Obesity and Risk of Sepsis: A Population-Based Cohort Study

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Abstract

OBJECTIVE—Sepsis, the syndrome of microbial infection complicated by systemic inflammation, is associated with significant morbidity and mortality. We sought to determine if obesity increases risk of sepsis events.

DESIGN AND METHODS—We used data from the 30,239 subject population-based longitudinal cohort study <u>RE</u>asons for <u>G</u>eographic <u>a</u>nd <u>R</u>acial <u>D</u>ifferences in <u>S</u>troke (REGARDS). Using measurements at the start of the study, we defined obesity using body mass index (BMI; <18.5 kg/m^2=underweight, 18.5–24.9 =normal, 25.0–29.9=overweight, 30.0–39.9=obese, 40=morbidly obese) and waist circumference (WC; [male 102 cm or female 88 cm]= normal, [male>102 cm or female>88 cm]=obese). Over an 8-year observation period, we evaluated the association between obesity and subsequent sepsis events, adjusting for sociodemographic factors, health behaviors, chronic medical conditions, statin use and high-sensitivity C-reactive protein.

RESULTS—There were 975 incident sepsis events. Compared to those with a BMI of 18.5–24.9, sepsis risk was higher only for BMI 40 (HR 1.57, (1.16–2.14)). Risk of sepsis was associated with increased WC (HR 1.34 (1.14–1.56)). In a model with both BMI and WC, sepsis risk was associated with increased WC (HR 1.47 (1.20–1.79)) but not BMI.

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<u>**CONFLICTS OF INTEREST**</u>
None.

CONCLUSIONS—Obesity is independently associated with future sepsis events. WC is a better predictor of future sepsis risk than BMI.

Keywords

sepsis; infections; obesity; epidemiology

INTRODUCTION

Obesity remains one of the nation's most important public health problems, afflicting over one-third of US citizens.[1] Obesity has been attributed to increased mortality, and obese individuals are at greater risk for serious medical conditions such as cardiovascular disease and diabetes.[2]

Sepsis, the syndrome of microbial infection complicated by systemic inflammation, is also a major public health problem associated with significant morbidity and mortality.[3] The substantial national burden of sepsis care in the US encompasses 750,000 hospital admissions, 570,000 Emergency Department visits, 200,000 deaths and $16.7 billion in medical expenditures annually.[4–6] There are interesting clinical and pathophysiological connections between obesity and sepsis. In animal models, obesity is associated with exacerbated inflammatory responses.[7,8] Sepsis often results in critical illness, and in these individuals obesity is associated with impairment of pulmonary function, antibiotic distribution and insulin function.[9,10]

Prior studies have examined the connection between obesity and outcomes after hospitalization for sepsis or other critical illness.[11–13] However, there has been relative little attention directed towards the connection between obesity and the risk of future sepsis events. The latter point is important because efforts to reduce the public health impact of sepsis have focused primarily on optimizing hospital outcomes after the onset of disease rather than identification of the antecedent risk factors for developing the condition.[14,15] As has been demonstrated for conditions such as cardiovascular disease and diabetes, the identification of obesity as an independent risk factor for sepsis would provide a target for sepsis risk prediction as well as a modifiable target for potential sepsis risk reduction. The objective of this study was to determine the association between baseline obesity and future risk of sepsis in community-dwelling individuals.

METHODS AND PROCEDURES

Study Design

The study was approved by the Institutional Review Board of the University of Alabama at Birmingham. This study utilized the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study, a national, population-based, longitudinal cohort.

Selection of Participants

Designed to evaluate reasons for geographic and racial variations in stroke mortality, REGARDS is one of the largest ongoing national cohorts of community-dwelling

individuals in the US, encompassing 30,239 individuals 45 years old.[16] REGARDS includes individuals from all regions of the continental US. Participant representation oversampled the Southeastern US, with 21% of the cohort originating from the coastal plains of North Carolina, South Carolina and Georgia (the "buckle" of the stroke belt), and 35% originating from the remainder of North Carolina, South Carolina and Georgia plus Tennessee, Mississippi, Alabama, Louisiana and Arkansas (the "stroke belt"). The cohort is 42% African American and 45% male, and 69% of individuals are >60 years old, and does not include Hispanics where stroke mortality disparities are small-to-non-existent.

