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Metabolically Healthy Obesity and Risk of Kidney Function Decline

Alex R Chang, MD, MS[1,2], **Aditya Surapaneni, PHD**[3], **H. Lester Kirchner, PHD**[4], **Amanda Young, MS**[4], **Holly J Kramer, MD, MPH**[5], **David J Carey, PhD**[6], **Lawrence J Appel, MD, MPH**[3], and **Morgan E Grams, MD, PHD**[3,7]

[1]Kidney Health Research Institute, Geisinger

[2]Department of Epidemiology and Health Services Research, Geisinger

[3]Welch Center for Prevention, Epidemiology, and Clinical Research, Johns Hopkins University

[4]Biomedical and Translational Informatics Institute, Geisinger

[5]Division of Nephrology, Loyola University Medical Center

[6]Department of Molecular and Functional Genomics, Geisinger

[7]Divison of Nephrology, Johns Hopkins University

Abstract

Objective—To examine the association between body mass index (BMI) categories, stratified by metabolic health status, and risk of kidney function decline

Methods—We classified 42,128 adult patients with stable BMI over a 3-year baseline window by BMI and metabolic health status (assessed by Adult Treatment Panel-III criteria). Kidney function decline (KFD) was defined as eGFR decline ≥ 30%, eGFR<15 ml/min/1.73m^2, or receipt of dialysis/transplant.

Results—Over a median of 5.1 years (IQR 2.1–8.9), 6,533 (15.5%) individuals developed KFD. Compared to the normal weight, metabolically healthy category, metabolically healthy obesity (MHO) was associated with higher risk of KFD [adjusted hazard ratio (aHR) 1.52, 95% CI: 1.22–1.89]. Adjusted HRs for KFD were 1.17 (95% CI: 0.89 –1.53), 2.21 (95% CI: 1.59 – 3.08), and 2.20 (95% CI: 1.55–3.11) for MHO with BMI 30–34.9, BMI 35–39.9, and BMI ≥ 40 kg/m^2. These associations were consistent among men and women, patients with eGFR ≥ or < 90 ml/min/1.73m^2, and age ≥ or < 55 y. Risk of KFD was highest among metabolically unhealthy individuals with BMI ≥ 40 (aHR 4.02, 95% CI: 3.40–4.75 vs. metabolically healthy, normal weight individuals).

Conclusions—Obesity, whether in the presence or absence of metabolic health, is a risk factor for KFD.

Contact Info: Mailing address: Alex R. Chang, MD MS, 100 N Academy Ave, Danville, PA 17822 achang@geisinger.edu.

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Keywords

obesity; metabolic health; metabolic syndrome; chronic kidney disease; end-stage renal disease

Introduction

The prevalence of overweight and obesity continues to rise worldwide(1). In the US, 38% of adults have obesity [body mass index (BMI ≥ 30 kg/m^2), and nearly 8% have class III obesity (BMI ≥ 40 kg/m^2)(2). Excess weight increases risk for the metabolic syndrome, a constellation of cardiovascular risk factors that includes abdominal adiposity, dyslipidemia, elevated blood pressure, insulin resistance, and a pro-inflammatory, prothrombotic state(3). However, not all individuals with excess weight develop the metabolic syndrome, and the term “metabolically healthy obesity” has been used to refer to these individuals(4). A meta-analysis of studies with long term follow-up suggested that, despite the absence of the metabolic syndrome, metabolically healthy individuals with obesity remain at higher risk for cardiovascular disease and mortality compared to lean, metabolically healthy individuals(5).

Obesity and elements of the metabolic syndrome have also been implicated as risk factors for chronic kidney disease (CKD) and end-stage renal disease (ESRD)(6–11). CKD affects 1 in 7 US adults, and is associated with high risk of cardiovascular disease, end-stage renal disease (ESRD), and premature death(12, 13). Further, CKD and ESRD impart high economic costs to health systems(14, 15). Understanding the relationship between obesity and CKD is very important from a public health perspective given worldwide increases in obesity prevalence.

Whether or not metabolically healthy obesity poses increased risk of CKD and ESRD is unclear. Two large Korean studies found that metabolically healthy obesity was associated increased risk of incident CKD, whereas a Japanese study found no increased risk(16–18). An American research cohort of older adults investigated the relationship between body mass index (BMI) and metabolic health with end-stage renal disease (ESRD), and found that metabolically healthy obesity was associated with lower risk of ESRD. All studies were limited by the use of a single measurement of BMI to classify BMI category, which could result in misclassification of obesity and resultant bias.

Using data from a large, US integrated health system, we investigated the association between metabolically healthy and metabolically unhealthy obesity with kidney function decline. Because a major concern with studies examining BMI and outcomes is that weight may decrease as a result of illness such as CKD, we required stable BMI over a 3-year baseline window to define BMI groups.

