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Erin M. Sullivan Date

Understanding the Association of Harmful Risk Factors with Lower Mortality Among those with Disease: An Illustration Using Obesity and End-stage Renal Disease

By

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Master of Public Health

Epidemiology

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Bachelor of Arts
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Thesis Committee Chair: W. Dana Flanders, MD, DSc

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

Understanding the Association of Harmful Risk Factors with Lower Mortality Among those with Disease: An Illustration Using Obesity and End-stage Renal Disease

By Erin M. Sullivan

Background: Obesity has been shown to increase the risk of developing chronic disease as well as the risk of all-cause mortality. However, an "obesity paradox" has been observed, in that obese individuals tend to live longer than normal weight individuals after developing disease. The reasons for this are unclear, but may be related to analytic methods.

Methods: Using the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, a longitudinal nationally recruited cohort study of adults age 45 and older, we conducted a survival analysis of end-stage renal disease (ESRD) patients, stratified by obesity status. We measured three primary outcomes: hazards of developing ESRD, overall mortality, and mortality after ESRD, truncated at age 60 years. We compared obese and overweight individuals to normal weight individuals, defined by body mass index, controlling for race, gender and smoking status.

Results: Obese persons had, on average, slightly lower hazard of developing ESRD and mortality after ESRD, but a slighter higher hazard of all-cause mortality, compared to normal weight persons; however, these results were not statistically significant. Overall, differences in disease-free, overall, and with-ESRD survival time between normal weight, overweight, and obese persons did not differ meaningfully in our analyses. Our findings were not affected by excluding those with chronic kidney disease at baseline, and were impacted only mildly by adjusting for age.

Discussion: Our findings highlight the need for greater understanding of the complicated relationship between obesity and both the development and the progression of chronic disease. With respect to ESRD, further study among a cohort focused upon kidney disease risk factors would provide greater insight into important factors involved in this relationship.

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Background and Literature Review

Introduction

In the United States, chronic diseases account for the top 4 leading reported causes of death, and comprise 7 of the top 10 leading causes (1). Studying chronic disease risk factors is therefore an important health issue; years of research have led to an understanding in the medical profession of many of these factors, which include high blood pressure, high cholesterol, and obesity, among others (2). While such characteristics have shown independent associations with both the development of chronic disease and an increased risk of early mortality, an interesting and unexpected phenomenon has also been observed: such factors are also frequently associated with lower mortality among those with disease (3, 4, 5, 6). In the context of end-stage renal disease (ESRD), this pattern has been seen with factors such as high cholesterol, systolic and diastolic blood pressure, and creatinine (7, 8).

For this manuscript, we explore this phenomenon using obesity and ESRD as an illustrative example. Substantial evidence has shown a clear and potentially causal association between obesity and both ESRD and early mortality in the general population, but among those with ESRD, the opposite association with mortality has been observed (6, 9, 10, 11). Such counterintuitive, seemingly "paradoxical" observations have led to several proposed explanations in the medical literature. These include the presence of unmeasured confounding, bias due to the selection of a diseased population for study, and the idea that the effect of obesity on mortality may be different for those with and without ESRD (12, 13, 14, 15). Hernan et al. have suggested that, by conditioning on disease status (as in a traditional survival analysis), a collider bias can result (16) (Figure

1). As individuals must have survived to develop end-stage renal disease to be included in analysis, a false association may be observed between obesity and factors that cannot be controlled in analysis. In this manuscript, we explore these relationships and propose a plausible explanation as to why such harmful disease risk factors can lead to apparent lower mortality among obese persons with ESRD.

Overview of End-Stage Renal Disease

End-stage renal disease is a potentially fatal condition that occurs when there is complete or near complete failure of kidney function (17). In patients with ESRD, the kidneys have been damaged to the point where they are no longer able to filter blood properly, causing wastes to build up in the body. This can lead to other health problems, including cardiovascular disease (CVD), anemia, and bone disease (18). ESRD is considered a permanent condition which, while it can be treated, cannot be reversed (19). It usually occurs after a period of suffering with chronic kidney disease (CKD), in which the kidneys gradually, over many months or years, lose their ability to function properly. In the United States, over 20 million people have CKD; related complications from the disease are so common that these individuals are 16 to 40 times more likely to die of complications from CKD than they are to reach onset of end-stage renal disease (18). The best way to prevent ESRD is to carefully treat and monitor CKD before it worsens.