REGARDS enrolled participants during 2003–7, obtaining baseline data for each participant using both phone interview and in-person evaluations. Baseline data included medical history, functional status, health behaviors, physical characteristics (height, weight), physiologic measures (blood pressure, pulse, electrocardiogram), and an inventory of medications. Each participant provided blood and urine specimens. Self-administered questionnaires evaluated diet, family history of diseases, psychosocial factors and prior residences. On a semi-annual basis, the study contacted each participant to determine the date, location and attributed reason for all emergency department visits and hospitalizations during the follow-up interval. If the participant died, the study team reviewed death certificates and related medical records and interviewed proxies to ascertain the circumstances of the participant's death.

Identification of Sepsis Events

Using infection taxonomies developed by Angus, et al., we reviewed all reported hospitalizations and Emergency Department visits attributed by participants to a serious infection.[4] Two trained abstractors independently reviewed all relevant medical records to confirm the presence of a serious infection on initial hospital presentation, and the relevance of the serious infection as a major reason for hospitalization. The abstractors identified clinical and laboratory information from the first 28-hours of hospitalization a time period encompassing Emergency Department and up to one full day of inpatient treatment. The abstractors adjudicated discordances, with additional physician-level review as needed.

Consistent with international consensus definitions, sepsis consisted of presentation to the hospital with an infection plus two or more systemic inflammatory response syndrome (SIRS) criteria, including 1) heart rate >90 beats/minute, 2) fever (temperature >38.3°C or <36°C), 3) tachypnea (>20 breaths/min) or PCO_2<32 mmHg, and 4) leukocytosis (white blood cells [WBC] >12,000 or <4,000 cells/mm^3 or >10% band forms). Presentation to the hospital consisted of the time of Emergency Department triage or admission to inpatient unit (for participants admitted directly to the hospital). To allow for acute changes in the participant's condition during early hospitalization, we used vital signs and laboratory test results for the initial 28-hours of hospitalization. We did not include vital signs or laboratory findings at later time points, not did we include sepsis developing at later phases of hospitalization. We did not include organ dysfunction in the definition of sepsis. Initial review of 1,349 hospital records indicated excellent inter-rater agreement for presence of a serious infection (kappa=0.92) and the presence of sepsis (kappa=0.90) upon hospital presentation.

Definition of Obesity

Following standardized protocols, weight, height and waist circumference were measured during initial subject examination at the beginning of the REGARDS study. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2), and was categorized as underweight (<18.5 kg/m^2), normal (18.5–25.0 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (30–39.9 kg/m^2), and morbidly obese (40 kg/m^2).[17] Waist circumference was determined with the subject standing and was measured midway between the lowest rib and the iliac crest, with normal WC defined as 102 cm for males and 88 cm for females and large WC as >102 cm for males and >88 cm for females.[18]

Covariates

We considered covariates that may confound the relationship between obesity and sepsis, including sociodemographic characteristics, health behaviors and chronic medical conditions. Sociodemographic characteristics included age, sex, race, geographic region, self-reported annual household income and self-reported education (years of school). Geographic region was defined as participant residence in the stroke "buckle," stroke "belt," and elsewhere, included here to account for the sampling strategy used to recruit the REGARDS cohort.[16] Health behaviors included tobacco and alcohol use, and exercise. Smoking status use was defined as current, past and never. We defined alcohol use according to the National Institute on Alcohol Abuse and Alcoholism classification; i.e., moderate (1 drink per day for women or 2 drinks per day for men) and heavy alcohol use (>1 drink per day for women and >2 drinks per day for men).[19] Participants reported the number of times per week of exercise (none, 1–3, 4 or more).