Methods

Study Population

Our study population was derived from patients at least 18 years of age receiving primary care between May 10, 1999 and October 20, 2015 in the Geisinger Health System, a fully integrated, health care system serving central and northeastern Pennsylvania. We excluded

patients with BMI <18.5 kg/m^2, eGFR <15 ml/min/1.73m^2, a history of ESRD, and a history of malignancy (except for non-melanoma skin cancer). In order to classify participants as metabolically healthy or unhealthy, we required baseline information on blood pressure, fasting blood glucose, triglycerides, HDL cholesterol, and serum creatinine. To minimize the possibility of reverse causality, we required patients to have BMI values that remained in the same World Health Organization (WHO) BMI category over a 3-year (+/− 6 months) baseline period, for a total study population of 42,148. The Geisinger institutional review board approved the use of deidentified data for this study.

BMI Categories and Metabolic Health Status

BMI categories were defined using WHO classifications (normal weight, 18.5–24.9 kg/m^2; overweight, 25–29.9 kg/m^2; class I obesity, 30–34.9 kg/m^2; class II obesity, 35–39.9 kg/m^2; class III obesity, ≥ 40 kg/m^2). Metabolic health status was defined using modified National Cholesterol Education Program – Adult Treatment Panel III (NCEP-ATP III) criteria as we lacked waist circumference values(3); this modified definition had been previously validated in a study comparing multiple metabolic syndrome definitions(4). Because waist circumference measures were unavailable, we considered participants to be metabolically healthy if they had 0 or 1 of the following metabolic abnormalities: 1) systolic BP ≥ 130 mmHg, diastolic BP ≥ 85 mmHg, or antihypertensive drug treatment; 2) fasting blood glucose ≥ 100 mg/dL or use of blood glucose lowering agents; 3) low HDL-cholesterol level, defined as <40 mg/dL for males or <50 mg/dL for females; and 4) fasting triglycerides ≥150 mg/dL.

Other Variables of Interest

We abstracted data from the electronic health record including age, gender, race, serum creatinine, smoking status, and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis-coded history of hypertension, diabetes, dyslipidemia, myocardial infarction, stroke, peripheral vascular disease, congestive heart failure, and prescription of statin and blood pressure medications. We also calculated weight slopes in kilograms/year for the baseline time window using simple linear regression since a change in weight could indicate a change in health status.

Outcomes

We calculated eGFR values from outpatient serum creatinine from the electronic health record using the CKD-EPI equation(19). Serum creatinine was measured at a single laboratory using the isotope-dilution mass spectrometry-traceable Roche enzymatic method (Roche Diagnostics, Indianapolis, IN) according to manufacturer specifications. No changes in assay or calibration techniques occurred during the study period (coefficient of variation 1.5–2%). Data was linked to the United States Renal Data System (USRDS) to determine initation of renal replacement therapy.

The primary outcome of kidney function decline included a confirmed eGFR decline ≥ 30% (in other words, meeting this criteria on two consecutive creatinine measurements) or kidney failure, defined as eGFR <15 ml/min/1,73 m^2 or initiation of renal replacement therapy ascertained by linkage to the United States Renal Data System(20, 21). Time at risk started

from the index date, defined as the last BMI measurement in each patient's 3-year baseline window. Patients were followed until the time of a renal outcome or the last available creatinine value prior to the end date of the study, October 20, 2015. The antecedent eGFR value closest to the index date was considered baseline eGFR. The secondary outcome was kidney failure as defined above.

Statistical Analysis

Baseline characteristics were analyzed across BMI (normal weight, overweight, obesity) and metabolic health (healthy/unhealthy) groups. Cross-sectional associations between baseline characteristics and higher BMI category (an ordinal variable) were examined separately for metabolically healthy and metabolically unhealthy subgroups, using linear regression for continuous variables and logistic regression for categorical variables. We calculated crude incidence rates and 95% confidence intervals by BMI/metabolic health groups, and used Cox proportional hazards models to examine associations between BMI/metabolic health groups and kidney outcomes (reference group: metabolically healthy with normal BMI). Our main analyses examining the association of BMI/metabolic health groups with kidney outcomes adjusted for age, gender, race, and current smoking. All analyses were performed using Stata version 14.2 (College Station, TX). P values <0.05 were considered statistically significant.

We conducted multiple sensitivity analyses: accounting for competing risk of death using the method of Fine and Gray(22); excluding the first 3 years of follow-up after the index date to further minimize the possibility of reverse causation; adjusting for weight trajectory during the baseline window; adjusting for baseline eGFR and atherosclerotic cardiovascular disease (myocardial infarction, stroke, peripheral vascular disease), which could be confounders or mediators in the causal pathway; defining metabolically healthy status as having no metabolic abnormalities. We also examined whether associations between metabolically healthy obesity and kidney function decline varied by gender, baseline eGFR ≥ or < 90 ml/min/1.73m^2, and age ≥ or < 55 years by adding relevant interaction terms and conducting subgroup analyses.

