diabetes [ascertained by self-report or current therapy with diabetes medications]).

Trained interviewers conducted computer-assisted telephone interviews to obtain information including participants' socio-demographics, cardiovascular risk factors, tobacco usage, physical activity, and use of medications. Following this call, an in-home study visit was conducted that included an electrocardiograph (ECG) recording, inventory of medications and collection of blood and urine samples. Waist circumference (in centimeters) was measured during the in-home visit using a tape measure positioned midway between the lowest rib and the iliac crest with the participant standing. Systolic and diastolic blood pressure was defined as the average of two seated measures taken after a five-minute rest.

Ascertainment of Covariates of Interest

Age, race, sex, annual family income, educational attainment, cigarette smoking and alcohol use were determined by self-report. Physical activity was assessed through a single question: "How many times per week do you engage in intense physical activity, enough to work up a sweat," with response options of: none, 1-3 times/week or 4 times/week. History of CHD was defined as having any of the following: evidence of myocardial infarction on the baseline ECG, self-report of a prior history of a cardiac procedure (coronary artery bypass surgery or percutaneous angioplasty), or self-reported history of myocardial infarction. History of stroke was ascertained by self-report. Serum creatinine was calibrated to an

international isotope dilution mass spectroscopic (IDMS)-traceable standard, measured by colorimetric reflectance spectrophotometry. eGFR was calculated using the CKD-EPI equation.[42] Albumin and creatinine were measured in a random spot urine specimen by nephelometry (BN ProSpec Nephelometer, Dade Behring, Marburg, Germany) and Modular-P chemistry analyzer (Roche/Hitachi, Indianapolis, IN), respectively. Spot urine ACR was calculated in mg/g and albuminuria was defined as an ACR 30 mg/g.

Ascertainment of Outcomes

The outcome of interest was the development of ESRD subsequent to the in-home visit as assessed via linkage with the United States Renal Data Service (USRDS) through August 31st, 2012. The USRDS is a registry of ESRD and captures over 95% of all incident cases in the US.

Statistical Analyses

Standard descriptive statistics were used to examine baseline demographic, clinical and laboratory characteristics of REGARDS participants according to categories of BMI (18.5 – 24.9 kg/m^2, 25 – 29.9 kg/m^2, 30 kg/m^2) and metabolic syndrome (yes, no). Next, ESRD rates were calculated by categories of BMI and presence/absence of metabolic syndrome. After confirming the proportionality of hazards, Cox regression models were used to estimate the hazard ratio (HR) for incident ESRD as a function of BMI and metabolic health categories in sequential models. Model 1 was adjusted for age, race, sex, and geographic region of residence (stroke belt, stroke buckle or other). Model 2 was adjusted for variables in Model 1 plus lifestyle factors (self-reported physical activity, current smoking), comorbidities (history of heart disease and stroke), educational achievement (< vs. high school), and annual family income (< vs. $20,000/year). We did not adjust for diabetes or hypertension in these models because they were used in defining metabolic syndrome. In addition, we did not adjust for eGFR or ACR since lower eGFR and higher ACR are likely mediators of the association of obesity and/or metabolic syndrome with ESRD risk. Cox regression models with restricted quadratic splines were used to model the association of BMI with risk of ESRD in the fully study sample and stratified by absence or presence of the metabolic syndrome. In pre-specified analyses, we examined for effect modification by race, gender and age by testing the statistical significance of interaction terms by creating multiplicative variables and testing them in individual models. In addition, since we previously reported that metabolic health modified the association of weight with mortality in CKD patients, we examined whether the presence of absence of the metabolic syndrome modified the association between BMI and incident ESRD by including multiplicative interaction terms in the model. A two-tailed P value < 0.05 was considered statistically significant for all analyses. All analyses were conducted using SAS software version 9.2 (SAS Institute, Cary, NC).