Evaluated chronic medical conditions included hypertension, diabetes, dyslipidemia, coronary artery disease, chronic kidney disease, and chronic lung disease. Hypertension consisted of systolic blood pressure 140 mm Hg, diastolic blood pressure 90 mm Hg, or the self-reported use of antihypertensive agents. Diabetes included a fasting glucose 126 mg/L (or a glucose 200 mg/L for those not fasting) or the use of insulin or oral hypoglycemic agents. Dyslipidemia included individuals with self-reported high cholesterol or the use of lipid lowering medications. A history of coronary artery disease consisted of individuals with a self-reported history of myocardial infarction, coronary intervention or baseline electrocardiographic evidence of myocardial infarction.

Chronic kidney disease consisted of an estimated glomerular filtration rate <60 ml/min/1.73 m^2, calculated using the CKD-EPI equation.[20] Because REGARDS did not collect information on pulmonary conditions such as asthma and chronic obstructive pulmonary disease, we defined participant use of pulmonary medications as a surrogate for chronic lung disease. Obtained from each participant's medication inventory, pulmonary medications included beta agonists, leukotriene inhibitors, inhaled corticosteroids, combination inhalers, and other pulmonary medications such as ipatropium, cromolyn, aminophylline and theophylline. We determined statin use through the participant's medication inventory.

Data Analysis

We compared demographic, health behavioral and clinical characteristics between BMI and WC categories using a chi-square test. We used a Cox proportional hazards model to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the association between elevated obesity and first episode of sepsis during follow-up. We defined person-time at risk as the time (days) from first in-person examination to the first episode of sepsis or the last follow-up interview, whichever came first.

We fit separate models for BMI and WC. We adjusted the models for demographic characteristics (age, sex, race, income, education, geographic region), health behaviors (smoking and alcohol use, exercise), chronic medical conditions (hypertension, diabetes, dyslipidemia, coronary artery disease, chronic kidney disease, chronic lung disease) and statin use. To test whether the proportionality assumption of the Cox model was met for both models, interactions with time for all variables in the model were included.

To further evaluate the robustness of the findings, we fit a model with both BMI and WC, as well as models of WC stratified by BMI. We examined variance inflation factor values to identify potential collinearity between WC and BMI. We also explored diabetes as a potential effect modifier by evaluating [BMI X diabetes] and [WC X diabetes] interactions.

Due to the time lag in observations and medical record retrieval, we could not review records for a portion of participants with reported hospitalizations for a serious infection. In a sensitivity analysis, we repeated assessment of the association between obesity measures and first sepsis event, excluding all data on individuals with unretrieved medical records. The sensitivity analysis excluded *all* hospital events for the participant – not just the individual unretrieved hospital event.

We considered p-values <0.05 to be statistically significant. We conducted all analyses using SAS v.9.3.

RESULTS

Among the REGARDS participants, from February 5, 2003 through July 30, 2012, there were 2,157 hospitalizations for a serious infection, including 1,297 sepsis events. A total of 975 unique individuals experienced a sepsis event. Mean follow-up time was 4.6 years. Among the 975 incident sepsis events, the most common infection types were pneumonia, kidney and urinary tract infections, and abdominal infections. (Table 1)

Mean BMI was 29.3±6.2 kg/m^2. Mean WC was 100.2±13.7 cm for males and 92.9±16.4cm for females. BMI and WC were higher among younger, female and African American subjects. (Tables 2 and 3) Subjects with high BMI and WC were more likely to have chronic medical conditions.

After adjustment for confounders, only the highest BMI category (morbid obesity) was independently associated with increased sepsis risk (adjusted HR 1.57, 95% CI 1.16–2.14) (Table 4). Large WC was independently associated with increased sepsis risk (adjusted HR 1.34, 95% CI: 1.15–1.56). For both models the interactions with time were not statistically

significant, suggesting that the proportionality assumption was satisfied. In a model with both BMI and WC as independent variables, large WC – but not BMI – remained independently associated with sepsis (HR 1.47, 95% CI 1.20–1.79). The tolerance was 0.42 and the variance inflation factor was 2.4, suggesting no problems of collinearity between WC and BMI.