Results

Of the 42,128 individuals included in our study, mean age was 59.8 years, 96.3% were white, 55.7% were female, 52.6% had obesity, and 18.3% were classified as metabolically healthy (0 or 1 metabolic abnormalities). There were 2,184 metabolically healthy individuals with obesity, comprising 5.2% of the total population and 9.9% of the population with obesity. By comparison, 39.3% of normal weight and 21.7% of overweight individuals were metabolically healthy.

Higher BMI category was associated with younger age, lower prevalence of current smoking, lower HDL cholesterol, and higher triglycerides, fasting glucose, and blood pressure for both metabolic healthy and unhealthy individuals (Table 1). Compared to metabolically healthy individuals, metabolically unhealthy individuals were older, more likely to be white, have atherosclerotic cardiovascular disease, congestive heart failure, and baseline estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2. Among the BMI/

metabolic health groups, the normal BMI/unhealthy group had the highest prevalence of baseline eGFR <60 ml/min/1.73m^2, stroke, peripheral vascular disease, and congestive heart failure. Median weight trajectories over the baseline time window were 0.08 kg/year for the normal BMI/healthy group, 0.20 kg/year for the overweight/healthy group 0.41 kg/year for the obesity/healthy group, −0.21 kg/year for the normal weight/unhealthy group, −0.03 kg/year for the overweight/unhealthy group, and 0.12 kg/year for the obesity/unhealthy group.

Over a median of 5.1 years (IQR 2.1–8.9), 6,533 (15.5%) individuals developed kidney function decline (eGFR decline ≥30% or kidney failure), and over a median follow up of 5.4 years 595/42,148 (1.4%) individuals developed kidney failure (468 eGFR <15 ml/min/1.73m^2, 127 cases of ESRD treated with dialysis or transplantation), corresponding to incidence rates (IR) of 27.7 per 1000 person-years for kidney function decline and 2.39 per 1000 person-years for kidney failure.

Metabolically Healthy BMI Groups and Risk of Kidney Function Decline or Kidney Failure

Compared to metabolically healthy individuals with normal BMI, metabolically healthy obesity (BMI ≥ 30 kg/m^2) was associated with increased risk of kidney function decline (aHR 1.52, 95% CI: 1.22–1.89, p<0.001). When metabolically healthy obesity was stratified into class I (BMI 30–34.9 kg/m^2), II (BMI 35–39.9 kg/m^2), and III (BMI ≥ 40 kg/m^2) obesity, there was a graded relationship between increasing BMI and eGFR decline (Table 2, Figure 1, dashed line). Adjusted HRs for kidney function decline were 1.17 (95% CI: 0.89–1.53, p=0.25) for metabolically healthy class I obesity, 2.21 (95% CI: 1.59–3.08, p<0.001) for metabolically healthy class II obesity, and 2.20 (95% CI: 1.55–3.11, p<0.001) for metabolically healthy class III obesity. The overweight/metabolically healthy group was not at significantly increased risk of kidney function decline (aHR 1.10, 95% CI: 0.89–1.35, p=0.39).

Metabolically healthy obesity (BMI ≥ 30 kg/m^2) was not significantly associated with kidney failure (aHR 0.82, 95% CI 0.27–2.52, p=0.73), although there were few kidney failure events (n=25) in metabolically healthy individuals. When metabolically healthy obesity was stratified into classes I–III, risk of kidney failure was not significantly increased for metabolically healthy class I obesity (aHR 0.52, 95% CI: 0.11–2.45, p=0.41), metabolically healthy class II obesity (aHR 1.76, 95% CI: 0.37–8.31, p=0.47), or metabolically healthy class III obesity (aHR 0.98, 95% CI: 0.12–7.84, p=0.98) (Table 2, Figure 2, dashed line).

Metabolically Unhealthy BMI Groups and Risk of Kidney Function Decline or Kidney Failure

Poor metabolic health was a risk factor for both kidney function decline and kidney failure, regardless of BMI category (Table 2, Figure 1, solid line). Compared to metabolically healthy individuals with normal BMI, adjusted HRs for kidney function decline were 2.00 (95% CI: 1.68– 2.38, p<0.001) for metabolically unhealthy normal BMI, 1.90 (95% CI: 1.61–2.23, p<0.001) for metabolically unhealthy overweight, 2.25 (95% CI: 1.91–2.65, p<0.001) for metabolically unhealthy class I obesity, 2.75 (95% CI: 2.32–3.25, p<0.001) for metabolically unhealthy class II obesity, and 4.02 (95% CI: 3.40–4.75, p<0.001) for

metabolically unhealthy class III obesity. Adjusted HRs for kidney failure were 3.52 (95% CI: 1.68–7.36, p=0.001) for metabolically unhealthy normal BMI, 3.17 (95% CI: 1.56–6.47, p=0.001) for metabolically unhealthy overweight, 3.56 (95% CI: 1.74–7.26, p<0.001) for metabolically unhealthy class I obesity, 4.25 (95% CI: 2.06–8.80, p<0.001) for metabolically unhealthy class II obesity, and 7.44 (95% CI: 3.63– 15.24, p<0.001) for metabolically unhealthy class III obesity groups.

