Metabolically Healthy Obesity and Risk of Kidney Function Decline

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Objective: The aim of this study was to examine the association between BMI categories, stratified by metabolic health status, and the risk of kidney function decline (KFD).

Methods: In this study, 42,128 adult patients with a stable BMI were classified over a 3-year baseline window by BMI and metabolic health status (assessed by Adult Treatment Panel-III criteria). KFD was defined as an estimated glomerular filtration rate (eGFR) decline ≥30%, eGFR <15 mL/min/1.73 m², or receipt of dialysis and/or transplant.

Results: Over a median of 5.1 years (interquartile range 2.1-8.9), 6,533 (15.5%) individuals developed KFD. Compared with the normal weight, metabolically healthy category, metabolically healthy obesity was associated with a higher risk of KFD (adjusted hazard ratio [aHR] 1.52; 95% CI: 1.22-1.89). aHRs 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 metabolically healthy obesity with BMI 30 to 34.9, BMI 35 to 39.9, and BMI 40 kg/m². These associations were consistent among men and women, patients with eGFR <90 mL/min/1.73 m², and age <55 years. The risk of KFD was highest among metabolically unhealthy individuals with BMI ≥40 (aHR 4.02; 95% CI: 3.40-4.75 vs. metabolically healthy individuals with normal weight).

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

Introduction

The prevalence of overweight and obesity continues to rise worldwide (1). In the United States, 38% of adults have obesity (BMI ≥30 kg/m²), and nearly 8% have class III obesity (BMI ≥40 kg/m²) (2). Excess weight increases the risk for metabolic syndrome, a constellation of cardiovascular risk factors that includes abdominal adiposity, dyslipidemia, elevated blood pressure, insulin resistance, and a proinflammatory, prothrombotic state (3). However, not all individuals with excess weight develop 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 metabolic syndrome, metabolically healthy individuals with obesity remain at a higher risk for cardiovascular disease and mortality compared with lean, metabolically healthy individuals (5).

Obesity and elements of metabolic syndrome have also been implicated as risk factors for chronic kidney disease (CKD) and end-stage renal disease (ESRD) (6-11). CKD affects one in seven US adults and is associated with a high risk of cardiovascular disease, ESRD, and premature death (12,13). Furthermore, 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 the worldwide increases in obesity prevalence.

Whether or not metabolically healthy obesity poses an increased risk of CKD and ESRD is unclear. Two large Korean studies found that metabolically healthy obesity was associated with increased risk of incident CKD, whereas a Japanese study found no increased risk (16-18). The relationship between BMI and metabolic health with ESRD was investigated in an American research cohort of older adults, with the finding that metabolically healthy obesity was associated with a lower risk of ESRD (19). All studies were limited by the use of a single measurement of BMI to classify BMI category, which could result in the misclassification of obesity and resultant bias.

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By using data from a large US integrated health system, we investigated the association between metabolically healthy and metabolically unhealthy obesity with kidney function decline (KFD). Because a major concern with studies examining BMI and outcomes is that weight may decrease as a result of an 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, estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m², a history of ESRD, and a history of malignancy (except for nonmelanoma skin cancer). In order to classify participants as metabolically healthy or unhealthy, we required baseline information on blood pressure, fasting blood glucose, triglycerides, high-density lipoprotein (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 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 by using the World Health Organization classifications (normal weight, 18.5-24.9; overweight, 25-29.9; class I obesity, 30-34.9; class II obesity, 35-39.9; class III obesity, ≥ 40). Metabolic health status was defined by using modified National Cholesterol Education Program-Adult Treatment Panel 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 zero or one of the following metabolic abnormalities: (1) systolic blood pressure ≥ 130 mmHg, diastolic blood pressure ≥ 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 the International Classification of Diseases, Ninth Revision, Clinical Modification 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 per year for the baseline time window by using simple linear regression because 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 by using the Chronic Kidney Disease Epidemiology Collaboration equation (20). Serum creatinine was measured at a single laboratory by using the isotope-dilution mass spectrometry-traceable Roche enzymatic method (Roche Diagnostics, Indianapolis, Indiana) according to manufacturer specifications. No changes in assay or calibration techniques occurred during the study period (coefficient of variation 1.5%-2%). Data were linked to the United States Renal Data System to determine initiation of renal replacement therapy.