We repeated the analysis examining the association between WC and risk of sepsis, stratified by BMI. We observed that WC was associated with increased sepsis risk for BMI 25–29.9 and 30–39.9 but not BMI<25 or BMI 40. (Table 5) Interactions between BMI and diabetes as well as WC and diabetes were not significant, suggesting no effect modification by diabetes.

There were 1,157 participants with reported serious infection hospitalizations that had not yet been reviewed or adjudicated, a figure expected to yield an additional 300 first sepsis events. Analyses excluding these individuals revealed results similar to the primary analysis. (Appendix) Compared with the remainder of the cohort, the excluded individuals exhibited similar BMI and WC. Compared with the remainder of the cohort, excluded individuals were older (p=0.002), more likely to be female (p=0.02), exhibited lower income (p=0.006), reported more alcohol use (p=0.004), reported less exercise (p=0.02), and were more likely to have hypertension (p<0.001), dyslipidemia (p=0.04), coronary artery disease (p=0.001), atrial fibrillation (p<0.001), deep vein thrombosis (p=0.002) chronic kidney disease (p<0.001), chronic lung disease (p<0.001) and elevated C-reactive protein (p<0.001).

DISCUSSION

Prior studies have evaluated the association between obesity and the outcomes of individuals suffering from sepsis or other critical illness.[11–13] Our study extends upon these findings, suggesting a connection between obesity at a stable phase of health and the development of *future* sepsis events.

There are plausible connections between the hypothesized pathophysiologic features of obesity and susceptibility to future sepsis events. One hypothesized mechanism of obesity suggests that increased adiposity induces a chronic inflammatory state characterized by increased cytokine production by adipocytes or macrophages infiltrating adipose tissue.[21] Exaggerated inflammatory response to microbial infection is a prominent feature of sepsis.[22] Yende, et al. described associations between baseline inflammatory markers (IL-6, TNF-alpha) and future risk of pneumonia, suggesting that individuals with a chronic hyperinflammatory state may be at increased risk for future infection or sepsis events.[23] Adipose tissue secretes proinflammatory adipokines such as such as interleukin-6, tumor necrosis factor-alpha and calcitonin, which are commonly associated with sepsis pathophysiology.[24] Adipocytes also express Toll-like receptors, which are responsive to endotoxin. We have previously reported that individuals with elevated baseline TNF-alpha are increased risk of future sepsis events.[25]

Another hypothesized mechanism of obesity is the presence of systemic lipotocixity resulting from adiposity, leading to the production of toxic metabolites and over-activation

of oxidative pathways.[26] Oxidative stress and high lipid concentrations may lead to apoptosis and endothelial dysfunction.[26,27] The endothelium plays a prominent role in immune response and sepsis pathophysiology, facilitating leukocyte trafficking, activation of coagulation and increased vascular leakage.[28] An animal study suggests that obesity exacerbates sepsis-induced microvascular dysfunction.[7] While endothelial cell activation plays a prominent role in acute sepsis, we have identified that chronically elevated markers of endothelial cell activation may predict future episodes of sepsis.[25]

Prior studies have pointed to associations between obesity and diabetes as well as diabetes and infection risk.[29] Specifically, defects in neutrophil function, including abnormalities in adhesions, chemotaxis and intracellular killing, have been observed in diabetes and may be heighten the risk of infections and sepsis. In this context, one would expect obesity to act as a surrogate marker for diabetes. However, our study found that obesity was independently associated with sepsis, even after accounting for the confounding influence of diabetes. Furthermore, on examination of obesity and diabetes interactions, we did not find any evidence of effect modification. Therefore, the findings of our study cannot be completely attributed to the coexistence of diabetes.