Metabolically Healthy Obesity and Kidney Function Decline By Gender, Age, and Baseline eGFR

Associations between metabolically healthy obesity and kidney function decline did not differ significantly for any subgroup (p>0.05 for all interaction terms) (Figure 3). Adjusted HRs were 1.45 (95% CI: 0.97–2.17, p=0.069) for men, 1.75 (95% CI: 1.34–2.28, p<0.001) for women, 1.55 (95% CI: 1.08–2.22, p=0.017) for individuals younger than 55 years of age, 1.65 (95% CI: 1.30– 2.10, p<0.001) for individuals 55 years and older, 1.96 (95% CI: 1.36–2.85, p<0.001) for individuals with eGFR ≥90 ml/min/1.73m^2, and 1.46 (95% CI: 1.11–1.94, p=0.007) for individuals with eGFR <90 ml/min/1.73m^2.

Sensitivity Analyses

The association between metabolically healthy obesity and kidney function decline was consistent in sensitivity analyses accounting for the competing risk of death (sub-HR 1.60, 95% CI: 1.29–1.98, p <0.001), in analyses excluding the first 3 years of follow-up after the index date (aHR 1.55, 95% CI: 1.22–1.99, p<0.001), adjusting for weight trajectory over the baseline window (aHR 1.53 (1.23–1.90), p<0.001), and adjusting for baseline eGFR and history of atherosclerotic cardiovascular disease (aHR 1.51, 95% CI: 1.22–1.88, p<0.001; Tables S1–4 in the Supplement). When metabolically healthy was defined as having no metabolic abnormalities, results were consistent although this analysis was limited by sample size (1867 patients with 0 metabolic abnormalities; normal BMI 50.5%, overweight 35.8%, obesity 13.7%; Table S5). Patients with obesity and 0 metabolic abnormalities tended to be at increased risk for KFD compared to patients with normal weight and 0 metabolic abnormalities (aHR 1.94, 95% CI: 0.93–4.05, p=0.08)

Discussion

In a well-characterized cohort of over 42,000 adults in a large rural healthcare system, we found that obesity, even in the absence of the metabolic syndrome, was associated with a heightened risk of kidney function decline. Metabolically healthy obesity was significantly associated with increased risk of kidney function decline, but not kidney failure over a median 5-year period. Risk of kidney function decline was more than 2-fold higher for those with metabolically healthy, class II and III obesity (BMI ≥ 35 kg/m^2), compared to metabolically healthy, lean individuals. Metabolically unhealthy obesity was even more strongly associated with increased risk of both kidney function decline and kidney failure in a graded fashion, with the highest risk among those with class III obesity.

Other studies examining metabolically healthy obesity and CKD outcomes have reported varied findings(23). Four out of five cohort studies in Asian populations found that

metabolically healthy obesity (using an Asian-specific BMI cutpoint of ≥ 25 kg/m^2) was associated with an increased risk of incident CKD(16–18, 24, 25). In the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a population-based cohort study of 21,840 black and white US adults at least 45 years of age, higher BMI was associated with lower risk of ESRD among those who were metabolically healthy(26). The REGARDS findings differ from results from our study and could be due to differences in study populations (older, more African- Americans), or definition of metabolic health. While the REGARDS study included waist circumference data in their metabolic health definition, we lacked waist circumference data but used multiple BMI measurements over a 3-year baseline window to improve characterization of BMI categories and conducted a sensitivity analysis adjusting for weight change trajectory over the baseline window.

Longer follow-up time may be needed to examine the association between metabolically healthy obesity and ESRD. A meta-analysis found that risk of incident type 2 diabetes was 4-fold higher for metabolically healthy individuals with obesity compared to metabolically healthy, normal-weight adults (mean follow-up ranging from 5 to 20 years)(27). Since much of the association between obesity and kidney function decline appears to be mediated by metabolic abnormalities, it may take many years for someone with metabolically healthy obesity to develop ESRD. Alternatively, BMI may have different prognostic value once individuals develop CKD(28), a condition often accompanied by malnutrition and inflammation(29). However, we found that metabolically healthy obesity was similarly associated with increased risk of eGFR decline ≥ 30% in patients with eGFR < and ≥ 90 ml/min/1.73m^2.