The primary outcome of KFD 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 m² or initiation of renal replacement therapy ascertained by linkage to the United States Renal Data System (21,22). The 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 by using linear regression for continuous variables and logistic regression for categorical variables. We calculated crude incidence rates and 95% confidence intervals (CI) 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 were adjusted for age, gender, race, and current smoking. All analyses were performed by using Stata version 14.2 (StataCorp LLC, College Station, Texas). P < 0.05 were considered statistically significant.

We conducted multiple sensitivity analyses, including accounting for competing risk of death by using the method of Fine and Gray (23); 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; and defining metabolically healthy status as having no metabolic abnormalities. We also examined whether associations between metabolically healthy obesity and KFD varied by gender, baseline eGFR ≥ or < 90 mL/min/1.73 m², and age ≥ or < 55 years by adding relevant interaction terms and conducting subgroup analyses.

Results

Of the 42,128 individuals included in our study, the 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 (zero or one of the metabolic abnormalities). There were 2,184 metabolically healthy individuals with obesity, who made up 5.2% of the total
## TABLE 1 Baseline characteristics

|                      | Metabolically healthy (n = 7,706) |                      | Metabolically unhealthy (n = 34,442) |                      |
|----------------------|-----------------------------------|----------------------|--------------------------------------|----------------------|
|                      | Normal weight | Overweight | Obesity         | P value for trend | Normal weight | Overweight | Obesity         | P value for trend |
| n (%)                | 2,639 (34.2)  | 2,883 (37.4)| 2,184 (28.3)    | <0.001                | 4,081 (11.8)   | 10,392 (30.2)| 19,969 (58.0)   | <0.001                |
| 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 (%)           | 1,872 (70.9)  | 1,605 (65.7) | 1,286 (63.5)   | <0.001                | 2,621 (64.2)  | 4,991 (48.0) | 10,988 (65.0) | <0.001                |
| White (%)            | 2,491 (94.4)  | 2,741 (95.1) | 2,047 (93.7)   | 0.04               | 3,943 (96.6) | 10,062 (96.8)| 19,332 (96.8) | 0.50                |
| Current smoker (%)   | 510 (19.3)    | 498 (14.2)   | 243 (11.1)     | <0.001                | 917 (22.5)    | 1,591 (15.3) | 2,446 (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/m²)          | 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      | 0.20         | 0.41           | <0.001                | -0.77 (0.25)  | -0.54 (0.45) | -0.60 (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)   | 76.7 (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 (55.7)   | 90.4 (38.7)  | 90.3 (39.7)    | <0.001                | 138.9 (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 (22.2) | 105.3 (38.6) | <0.001                |
| eGFR (mL/min/1.73 m²) | 90.8 (20.2)  | 88.1 (18.1)  | 88.9 (19.0)    | <0.001                | 77.5 (22.6)   | 78.1 (21.1)  | 82.3 (21.8)    | <0.001                |
| eGFR < 60 mL/min/1.73 m² | 200 (7.6)   | 203 (7.0)   | 142 (6.5)       | 0.15               | 939 (23.0)    | 2,071 (19.9) | 3,186 (16.0)   | <0.001                |
| ICD diagnoses        |                      |                      |                      |                      |                      |                      |                      |
| Hypertension (%)     | 640 (24.3)    | 864 (30.0)   | 822 (37.6)     | <0.001                | 2,578 (63.2)  | 6,908 (66.5) | 14,633 (73.3)  | <0.001                |
| Type 2 diabetes (%)  | 39 (1.5)      | 39 (1.4)     | 15 (0.7)       | 0.01               | 880 (21.8)    | 2,723 (26.2) | 7,321 (36.7)  | <0.001                |
| Dyslipidemia (%)     | 1,045 (39.6)  | 1,360 (47.2) | 970 (44.4)     | <0.001                | 3,114 (76.3)  | 8,285 (79.7) | 15,465 (74.4) | <0.001                |
| Coronary artery disease (%) | 131 (5.0)  | 176 (6.1)   | 109 (5.0)      | 0.03               | 945 (23.2)    | 2,307 (22.2) | 3,737 (18.7)  | <0.001                |
| Stroke (%)           | 163 (6.2)     | 146 (6.1)    | 72 (3.3)       | <0.001                | 749 (18.4)    | 1,475 (14.2) | 2,003 (10.0)  | <0.001                |
| Peripheral vascular disease (%) | 57 (2.2)  | 33 (1.1)    | 18 (0.8)       | <0.001                | 420 (13.2)    | 789 (7.6)    | 1,065 (6.3)   | <0.001                |
| Congestive heart failure (%) | 65 (2.5)  | 50 (1.7)    | 43 (2.0)       | 0.05               | 387 (9.5)    | 738 (7.1)    | 1,572 (7.9)   | <0.001                |
| Taking statins (%)   | 298 (11.3)    | 468 (16.2)   | 276 (12.6)     | <0.001                | 1,634 (40.3)  | 4,853 (46.7) | 9,061 (45.4)  | <0.001                |
| Taking antihypertensive medications (%) | 737 (27.9) | 954 (33.1) | 897 (41.1) | <0.001                | 2,600 (63.7)  | 6,995 (67.3) | 14,880 (74.5) | <0.001                |