An interesting observation was that WC was a stronger predictor of future sepsis events than BMI. This finding is not surprising since WC and sagittal diameter are better predictors of dyslipidemia, metabolic syndrome, cardiovascular disease, sudden cardiac death, and all-cause mortality than BMI.[30–32] In a study of 403 intensive care unit patients (including one-third with sepsis or septic shock), sagittal abdominal diameter was a stronger predictor of death than BMI.[32] WC may better reflect central abdominal and visceral obesity, which have stronger connections with cardiovascular and metabolic abnormalities than general obesity.[10] For example, in a study of men with similar BMI, viscerally obese individuals exhibited lower levels of adiponectin, which plays a key role in glucose regulation and fat catabolism.[33] Compared with subcutaneous fat, visceral fat expresses more proinflammatory cytokines; as discussed previously, a chronic hyperinflammatory state may be associated with sepsis risk. CRP levels also appear to be elevated in individuals with abdominal obesity; we have previously found that elevated high sensitivity CRP is associated with sepsis risk.[34,35]

Obesity is a modifiable condition. Therefore, the most important question raised by our study is whether weight reduction could lower the future risk of sepsis events. Exercise and weight reduction have been demonstrated to reduce the risk of medical conditions such as diabetes and cardiovascular disease.[36,37] Weight loss may also alter metabolic profiles. Shai, et al. showed that weight loss increased adiponectin and reduced high sensitivity C-reactive protein (hsCRP), which we have shown to be associated with sepsis risk.[35,38] Pharmacotherapy may help to prevent or alter the course of obesity-related cardiovascular disease in obese individuals and could potentially play a similar role in sepsis.[10] While often difficult to achieve or maintain, the associations identified in this study offer additional factors for motivating weight reduction.

LIMITATIONS

Due to time lags in event reports and record retrieval, there were 1,157 individuals with unretrieved medical records for reported serious infection hospitalizations. However, we repeated the analysis excluding these individuals and found similar results. Because REGARDS is not a surveillance study, we likely did not detect all sepsis events. However, there is no reason to believe that misclassification of sepsis events occurred between BMI or WC groups. Hence, our reported associations likely reflect underestimates of the true association.

We did not examine severity variants of sepsis such as severe sepsis and septic shock because these conditions often develop later in the hospital course; however, it is possible that associations between obesity and various forms of sepsis may differ than those reported here. We also did not examine death after sepsis; prior studies suggest that obesity may be protective against death after the development of sepsis.[11,13] Our objective, however, was to evaluate the associations with the risk of developing sepsis – not sepsis recovery.

By design, the REGARDS cohort includes only African Americans and whites, and thus these results may not generalize to other ethnic groups. History of cancer was not ascertained by REGARDS, which may represent an important risk factor for subsequent sepsis. Also, our study was able to detect the presence of chronic medical conditions but not their level of severity. Our analysis utilized baseline obesity measurements; we could not assess the effect of changes in weight, BMI or WC over time.

CONCLUSION

In this study obesity was associated with increased risk of future sepsis. WC was a better predictor of sepsis risk than BMI. Weight reduction or the control of its sequelae may provide options for sepsis risk prediction, mitigation or prevention.

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APPENDIX

Sensitivity analysis. Hazard ratios (HRs) and 95% confidence intervals (CI) for the association between obesity and first sepsis episode. Analysis excludes 1,157 individuals with unadjudicated medical records for reported serious infection hospitalizations.

Measure of Obesity	N	Risk of sepsis (per 1000)	Unadjusted HR For Sepsis (95% CI) – Separate Models for BMI and WC	[†] Adjusted HR for Sepsis (95% CI) – Separate Models for BMI and WC	[*] Adjusted HR for Sepsis (95% CI) – Separate Models for BMI and WC	[*] Adjusted HR for Sepsis (95% CI) - Model including both BMI and WC
Body Mass Index (BMI)						
<18.5 kg/m^2	304	32.9	1.50 (0.79–2.84)	1.78 (0.94–3.37)	1.20 (0.59–2.46)	1.26 (0.62–2.58)
18.5 – 24.9 kg/m^2	6,846	25.1	Ref	Ref	Ref	Ref
25.0 – 29.9kg/m^2	10,674	25.5	0.99 (0.82–1.19)	1.08 (0.88–1.32)	0.98 (0.79–1.21)	0.84 (0.67–1.05)
30.0 – 39.9 kg/m^2	9,227	3.0	1.20 (0.99–1.46)	1.53 (1.24–1.87)	1.07 (0.85–1.34)	0.77 (0.58–1.02)
40.0 kg/m^2	1,767	4.1	1.74 (1.33–2.29)	2.84 (2.10–3.83)	1.52 (1.08–2.13)	1.07 (0.73–1.57)
Waist Circumference (WC)						
Male 102 cm or Female 88 cm	14,922	21.9	Ref	Ref	Ref	Ref
Male > 102 cm or Female > 88 cm	14,104	35.1	1.66 (1.44–1.91)	1.93 (1.66–2.25)	1.36 (1.15–1.62)	1.28 (1.08–1.53)