All elements of the metabolic syndrome have been implicated as potential mediators of kidney injury(30). Observational studies demonstrate a strong association between blood pressure and ESRD, and data from clinical trials suggest that blood pressure lowering reduces the risk of ESRD(31–34). Diabetic nephropathy is the most common cause of ESRD, and intensive glycemic control in patients with diabetes has been shown to reduce renal complications in clinical trials(15, 35). Elevated triglycerides and low HDL cholesterol are associated with increased risk for CKD and ESRD although clinical trials have been inconclusive in demonstrating an effect of statins on CKD progression(36–40). Metabolic syndrome is also associated with glomerular hyperfiltration, which may increase risk for future kidney function decline(41, 42).

Post-hoc findings from the Look AHEAD study, a randomized trial comparing an intensive lifestyle intervention to a control group (diabetes support and education), support a causal relationship between obesity and kidney disease(43). In Look AHEAD, the intensive lifestyle intervention group experienced greater 1-year weight loss (8.6% vs. 0.7%) than the control group, accompanied by a 31% decreased risk of very-high-risk CKD, a composite outcome that included eGFR and albuminuria status and indicates a high risk for ESRD (HR 0.69, 95% CI: 0.55– 0.87, p<0.001). A mediation analysis adjusting for time-varying weight, hemoglobin A1c, and blood pressure partially attenuated the protective effect of the intensive lifestyle intervention on very-high-risk CKD (HR 0.77, 95% CI: 0.60–0.99, p=0.04). In this model, time-varying weight remained significantly associated with very-high-risk CKD, supporting an effect of obesity on CKD independent of metabolic factors.

An important limitation of our study was the possibility of sampling bias, since screening recommendations for dyslipidemia and hyperglycemia are based, in part, on BMI(44, 45). Thus, individuals with normal BMI who were tested for dyslipidemia and hyperglycemia may have been unhealthier than individuals with normal BMI who were not tested, which would result in underestimation of risk associated with metabolically healthy and unhealthy obesity. Data was largely unavailable for waist circumference, albuminuria, dietary quality and physical activity, which could impact metabolic and kidney health, and assessed confounders only during the 3-year baseline period. Findings may not be generalizable to other populations as we were limited to a mostly white population in central and northeastern Pennsylvania.

There were several strengths of our study. First, we used a 3-year baseline window to define BMI categories and minimize potential bias due to reverse causality. Second, we captured kidney outcomes using the USRDS registry to ascertain kidney failure treated by dialysis or transplant, and also had a large number of outpatient eGFR values to ascertain untreated kidney failure and confirmed kidney function decline. Lastly, we conducted several sensitivity analyses with robust findings.

In conclusion, both metabolically healthy and metabolically unhealthy obesity are associated with kidney function decline. Given trends in rising prevalence of obesity worldwide, public health efforts are urgently needed to help prevent obesity-related CKD and its adverse sequelae.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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What is already known about this subject?

- Obesity is sometimes but not always accompanied by the metabolic syndrome.
- Individuals with obesity who do not have the metabolic syndrome [termed metabolically healthy obesity (MHO)] are at increased risk of cardiovascular disease and mortality compared to lean, metabolically healthy individuals.
- While obesity is associated with increased risk of kidney disease, conflicting data exist on whether MHO specifically poses increased kidney risk.

What does your study add?

- We demonstrate that obesity, whether in the presence or absence of metabolic health, is a risk factor for kidney function decline in a large US integrated health system cohort.
- Our study also demonstrates that this association is graded, with marginally increased risk of kidney function decine for class I MHO (BMI 30–34.9 kg/m^2), and more than doubling of risk for class II and III MHO (BMI ≥ 35 kg/m^2).

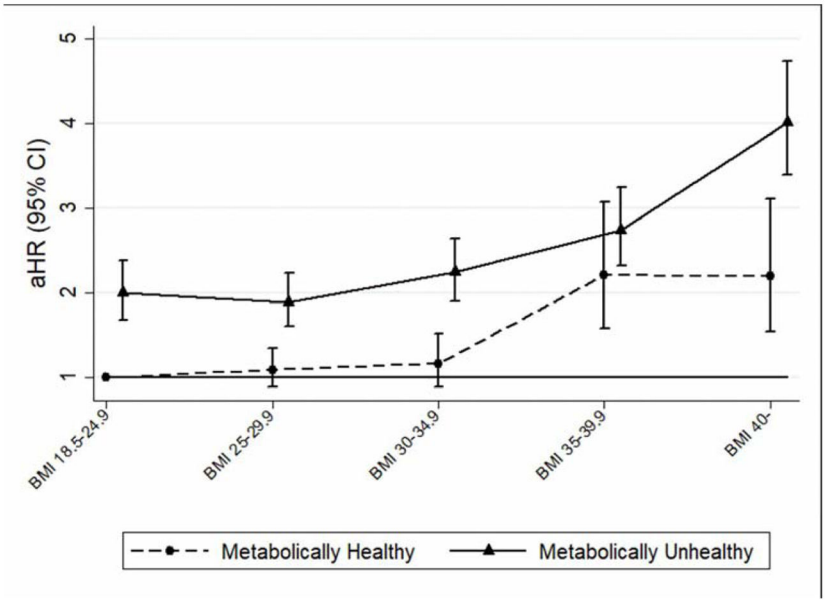

Figure 1. Risk of Kidney Function Decline by BMI/Metabolic Health Group

Models are adjusted for age, sex, race, and current smoking.