Common symptoms of ESRD include general ill feeling or fatigue, itchy or dry skin, headaches, unintentional weight loss, loss of appetite, and nausea. Typically, a test for glomerular filtration rate (GFR, measuring the kidneys' filtration of creatinine) can be used for diagnosis. An estimated GFR of less than 60 mL/min/1.73 m^2 for 3 months or longer is a common standard for kidney disease diagnosis (20).

Treatment for ESRD typically involves one of two options: dialysis or a kidney transplant. In the United States, more than 871,000 people were living with ESRD at the end of 2009. This represents an increase of nearly 600% since 1980 (20). Of these individuals, 398,861 persons were being treated with some form of dialysis, and 172,553 patients were living with a working transplanted kidney. The most common form of dialysis is hemodialysis, which typically involves outpatient visits to a clinic several days a week for several hours at a time, for mechanical filtration of the blood; more than 10 times as many patients receive this type of treatment as compared to peritoneal (a procedure which uses blood vessels in the stomach to stand in for the function of the kidney) and at-home dialysis combined. However, kidney transplant remains the most effective form of treatment for ESRD; the 5 year survival rate of 85.5% for transplant recipients is more than twice that of the 5 year survival rate of 38.5% for dialysis patients (18).

Risk Factors for End Stage Renal Disease and Mortality from ESRD

The most commonly implicated risk factor for the development of kidney disease and subsequent ESRD is diabetes mellitus. In 2007, an estimated 44% of new cases of ESRD were attributed to diabetes (21). A 1997 analysis of male participants enrolled in the Multiple Risk Factor Intervention Trial (MRFIT) showed that the age-adjusted incidence of all-cause ESRD in men with diabetes was 199.8 per 100,000 person-years, compared with 13.7 per 100,000 person years in non-diabetic men, indicating a risk of ESRD that was 12.7 times greater in diabetics than non-diabetics. Diabetics in this study were also at higher risk for ESRD ascribed to causes other than diabetes, even when controlling for factors such as age, ethnicity, income, blood pressure, serum cholesterol

level, and history of myocardial infarction (22). Due to this elevated risk, health practitioners, including the American Diabetes Association, recommend that diabetics undergo regular screening of GFR and urine protein levels to monitor their risk of kidney disease (23).

Chronic hypertension is the second most commonly implicated cause of ESRD. Chronically high blood pressure can cause damage to blood vessels throughout the body (24). Blood vessel damage to the kidneys impacts their ability to effectively remove wastes from the blood, and excess fluid in the blood vessels may then raise blood pressure even higher, feeding a dangerous cycle. Over 25,000 new cases of kidney failure in the United States each year are attributed to hypertension, which represent more than one quarter of all cases of kidney failure in the US. The National Heart, Lung, and Blood Institute of the National Institutes of Health (NIH) recommends that people with CKD carefully monitor their blood pressure to ensure that it stays below 130/80 mmHg. Recommended hypertension control measures include antihypertensive medication, weight control, or special dietary patterns, such as the "DASH" (Dietary Approach to Stop Hypertension) diet (25).

Survival with ESRD depends on a variety of factors, including the presence of comorbid conditions as well as adherence to treatment regimens and doctors' recommendations. To date, one of the best predictors of survival with ESRD is the receipt of a kidney transplant. Individuals are considered better candidates for kidney transplants when they are in otherwise good general health and practice healthy lifestyle habits, such as not smoking or drinking alcohol (26). A 2010 study from the University of Ottawa studied factors associated with reduced survival after kidney transplant and found the

following variables to be independent predictors of survival: age, race, cause of kidney failure, body mass index, comorbid disease, smoking, employment status, serum albumin level, year of first renal replacement therapy, previous kidney transplantation, time to transplant wait-listing and time spent on the transplant wait-list (27).