Data presented as mean (standard deviation) except for weight trajectory, which is shown as median (interquartile range). Metabolic health status defined by using modified National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults-Adult Treatment Panel III criteria, which was metabolically healthy if zero or one of the following metabolic abnormalities was present: (1) blood pressure ≥ 130/85 mmHg or on antihypertensive medication, (2) fasting glucose ≥ 100mg/dL or on glucose lowering medication, (3) HDL cholesterol < 40mg/dL for males or < 50mg/dL for females, and (4) fasting triglycerides ≥ 150mg/dL (3). Comparisons of trend across BMI categories among metabolically healthy and metabolically unhealthy subgroups.

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.

BP, blood pressure; HDL, high-density lipoprotein; eGFR, estimated glomerular filtration rate; ICD, International Classification of Diseases.
TABLE 2 BMI/metabolic health groups and risk of kidney function decline or kidney failure

| Event/N         | IR (per 1,000 PY) | HR (95% CI) | P value |
|-----------------|-------------------|-------------|---------|
| **Kidney function decline** |                   |             |         |
| Priority group   |                   |             |         |
| Normal BMI/healthy | 159/2,639         | 11.11 (9.51-12.98) | Ref     |
| Overweight/healthy | 192/2,883         | 12.04 (10.45-13.87) | 1.10 (0.89-1.35) | 0.39      |
| Obesity class I/healthy | 82/1,241         | 12.01 (9.67-14.91) | 1.70 (0.89-1.53) | 0.25      |
| Obesity class II/healthy | 45/471          | 19.06 (14.23-25.53) | 2.21 (1.59-3.08) | <0.001    |
| Obesity class III/healthy | 41/472          | 16.27 (11.93-22.18) | 2.20 (1.55-3.11) | <0.001    |
| Normal BMI/unhealthy | 671/4,081        | 32.24 (29.89-34.78) | 2.00 (1.68-2.38) | <0.001    |
| Overweight/unhealthy | 1,738/10,392     | 28.91 (27.58-30.31) | 1.90 (1.61-2.23) | <0.001    |
| Obesity class I/unhealthy | 1,652/9,669     | 29.87 (28.46-31.34) | 2.25 (1.91-2.65) | <0.001    |
| Obesity class II/unhealthy | 918/5,182       | 31.75 (29.76-33.87) | 2.75 (2.32-3.25) | <0.001    |
| Obesity class III/unhealthy | 1,035/10,392 | 36.25 (34.11-38.53) | 4.02 (3.40-4.75) | <0.001    |