Kidney function decline defined as eGFR decline ≥ 30% (2 consecutive, qualifying values), or kidney failure. Kidney failure was defined as eGFR < 15 ml/min/1.73m^2 or requiring dialysis or transplantation per the USRDS registry

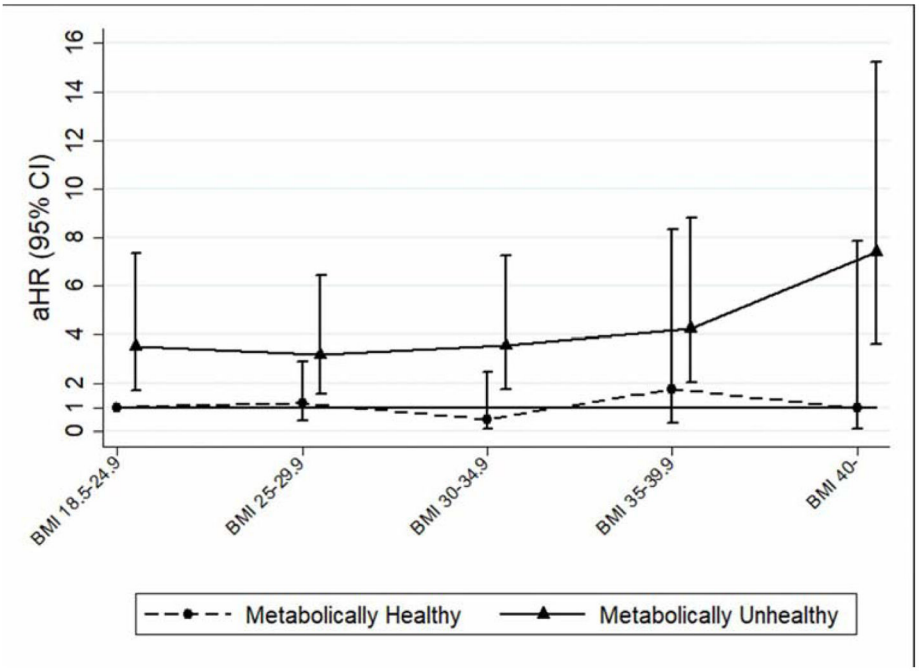

Figure 2. Risk of Kidney Failure by BMI/Metabolic Health Group

Models are adjusted for age, sex, race, and current smoking.

Kidney failure was defined as eGFR < 15 ml/min/1.73m^2 or requiring dialysis or transplantation per the USRDS registry

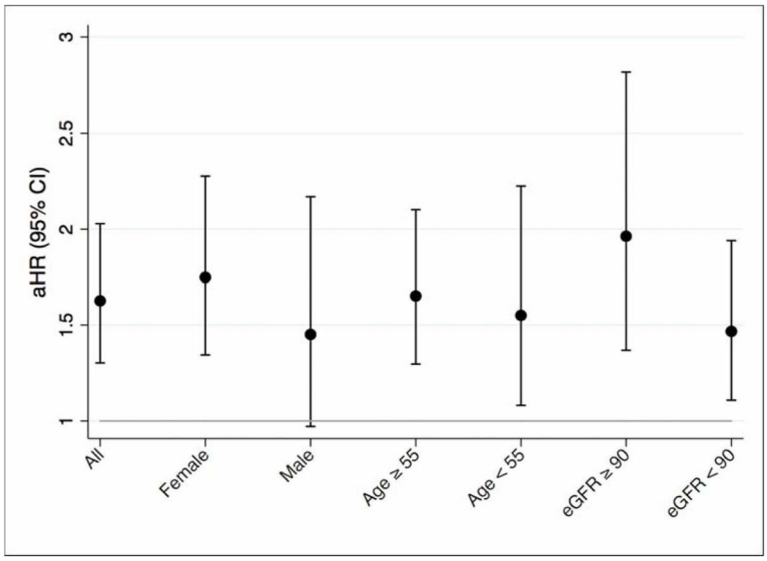

Figure 3. Metabolically Healthy Obesity and Risk of Kidney Function Decline by Subgroups

Models are adjusted for age, sex, race, and current smoking. Kidney function decline defined as eGFR decline ≥ 30% (2 consecutive, qualifying values), or kidney failure.