Obesity as a Risk Factor for ESRD, Chronic Disease, and Mortality

Obesity is one of the most commonly implicated risk factors for chronic disease, and end-stage renal disease is no exception. Obesity is most often defined in the medical literature as a body mass index (BMI) of 30.0 kg/m^2 or greater; overweight is typically classified as a BMI of 25.0 to 29.9 kg/m^2. A retrospective cohort study of over 300,000 adult volunteers in Northern California showed a dose-response relationship between weight and ESRD risk. Increasing degree of overweight corresponded to a progressively higher risk of developing ESRD; this ranged from close to 2 times greater risk among overweight persons to about 7 times greater risk among the extremely obese (a BMI of over 40 kg/m^2), in comparison to normal weight volunteers (28). This increased risk held true even when controlling for factors including age, race, sex, creatinine levels, and presence or absence of diabetes and hypertension.

Additionally, there is strong evidence that obesity serves as an indirect cause of ESRD, as it is a key risk factor for ESRD's two most common causes: diabetes and hypertension (8, 18). Individuals classified as overweight or obese are significantly more likely to develop diabetes and hypertension, as well as other chronic diseases including heart disease and cancer (29, 30, 31). A collection of symptoms that includes abdominal obesity, hypertension, low HDL cholesterol, high triglycerides, and high fasting blood

glucose is referred to as the "metabolic syndrome," which is a condition that has been associated with increased risk for a variety of chronic conditions, including kidney disease (32).

In addition to its association with disease, obesity has also been shown to be associated with increased all-cause mortality. While an association between slight to moderate overweight and early mortality is less clear (likely due in part to issues with the validity of using a height to weight ratio measurement such as BMI to indicate body fat), research has shown that severe obesity, on average, may be associated with a 5 to 20 year decrease in lifespan (33). This has been shown even when controlling for factors such as sex, age, race, and smoking status.

Risk Factor-Mortality Relationships

Despite strong evidence for the impact of obesity on both the development of disease and early mortality, increased longevity among obese persons with certain chronic diseases has been well documented in the literature. Such a pattern has been referred to as "reverse epidemiology," as it represents the opposite association of what would be expected based on observed data under a traditional epidemiologic analysis (34). These associations have been observed among patients with cardiovascular disease, diabetes, and most prominently, kidney disease (3, 5, 6, 13, 31, 34). With respect to kidney disease, risk of mortality has consistently been shown to have a near perfect inverse relationship with increasing BMI, even into categories of extreme obesity (e.g., a BMI of greater than 45 kg/m^2) (7). This trend has been seen not only in the obese but also in those with other chronic disease risk factors such as high cholesterol and high blood

pressure; despite being one of the major attributed causes of ESRD, research has indicated that among hemodialysis patients, high blood pressure may not affect the risk of all-cause mortality (7, 8). Some research indicates that among those with hypertension, risk of all-cause mortality may even be lowered (7).

In public health application, such findings are not only puzzling, but also important to interpret for clinical practice. If one of the primary goals of public health is to reduce the overall burden of disease, it is important to understand how to educate the population about ways to stay healthy and reduce the likelihood of developing disease; however, if the same factors which increase the likelihood of disease also increase longevity, the message from clinicians becomes less clear. Ideally, advances in public health should lead not only to longer lifespans, but healthier ones as well; this leads to an improved quality of life in the population as well as reduced costs to the healthcare system. Therefore, before interpreting this "obesity paradox" as an indication that obesity confers a health advantage, it is important to consider the potentially causal mechanisms at work.

Though this reverse pattern could seem counterintuitive at first, deeper analysis, based on collider bias as proposed by Dahabreh and Kent ("index event bias") and a similar issue based on survival proposed by Flanders et. al. ("survival bias") gives away to a more logical explanation (12, 35, 36). In a potential outcomes model, one can consider the idea of a "counterfactual"; this model compares what would happen to a single individual with and without a given exposure, keeping all other factors identical (35). Such a model exists strictly in theory, as only one of these outcomes can ever be observed in reality. The model posits that each person has an age at which ESRD would

occur if obese, and an age at which ESRD would occur if not obese. Similarly, a potential-outcome model for death posits that each person has an age at which death would occur if obese, and an age when death would occur if not obese. In both cases, evidence indicates that obesity would cause a leftward shift in the age of event.