ACKNOWLEDGEMENTS

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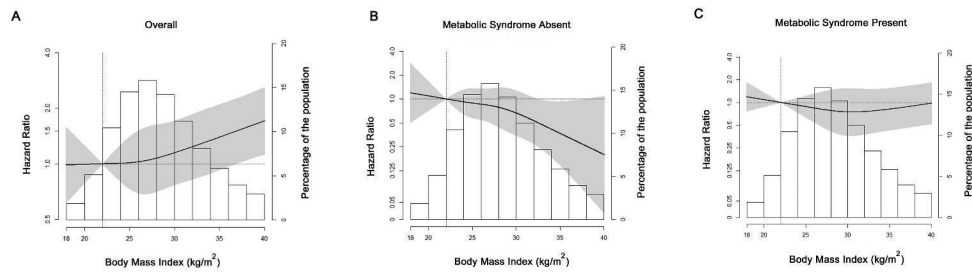
Figure 1.
Hazard ratios for incident end-stage renal disease (ESRD) as a function of body mass index (BMI) in the fully study sample (1A) and stratified by absence (1B) or presence (1C) of metabolic syndrome. BMI was modeled as a continuous variable and fitted in a Cox proportional hazards model using restricted quadratic spline regression adjusted for age, race, sex, geographic region of residence, education, income, physical activity, current smoking, history of coronary heart disease, and history of stroke. Knots for the spline were placed at a BMI of 25 and 30 kg/m^2 and the reference point was a BMI of 22 kg/m^2. Dashed horizontal lines correspond to reference values. Shaded areas represent 95% confidence intervals for hazard ratios. Histograms present distributions of BMI in study participants.
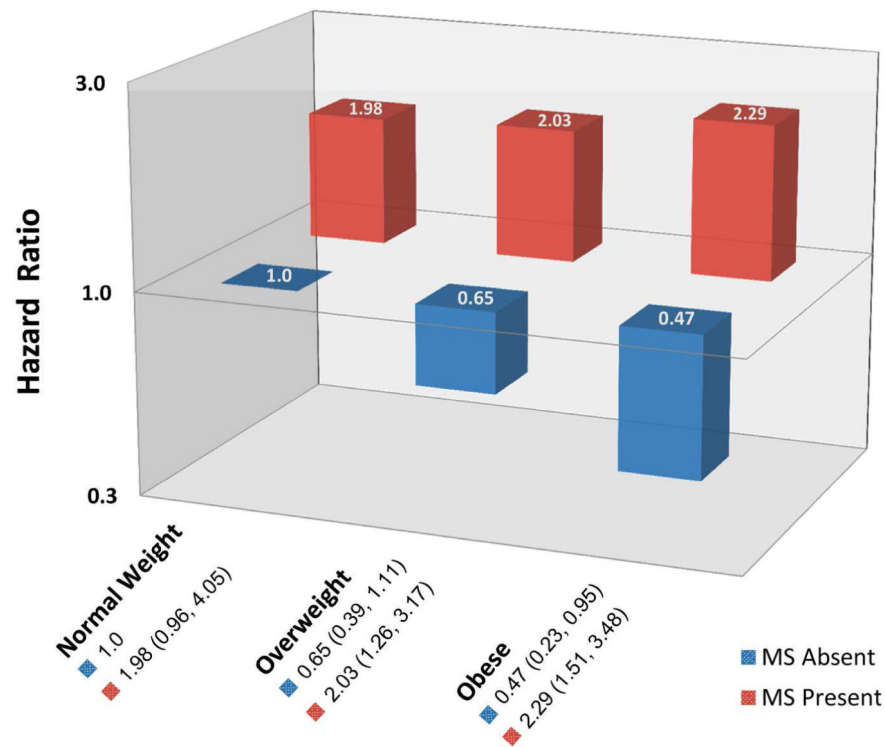
Figure 2.
Hazard ratios (95% confidence intervals) for incident ESRD among REGARDS participants by weight and metabolic subtype categories. Model was adjusted for age, race, sex, geographic region of residence, education, income, physical activity, current smoking, history of coronary heart disease, and history of stroke. P_{trend} for the association of weight categories (normal, overweight, obese) with ESRD risk in participants without the metabolic syndrome was 0.02; P_{trend} for the association of weight categories (normal, overweight, obese) with ESRD risk in participants with the metabolic syndrome was 0.16.

Table 1

Participant characteristics among the REGARDS participants by BMI and metabolic health. Data are given as mean (standard deviation), or frequencies.