Kidney failure was defined as eGFR < 15 ml/min/1.73m^2 or requiring dialysis or transplantation per the USRDS registry

Table 1

Baseline Characteristics

	Metabolically Healthy (n=7,706)				Metabolically Unhealthy (n=34,442)			
	Normal weight	**Overweight**	**Obesity**	**P value for trend[a]**	**Normal weight**	**Overweight**	**Obesity**	**P value for trend[a]**
N, %	2639 (34.2)	2883 (37.4)	2184 (28.3)		4081 (11.8)	10392 (30.2)	19969 (58.0)	
Age, y	53.3 (16.6)	54.1 (14.0)	51.2 (13.9)	<0.001	66.6 (15.2)	64.0 (13.5)	58.8 (13.3)	<0.001
Female, %	1872 (70.9)	1605 (55.7)	1386 (63.5)	<0.001	2621 (64.2)	4991 (48.0)	10988 (55.0)	<0.001
White, %	2491 (94.4)	2741 (95.1)	2047 (93.7)	0.04	3943 (96.6)	10062(96.8)	19332 (96.8)	0.50
Current smoker, %	510 (19.3)	408 (14.2)	243 (11.1)	<0.001	917 (22.5)	1591 (15.3)	2446 (12.2)	<0.001
Weight (kg)	61.6 (8.8)	77.7 (9.9)	102.3 (20.7)	<0.001	61.6 (8.9)	78.1 (10.3)	104.6 (21.2)	<0.001
BMI (kg/m^2)	22.3 (1.7)	27.4 (1.3)	36.6 (6.3)	<0.001	22.6 (1.5)	27.6 (1.3)	37.2 (6.3)	<0.001
Weight trajectory (kg/y)	0.08 (−0.31 −0.53)	0.20 (−0.24 −0.77)	0.41 (−0.20 −1.16)	<0.001	−0.21 (−0.77 −0.25)	−0.03 (−0.54 −0.45)	0.12 (−0.50 −0.82)	<0.001
Systolic BP (mmHg)	118.6 (17.0)	122.8 (15.5)	126.1 (15.5)	<0.001	128.1 (19.0)	129.9 (17.1)	131.1 (16.3)	<0.001
Diastolic BP (mmHg)	70.2 (9.7)	74.2 (9.3)	76.8 (9.4)	<0.001	71.7 (10.5)	74.5 (9.8)	76.6 (10.0)	<0.001
Cholesterol (mg/dL)	189.2 (35.3)	194.0 (33.7)	191.6 (34.2)	<0.001	189.1 (40.6)	190.4 (40.3)	188.6 (39.2)	<0.001
HDL Cholesterol (mg/dL)	67.4 (17.3)	61.9 (15.2)	58.7 (14.0)	<0.001	56.3 (17.2)	50.7 (14.5)	47.0 (12.5)	<0.001
Triglycerides (mg/dL)	84.6 (35.7)	94.0 (38.7)	99.3 (39.7)	<0.001	139.9 (81.0)	162.7 (93.7)	182.3 (124.6)	<0.001
Fasting Blood Glucose (mg/dL)	80.5 (13.9)	81.5 (11.5)	81.8 (10.2)	<0.001	95.7 (36.3)	98.3 (32.2)	105.3 (38.6)	<0.001
eGFR (ml/min/1.73m^2)	90.8 (20.2)	88.1 (18.1)	89.8 (19.0)	<0.001	77.5 (22.6)	78.1 (21.1)	82.3 (21.8)	<0.001
eGFR < 60 ml/min/1.73m^2	200 (7.6)	203 (7.0)	142 (6.5)	0.15	939 (23.0)	2071 (19.9)	3186 (16.0)	<0.001
ICD Diagnoses								
Hypertension, %	640 (24.3)	864 (30.0)	822 (37.6)	<0.001	2578 (63.2)	6908 (66.5)	14633 (73.3)	<0.001
Type II Diabetes, %	39 (1.5)	39 (1.4)	15 (0.7)	0.01	889 (21.8)	2723 (26.2)	7321 (36.7)	<0.001
Dyslipidemia, %	1045 (39.6)	1360 (47.2)	970 (44.4)	<0.001	3114 (76.3)	8285 (79.7)	15456 (77.4)	<0.001
Coronary Artery Disease, %	131 (5.0)	176 (6.1)	109 (5.0)	0.03	945 (23.2)	2307 (22.2)	3737 (18.7)	<0.001
Stroke, %	163 (6.2)	146 (5.1)	72 (3.3)	<0.001	749 (18.4)	1475 (14.2)	2003 (10.0)	<0.001
Peripheral vascular disease, %	57 (2.2)	33 (1.1)	18 (0.8)	<0.001	420 (10.3)	789 (7.6)	1065 (5.3)	<0.001
Congestive heart failure, %	65 (2.5)	50 (1.7)	43 (2.0)	0.05	387 (9.5)	738 (7.1)	1572 (7.9)	<0.001
Taking statins, %	298 (11.3)	468 (16.2)	276 (12.6)	<0.001	1643 (40.3)	4853 (46.7)	9061 (45.4)	<0.001