[†] Adjusted for age, sex, race, geographic region.

[*] Adjusted for age, race, gender, geographic region, income, education, smoking status, alcohol use, exercise, statin use, hsCRP level, hypertension, diabetes, dyslipidemia, coronary artery disease, chronic kidney disease, and chronic lung disease.

BMI= Body Mass Index. WC=Waist Circumference.

What is already known about this subject

- Obesity may influence outcomes after acute sepsis.

- The association between obesity and risk of future sepsis events is unknown.

What does this study adds

- Obesity is associated with risk of future sepsis events.

- Waist circumference is a better predictor of future sepsis events than body mass index.

TABLE 1

Infection types associated with hospitalizations for sepsis. Includes first sepsis events for 975 individuals.

Infection Type	Number of Sepsis Hospitalizations (n=975) N (%)
Pneumonia	427 (43.8)
Kidney and Urinary Tract Infections	155 (15.9)
Abdominal	133 (13.6)
Bronchitis, Influenza and other Lung Infections	84 (8.6)
Skin and Soft Tissue	71 (7.3)
Sepsis	63 (6.5)
Fever of Unknown Origin	14 (1.4)
Unknown/Other	14 (1.4)
Surgical Wound	6 (0.6)
Catheter (IV / Central / Dialysis)	5 (0.5)
Meningitis	3 (0.3)

TABLE 2

Demographic and health behavioral characteristics between obese and non-obese subjects as measured by Body Mass Index.

Characteristic	<18.5 (n=319)	18.5–24.9 (n=7,091)	25.0–29.9 (n=11,057)	30.0–39.9 (n=9,640)	40.0 (n=1,859)	p-value*
DEMOGRAPHICS						
Age (%)						
45–54	10.3	11.3	10.4	12.3	17.7	<0.001
55–64	32.8	32.1	35.2	42.1	49.2	
65–74	27.8	30.6	33.8	32.3	26.9	
75+	29.1	26.0	20.6	13.2	6.3	
Gender (%)						
Male	30.2	44.1	53.0	41.0	22.3	<0.001
Female	69.8	55.9	47.0	59.0	77.7	
Race (%)						
White	63.2	69.6	62.5	50.3	36.1	<0.001
African American	36.8	30.4	37.5	49.7	63.9	
Education (%)						
Less than high school	18.2	10.5	11.5	14.1	17.8	<0.001
High school graduate	26.1	24.3	25.2	27.3	28.2	
Some college	23.3	25.0	26.7	27.9	30.0	
College or higher	32.4	40.2	36.7	30.7	24.0	
Income (%)						
<$20k	27.4	16.8	15.4	19.7	28.5	<0.001
$20k–$34k	27.0	23.2	24.3	24.5	26.1	
$35k–$74k	16.7	29.0	30.7	30.1	24.8	
$75k	9.1	17.5	17.4	14.1	9.0	
Refused	19.8	13.5	12.2	11.6	11.5	
Geographic Region (%)						
Stroke Buckle	17.3	21.1	20.2	21.3	22.3	0.02
Stroke Belt	39.3	35.3	34.0	34.7	33.8	
Non-Belt/Buckle	43.4	43.6	45.7	44.0	43.9	

Body Mass Index (BMI - kg/m^2)