One can then imagine the potential outcomes for a person who would develop ESRD at a younger age if obese than if not obese, and similarly would die at a younger age; for this person, obesity caused an earlier onset of both ESRD and mortality. While obesity negatively impacted this individual, they would have developed ESRD in either case, whether obese or not – their obesity merely accelerated the onset of disease. However, it is plausible that obesity could also cause ESRD to occur in some obese people who would not have otherwise developed it before death had they not been obese. For such an individual, if not obese, the potential age at ESRD onset must logically exceed the age at death. However, if obesity were to cause ESRD in a person who is obese, the potential age at ESRD onset would necessarily be less than the age at death. In this case, the obesity-caused shift in age at ESRD onset would need to be greater than the obesity-caused shift in age at death. If such a pattern holds up generally, then individuals who are obese would, on average, have a longer observed lifespan with ESRD compared to otherwise similar non-obese individuals of the same age at diagnosis (35). Additionally, either experiencing ESRD (Dahabreh) or survival status (Flanders et al) acts as a collider (Figure 1) (12, 35). Stratification, especially with age adjustment, can then result in an observed association between obesity status and unmeasured risk factors. This can occur even if an unmeasured risk factor has no direct effects on ESRD (36). In theory, these biases could be avoided by studying the effect of obesity on certain

outcomes defined so that the collider biases would not arise for relatively simple estimators; potential examples include life expectancy, disease-free life expectancy and expected duration of life with ESRD –without adjustment for ESRD onset age (35). Additionally, collider bias could potentially be avoided by defining a multi-component outcome, such as ESRD onset at age "M", death after wards but before age "M+1," and so on (36).

Statement of Research Objectives

In this analysis, we will investigate the relationship between obesity, end-stage renal disease, and mortality. Using a national, population-based cohort study of chronic disease risk factors, we will conduct traditional survival analyses to look at the impact of obesity on three measured outcomes: the time of onset of ESRD (age at diagnosis), the overall risk of developing ESRD (number of cases diagnosed per person-years during the study), and overall mortality (age at death). We expect that, as has been observed in the literature, obese individuals will have a higher risk of developing ESRD and they will also experience both ESRD and mortality at an earlier age, on average, than non-obese individuals.

Additionally, we aim to examine the impact of obesity on the duration of life lived with ESRD. It has been observed that obesity tends to have a positive relationship with survival time after disease diagnosis. However, we posit that this relationship arises naturally in traditional analyses which control for age at diagnosis. We hypothesize that, by controlling for age, a false association is induced between obesity and the presence of risk factors that are unmeasured or unknown (factors which would, presumably, lead a

non-obese individual to be diagnosed with ESRD at the same age as a comparable obese individual). Such factors may also impact mortality, leading to a biased measure of survival time with the disease. In our analysis, we will look at the average survival time with end-stage renal disease for obese vs. non-obese individuals, not controlling for age at diagnosis. We hypothesize that in this simple analysis method, we may find that obese individuals, on average, live for a shorter period of time with ESRD than do non-obese persons (35, 36).

Methods

REGARDS Study

The data for this analysis were obtained from the REasons for Geographic and Racial Differences in Stroke (REGARDS) project, which is sponsored by the National Institutes of Health (NIH), National Institute for Neurological Disorders and Stroke (NINDS) (38). REGARDS is an ongoing (as of the publication of this paper) observational cohort study of risk factors for stroke in persons age 45 and older, who will be followed for many years. A detailed description of the methods and design behind the study has been described in the study's original publication (38).

The study contains data on 30,239 participants who were recruited between January 2003 and October 2007. Participants were recruited via mail and telephone using commercially available lists, with the goal of enrolling equal proportions of male and female and African-American and white participants. Participation involved an initial telephone interview, followed by an in-home physical exam. Information gathered via the telephone interview included personal and family history of illness (including cancer, diabetes, stroke, myocardial infarction, and end-stage renal disease), medications taken, hospitalizations, substance use, and physical activity and dietary habits. At the in-home exam, study team members obtained written informed consent from participants, administered an echocardiogram of the heart, and gathered data on basic vital signs such as height and weight as well as traditional chronic disease risk factors such as blood pressure and cholesterol levels. As part of the ongoing follow-up, participants are contacted by phone at six month intervals and are asked questions about stroke symptoms, medical procedures they have undergone, and their general

health status (38). In the database that is used for this research paper, follow-up data is recorded through March of 2012.