Variable	Normal Weight (18.5 – 24.9 kg/m^2)	Overweight (25.0 – 29.9 kg/m^2)	Obese (≥ 30 kg/m^2)	Absence of Metabolic Syndrome	Presence of Metabolic Syndrome
N	5316	8232	8292	13043	8797
Age, y Mean (SD)	66.2 (10.2)	65.4 (9.3)	63.0 (8.6)	64.6 (9.7)	64.8 (8.9)
Sex					
Male, N (%)	2324 (43.7)	4336 (52.7)	3208 (38.7)	6138 (47.1)	3730 (42.4)
Race					
Black, N (%)	1478 (27.8)	2903 (35.3)	4207 (50.7)	4714 (36.1)	3874 (44.0)
BMI, kg/m^2 Mean (SD)	22.8 (1.6)	27.5 (1.4)	35.3 (4.9)	27.1 (4.9)	32.6 (6.0)
Waist Circumference, cm Mean (SD)	81.9 (10.3)	93.0 (9.3)	107.6 (13.0)	89.9 (12.8)	104.7 (13.5)
Hypertension, N (%)	1971 (37.1)	4008 (48.7)	5401 (65.1)	4977 (38.2)	6403 (72.8)
Diabetes, N (%)	444 (8.4)	1314 (16.0)	2616 (31.5)	839 (6.4)	3535 (40.2)
Education < HS, N (%)	484 (9.1)	847 (10.3)	1137 (13.7)	1179 (9.0)	1289 (14.7)
Income < $20,000, N (%)	784 (14.7)	1172 (14.2)	1630 (19.7)	1719 (13.2)	1867 (21.2)
Current Smoking, N (%)	989 (18.6)	1077 (13.1)	973 (11.7)	1724 (13.2)	1315 (14.9)
CHD, N (%)	834 (15.7)	1417 (17.2)	1429 (17.2)	1816 (13.9)	1864 (21.2)
Stroke, N (%)	293 (5.5)	461 (5.6)	486 (5.9)	564 (4.4)	672 (7.6)
ACR category					
< 30 mg/g, N (%)	4501 (84.7)	6990 (84.9)	6617 (79.8)	11351 (87.0)	6757 (76.8)
30-299.9 mg/g, N (%)	526 (9.9)	795 (9.7)	1115 (13.4)	1105 (8.5)	1331 (15.1)
≥ 300 mg/g, N (%)	101 (1.9)	176 (2.1)	259 (3.1)	169 (1.3)	367 (4.2)
eGFR(mL/min/1.73 m2)					
≥ 60, N (%)	4782 (90.0)	7385 (89.7)	7329 (88.4)	12010 (92.1)	7486 (85.1)
30-59.9, N (%)	507 (9.5)	792 (9.6)	881 (10.6)	985 (7.6)	1195 (13.6)
15-29.9, N (%)	24 (0.5)	50 (0.6)	72 (0.9)	44 (0.3)	102 (1.2)
< 15, N (%)	3 (0.1)	5 (0.1)	10 (0.1)	4 (0.0)	14 (0.2)

Abbreviations: BMI, body mass index; HS, high school; CHD, coronary heart disease; ACR, urinary albumin to creatinine ratio; eGFR, estimated glomerular filtration rate; SD, standard deviation.

Table 2

Incidence rates of end-stage renal disease (95% confidence intervals) per 1000 person-years of follow-up among the REGARDS participants by weight and metabolic syndrome categories.

	Normal Weight (BMI 18.5 - 24.9 kg/m²)	Overweight (BMI 25 - 29.9 kg/m²)	Obese (BMI 30 kg/m²)
Metabolic Syndrome Present			
N	593	2661	5385
ESRD Events	10	49	119
IR (95% CI)	2.57 (1.38, 4.77)	2.81 (2.12, 3.72)	3.45 (2.88, 4.13)
Metabolic Syndrome Absent			
N	4688	5503	2792
ESRD Events	31	27	11
IR (95% CI)	1.04 (0.73, 1.48)	0.77 (0.53, 1.12)	0.63 (0.35, 1.14)

Abbreviations: ESRD, end-stage renal disease; IR, incidence rate; CI, confidence interval.