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	Metabolically Healthy (n=7,706)				Metabolically Unhealthy (n=34,442)			
	Normal weight	**Overweight**	**Obesity**	**P value for trend[a]**	**Normal weight**	**Overweight**	**Obesity**	**P value for trend[a]**
Taking antihypertensive medications, %	737 (27.9)	954 (33.1)	897 (41.1)	<0.001	2600 (63.7)	6995 (67.3)	14880 (74.5)	<0.001

Data presented as mean (standard deviation) except for weight trajectory, which is shown as median (IQR). Metabolic health status was defined using modified NCEP-ATP III criteria: metabolically healthy if 0 or 1 metabolic abnormalities were present: 1) BP ≥ 130/85 mmHg or on antihypertensive; 2) fasting glucose ≥ 100 mg/dL or on glucose lowering medication; 3) HDL cholesterol <40 mg/dL for males or <50 mg/dL for females; and 4) fasting triglycerides ≥150 mg/dL.[3]

[a]Comparisons of trend across BMI categories among metabolically healthy and metabolically unhealthy subgroups Abbreviations: BMI (body mass index), BP (blood pressure), HDL (high-density lipoprotein), eGFR (estimated glomerular filtration rate), ICD (international classification of diseases)

SI conversion factors: To convert cholesterol to mmol/L, multiply values by 0.0259. To convert triglycerides to mmol/L, multiply values by 0.0113. To convert glucose to mmol/L, multiply values by 0.0555.

Table 2

BMI/Metabolic Health Groups and Risk of Kidney Function Decline or Kidney Failure

	Kidney Function Decline				Kidney Failure			
	Event/N	**IR (per 1000 PY)**	**HR (95% CI)**	**p-value**	**Event/N**	**IR (per 1000 PY)**	**HR (95% CI)**	**p-value**
Normal BMI/healthy	159/2639	11.11 (9.51 – 12.98)	Ref		8/2639	0.54(0.27 – 1.09)	Ref	
Overweight/healthy	192/2883	12.04 (10.45 –13.87)	1.10 (0.89 – 1.35)	0.39	11/2883	0.68 (0.38 – 1.24)	1.17 (0.47 – 2.91)	0.74
Obesity Class I/healthy	82/1241	12.01 (9.67 – 14.91)	1.17 (0.89 – 1.53)	0.25	2/1241	0.29 (0.07 – 1.17)	0.52 (0.11 – 2.45)	0.41
Obesity Class II/healthy	45/471	19.06 (14.23 –25.53)	2.21 (1.59 – 3.08)	<0.001	2/471	0.85 (0.21 – 3.40)	1.76 (0.37 – 8.31)	0.47
Obesity Class III /healthy	41/472	16.27 (11.93 –22.18)	2.20 (1.55 – 3.11)	<0.001	2/472	0.41 (0.06 – 2.88)	0.98 (0.12 – 7.84)	0.98
Normal BMI/unhealthy	671/4081	32.24 (29.89 –34.78)	2.00 (1.68 – 2.38)	<0.001	62/4081	2.76 (2.15 – 3.54)	3.52 (1.68 – 7.36)	<0.001
Overweight/unhealthy	1738/10392	28.91 (27.58 –30.31)	1.90 (1.61 – 2.23)	<0.001	161/10392	2.52 (2.15 – 2.94)	3.17 (1.56 – 6.47)	0.002
Obesity Class I /unhealthy	1652/9669	29.87 (28.46 –31.34)	2.25 (1.91 – 2.65)	<0.001	148/9669	2.56 (2.18 – 3.00)	3.56 (1.74 – 7.26)	<0.001
Obesity Class II/unhealthy	918/5182	31.75 (29.76 –33.87)	2.75 (2.32 – 3.25)	<0.001	82/5182	2.72 (2.19 – 3.37)	4.25 (2.06 – 8.80)	<0.001
Obesity Class III/unhealthy	1035/5118	36.25 (34.11 –38.53)	4.02 (3.40 – 4.75)	<0.001	117/5118	3.78 (3.15 – 4.54)	7.44 (3.63 – 15.24)	<0.001

Models are adjusted for age, sex, race, and current smoking.

Kidney function decline defined as eGFR decline ≥ 30% (2 consecutive, qualifying values), or kidney failure. Kidney failure was defined as eGFR < 15 ml/min/1.73m^2 or requiring dialysis or transplantation per the USRDS registry

Abbreviations: eGFR (estimated glomerular filtration rate), IR (incidence rate), HR (hazard ratio), BMI (body mass index)