| Event/N         | IR (per 1,000 PY) | HR (95% CI) | P value |
|-----------------|-------------------|-------------|---------|
| **Kidney failure** |                   |             |         |
| Priority group   |                   |             |         |
| Normal BMI/healthy | 8/2,639           | 0.54 (0.27-1.09) | Ref     |
| Overweight/healthy | 11/2,883          | 0.68 (0.38-1.24) | 1.17 (0.47-2.91) | 0.74      |
| Obesity class I/healthy | 2/1,241         | 0.29 (0.07-1.17) | 0.52 (0.11-2.45) | 0.41      |
| Obesity class II/healthy | 2/471           | 0.85 (0.21-3.40) | 1.76 (0.37-8.31) | 0.47      |
| Obesity class III/healthy | 2/472          | 0.41 (0.06-2.88) | 0.98 (0.12-7.84) | 0.98      |
| Normal BMI/unhealthy | 62/4,081         | 2.76 (2.15-3.54) | 3.52 (1.68-7.36) | <0.001    |
| Overweight/unhealthy | 161/10,392      | 2.52 (2.15-2.94) | 3.17 (1.56-6.47) | 0.002     |
| Obesity class I/unhealthy | 148/9,669      | 2.56 (2.18-3.00) | 3.56 (1.74-7.26) | <0.001    |
| Obesity class II/unhealthy | 82/5,182       | 2.72 (2.19-3.37) | 4.25 (2.06-8.80) | <0.001    |
| Obesity class III/unhealthy | 117/5,118     | 3.78 (3.15-4.54) | 7.44 (3.63-15.24) | <0.001    |

Models adjusted for age, sex, race, and current smoking.
Kidney function decline defined as eGFR decline ≥ 30% (two consecutive qualifying values) or kidney failure.
Kidney failure defined as eGFR < 15 mL/min/1.73 m² or requiring dialysis or transplantation per the United States Renal Data System registry.
eGFR, estimated glomerular filtration rate; IR, incidence rate; HR, hazard ratio; PY, person-years.

population and 9.9% of the population with obesity. By comparison, 39.3% of individuals with normal weight and 21.7% of individuals with overweight were metabolically healthy.

A 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 with metabolically healthy individuals, metabolically unhealthy individuals were older and more likely to be white, have atherosclerotic cardiovascular disease, congestive heart failure, and baseline eGFR < 60 mL/min/1.73 m². Among the BMI/metabolic health groups, the normal BMI/unhealthy group had the highest prevalence of baseline eGFR < 60 mL/min/1.73 m², stroke, peripheral vascular disease, and congestive heart failure. Median weight trajectories over the baseline time window were 0.08 kg/y for the normal BMI/healthy group, 0.20 kg/y for the overweight/healthy group, 0.41 kg/y for the obesity/healthy group, −0.21 kg/y for the normal weight/unhealthy group, −0.03 kg/y for the overweight/unhealthy group, and 0.12 kg/y for the obesity/unhealthy group.

Over a median of 5.1 years (interquartile range 2.1–8.9), 6,533 (15.5%) individuals developed KFD (eGFR decline ≥ 30% or kidney failure), and over a median follow-up of 5.4 years, 595 out of 42,148 (1.4%) individuals developed kidney failure (468 with eGFR < 15 mL/min/1.73 m², 127 cases of ESRD treated with dialysis or transplantation), corresponding to incidence rates of 27.7 per 1,000 person-years for KFD and 2.39 per 1,000 person-years for kidney failure.

Metabolically healthy BMI groups and risk of KFD or kidney failure
Compared with metabolically healthy individuals with normal BMI, metabolically healthy obesity (BMI ≥ 30) was associated with increased risk of KFD (adjusted hazard ratio [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), II (BMI 35-39.9), and III (BMI ≥ 40) obesity, there was a graded relationship between increasing BMI and eGFR decline (Table 2; Figure 1, dashed line). aHRs for KFD 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.

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% (two consecutive qualifying values) or kidney failure. Kidney failure was defined as eGFR < 15 mL/min/1.73 m² or requiring dialysis or transplantation per the United States Renal Data System registry.
Metabolically Healthy Obesity and Kidney Function Decline

The overweight/metabolically healthy group was not at a significantly increased risk of KFD (aHR 1.10; 95% CI: 0.89-1.35; \( P = 0.39 \)).