Characteristic	Body Mass Index (BMI - kg/m²)					
	<18.5 (n=319)	18.5–24.9 (n=7,091)	25.0–29.9 (n=11,057)	30.0–39.9 (n=9,640)	40.0 (n=1,859)	p-value*
HEALTH BEHAVIORS						
Tobacco Use (%)						
Current	42.3	19.4	13.6	12.2	10.8	<0.001
Past	22.4	34.9	42.8	41.9	38.6	
Never	35.3	45.8	43.7	45.9	50.6	
Alcohol Use (%)						
Heavy	8.0	5.7	4.3	2.9	1.2	<0.001
Moderate	33.2	37.1	36.4	29.3	21.6	
None	58.8	57.2	59.3	67.9	77.2	
Exercise						
None	42.9	31.2	30.1	38.3	49.4	<0.0001
1–3 times/week	27.1	34.2	37.1	37.0	33.6	
4 times/week	30.0	34.6	32.8	24.7	17.0	
CHRONIC MEDICAL CONDITIONS						
Chronic Lung Disease (%)	12.3	8.2	8.1	10.0	13.5	<0.001
Chronic Kidney Disease (%)	28.8	22.4	22.2	27.2	32.4	<0.001
Peripheral Artery Disease (%)	4.4	2.4	2.2	2.0	1.8	0.01
Deep Vein Thrombosis (%)	6.7	4.4	4.6	6.0	8.0	<0.001
Diabetes (%)	6.4	9.9	17.9	31.3	43.8	<0.001
Stroke (%)	9.2	6.3	6.4	6.3	6.6	0.35
Myocardial Infarction (%)	8.9	7.2	8.6	9.3	7.4	<0.001
Coronary Artery Disease (%)	17.9	16.4	18.4	19.0	15.5	<0.001
Atrial Fibrillation (%)	9.9	8.9	8.3	8.8	10.3	0.06
Hypertension (%)	37.4	45.2	56.2	69.5	80.4	<0.001
Dyslipidemia (%)	16.1	25.8	35.1	37.6	35.6	<0.001
Elevated hsCRP (%)	23.0	24.8	32.3	48.3	68.6	<0.001
OTHER						
Statin use (%)	15.4	24.3	33.0	35.1	32.9	<0.001

*Based on chi-square test

TABLE 3

Demographic and health behavioral characteristics between obese and non-obese subjects as defined by waist circumference (WC). Normal WC = Male ≤ 102 cm or Female ≤ 88 cm. Large WC = Male >102 cm or Female >88 cm

	Normal WC (n=15,448)	Large WC (n=14,735)	p-value[*]
DEMOGRAPHICS			
Age (%)			
45–54	12.1	11.3	<0.0001
55–64	36.0	39.2	
65–74	31.0	33.1	
75+	20.8	16.4	
Gender (%)			
Male	55.0	34.3	<0.001
Female	45.0	65.7	
Race (%)			
White	65.4	51.4	<0.001
African American	34.6	48.6	
Education (%)			
Less than high school	10.2	15.0	<0.001
High school graduate	24.4	27.4	
Some college	26.1	27.6	
College or higher	39.3	29.9	
Income (%)			
<$20k	14.5	22.0	<0.001
$20k–$34k	22.9	25.6	
$35k–$74k	31.3	27.7	
$75k	19.0	12.3	
Refused	12.4	12.3	
Geographic Region (%)			
Stroke Buckle	21.0	20.8	0.40
Stroke Belt	34.3	35.0	
Non-Belt/Buckle	44.7	44.2	
HEALTH BEHAVIORS			
Tobacco Use (%)			
Current	15.9	13.3	<0.001
Past	39.3	41.0	
Never	44.9	45.6	
Alcohol Use (%)			
Heavy	4.9	3.1	<0.001
Moderate	38.3	28.1	
None	56.8	68.9	
Exercise			