Metabolically healthy obesity (BMI \( \geq 30 \)) 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 to III, the 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 KFD or kidney failure

Poor metabolic health was a risk factor for both KFD and kidney failure, regardless of BMI category (Table 2; Figure 1, solid line). Compared with metabolically healthy individuals with normal BMI, aHRs for KFD 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. aHRs 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 KFD by gender, age, and baseline eGFR

The associations between metabolically healthy obesity and KFD did not differ significantly for any subgroup (\( P > 0.05 \) for all interaction terms) (Figure 3). aHRs 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 \( \geq 90 \text{mL/min/1.73 m}^2 \), and 1.46 (95% CI: 1.11-1.94; \( P = 0.007 \)) for individuals with eGFR < 90 mL/min/1.73 m².

Sensitivity analyses

The association between metabolically healthy obesity and KFD was consistent in sensitivity analyses accounting for the competing risk of death (sub-HR 1.60; 95% CI: 1.29-1.98; \( P < 0.001 \)), analyses excluding the first 3 years of follow-up after the index date (aHR 1.55; 95% CI: 1.22-1.99; \( P < 0.001 \)), analyses adjusting for weight trajectory over the baseline window (aHR 1.53; 1.23-1.90; \( P < 0.001 \)), and analyses adjusting for baseline eGFR and history of atherosclerotic cardiovascular disease (aHR 1.51; 95% CI: 1.22-1.88; \( P < 0.001 \)) (Supporting Information Tables S1-S4). When metabolically healthy was defined as having no metabolic abnormalities, results were consistent; however, this analysis was limited by sample size (1,867 patients with zero metabolic abnormalities; normal BMI, 50.5%; overweight, 35.8%; obesity, 13.7%; Supporting Information Table S5). Patients with obesity and zero metabolic abnormalities tended to be at an increased risk for KFD compared with patients with normal weight and zero metabolic abnormalities (aHR 1.94; 95% CI: 0.93-4.05; \( P = 0.08 \)).

Discussion

In a well-characterized cohort of more than 42,000 adults in a large rural health care system, we found that obesity, even in the absence...
of metabolic syndrome, was associated with a heightened risk of KFD. Metabolically healthy obesity was significantly associated with an increased risk of KFD but not kidney failure over a median 5-year period. The risk of KFD was more than twofold for those with metabolically healthy class II and III obesity (BMI ≥ 35) compared with metabolically healthy lean individuals. Metabolically unhealthy obesity was even more strongly associated with an increased risk of both KFD 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 (24). Four out of five cohort studies in Asian populations found that metabolically healthy obesity (using an Asian-specific BMI cutoff of ≥ 25) was associated with an increased risk of incident CKD (16-18,25,26). 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 a lower risk of ESRD among those who were metabolically healthy (19). The REGARDS findings differ from results from our study, which could be because of the differences in study populations (older, more African American participants) or the definition of metabolic health. Though the REGARDS study included waist circumference data in their metabolic health definition, we lacked waist circumference data; however, we used multiple BMI measurements over a 3-year baseline window to improve the characterization of BMI categories and conducted a sensitivity analysis adjusting for weight change trajectory over the baseline window.

A longer follow-up time may be needed to examine the association between metabolically healthy obesity and ESRD. A meta-analysis found that the risk of incident type 2 diabetes was four times higher for metabolically healthy individuals with obesity compared with metabolically healthy adults with normal weight (mean follow-up ranging from 5 to 20 years) (27). Because much of the association between obesity and KFD 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 a 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 an increased risk of eGFR decline ≥ 30% in patients with eGFR < and ≥ 90 mL/min/1.73 m².

All elements of metabolic syndrome have been implicated as potential mediators of kidney injury (30). Observational studies have demonstrated a strong association between blood pressure and ESRD, and data from clinical trials have suggested 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 an 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 the risk for future KFD (41,42).

Post hoc findings from the Action for Health in Diabetes (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 this study, 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 indicated 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 because 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 an underestimation of the risk associated with metabolically healthy and unhealthy obesity. Data were 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 because of reverse causality. Second, we captured kidney outcomes by using the United States Renal Data System registry to ascertain kidney failure treated by dialysis or transplant, and we also had a large number of outpatient eGFR values to ascertain untreated kidney failure and confirmed KFD. Lastly, we conducted several sensitivity analyses with robust findings.

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

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