	Normal WC (n=15,448)	Large WC (n=14,735)	p-value[*]
None	28.3	40.8	<0.0001
1–3 times/week	36.6	35.3	
4 times/week	35.1	23.9	
CHRONIC MEDICAL CONDITIONS			
Chronic Lung Disease (%)	7.7	10.7	<0.001
Chronic Kidney Disease (%)	21.1	28.5	<0.001
Peripheral Artery Disease (%)	2.3	2.2	0.39
Deep Vein Thrombosis (%)	4.2	6.4	<0.001
Diabetes (%)	12.7	31.8	<0.001
Stroke (%)	5.8	7.1	<0.001
Myocardial Infarction (%)	7.7	9.3	<0.001
Coronary Artery Disease (%)	16.9	19.0	<0.001
Atrial Fibrillation (%)	8.2	9.4	<0.001
Hypertension (%)	49.4	69.6	<0.001
Dyslipidemia (%)	29.8	37.4	<0.001
Elevated hsCRP (%)	26.7	49.7	<0.001
OTHER			
Statin use (%)	28.2	34.8	<0.001

[*] Based on chi-square test.

TABLE 4

Hazard ratios (HRs) and 95% confidence intervals (CI) for the association between obesity and first sepsis episode.

Measure of Obesity	N	Risk of sepsis (per 1000)	Unadjusted HR For Sepsis (95% CI) – Separate Models for BMI and WC	† Adjusted HR for Sepsis (95% CI) – Separate Models for BMI and WC	* Adjusted HR for Sepsis (95% CI) – Separate Models for BMI and WC	* Adjusted HR for Sepsis (95% CI) - Model including both BMI and WC
Body Mass Index (BMI)						
<18.5 kg/m²	318	40.9	1.66 (0.95–2.91)	2.00 (1.14–3.53)	1.50 (0.81–2.77)	1.56 (0.84–2.88)
18.5 – 24.9 kg/m²	7,091	28.3	Ref	Ref	Ref	Ref
25.0 – 29.9kg/m²	11,057	29.2	1.00 (0.84–1.19)	1.11 (0.92–1.33)	1.01 (0.83–1.23)	0.87 (0.71–1.08)
30.0 – 39.9 kg/m²	9,640	34.1	1.20 (1.01–1.43)	1.52 (1.26–1.84)	1.10 (0.89–1.35)	0.81 (0.62–1.06)
40.0 kg/m²	1,859	47.9	1.78 (1.39–2.29)	2.96 (2.26–3.89)	1.57 (1.16–2.14)	1.14 (0.81–1.62)
Waist Circumference (WC)						
Male 102 cm or Female 88 cm	15,448	25.4	Ref	Ref	Ref	Ref
Male > 102 cm or Female > 88 cm	14,735	39.4	1.60 (1.41–1.82)	1.88 (1.64–2.16)	1.34 (1.15–1.56)	1.47 (1.20–1.79)

†
Adjusted for age, sex, race, geographic region.

*
Adjusted for age, race, gender, geographic region, income, education, smoking status, alcohol use, exercise, statin use, hsCRP level, hypertension, diabetes, dyslipidemia, coronary artery disease, chronic kidney disease, and hronic lung disease.

BMI= Body Mass Index. WC=Waist Circumference.

TABLE 5

Hazard ratios and 95% confidence intervals or the association between elevated waist circumference and first sepsis episode, stratified by body mass index category. All models adjusted for age, race, gender, income, education, smoking status, alcohol use, exercise, statin use, hsCRP level, hypertension, diabetes, dyslipidemia, coronary artery disease, chronic kidney disease, and chronic lung disease.

Waist Circumference		Body Mass Index (kg/m^2)			
		<25.0*	25.0 – 29.9	30.0 – 39.9	40.0
Male 102 cm or Female 88 cm		Referent	Referent	Referent	Referent
Male > 102 cm or Female > 88 cm		1.65 (0.99–2.73)	1.42 (1.10–1.83)	1.80 (1.12–2.90)	0.58 (0.08–4.33)

*
BMI <18.5 and 18.5–24.9 combined into a single category due to the low number of BMI<18.5 with abnormal waist circumference.

BMI=Body Mass Index.