REGARDS was designed with the intent of understanding why people living in certain parts of the country are more likely to develop strokes than those living in other parts of the country (with higher risk seen in the Southeast US), as well as to investigate why blacks are more likely to experience and die from strokes than are whites. Volunteers were recruited across the United States, but are most heavily concentrated in the Southeastern US. Specifically, 20% of participants reside in coastal North Carolina, South Carolina, and Georgia (known as the "Stroke Buckle"), 30% are from the remaining areas of North Carolina, South Carolina, and Georgia as well as Tennessee, Mississippi, Alabama, Louisiana, and Arkansas (known as the "Stroke Belt"), and 50% reside in the other 40 contiguous US states and the District of Columbia While the intent of the study is to investigate differences in stroke risk, the data collected is relevant to many chronic diseases and has been used to conduct research investigating myocardial infarction, kidney disease, diabetes, memory problems, and all-cause mortality, among other conditions (38).

Permission for Emory University School of Public Health researchers to use the data for the purposes of this and other research papers was obtained through the University of Alabama School of Public Health; the primary REGARDS study site as well as the location of its data coordination. Other participating organizations involved in the coordination of REGARDS include the University of Vermont, Wake Forest University School of Medicine, the University of Arkansas for Medical Sciences, Alabama Neurological Institute, and Examination Management Services, Inc. The dataset

obtained by Emory University is stripped of identifiable personal health information; Emory researchers do not have access to codes linking individuals to their health information. All data is stored on a private internal network, with access restricted to only approved study team members. Permission for access to the dataset for this project was obtained through Dr. William McClellan, MD of Emory University Rollins School of Public Health (personal communication), and approval to conduct the study was granted by the Emory Institutional Review Board (IRB).

US Renal Data System

The REGARDS dataset does not include participant information on diagnosis of End-Stage Renal Disease. Therefore, secondary information was obtained from the United States Renal Data System (USRDS) on the date of ESRD diagnosis and date of death for all enrolled volunteers (39). The USRDS is a national surveillance system that collect, analyzes, and distributes information about ESRD in the United States. All diagnosed cases of ESRD in the United States are reported to this system. Funding for the USRDS is provided by the National Institute of Diabetes and Digestive and Kidney Diseases. Permission for Emory University researchers to gain access to patient-specific data was obtained through request to the USRDS. All data is non-identifiable, and is accessible via REGARDS patient ID codes only.

Data Analysis

All statistical analyses and database management procedures were conducted in SAS 9.3. The dataset (titled 'calcvars2012') available for analysis to Emory researchers includes data on 30,183 volunteers. This dataset was merged with a dataset (titled

'esrd_date') on ESRD diagnosis dates and status for each volunteer. The dates of ESRD diagnosis represent the date when the participant was diagnosed with End-Stage Renal Disease. In this process, 20 volunteers were omitted from the dataset due to inconsistent study IDs between the two datasets. Additionally, 153 volunteers were omitted because they had ESRD diagnosis dates which predated their entrance to the REGARDS study (measured as the date of their in home visit). For the purposes of this analysis, all volunteers had to be alive and free of ESRD at the start of the study. For analysis, survival time was measured up until age 60 years; this eliminated all volunteers who were age 60 or older at baseline. All analyses were truncated at age 60 in order to elucidate the relationship between BMI and mortality, as this relationship has been shown to attenuate with increasing age (40). Twenty volunteers who were diagnosed with ESRD had to be analyzed as *not* having ESRD because the date of their ESRD diagnosis was later than their most recent follow-up date in the REGARDS study. Since volunteers could only be consistently analyzed up until their most recent REGARDS follow-up date, this information was considered non-observable and could not be accounted for in the analysis.

As the primary variables for analysis also included obesity status, all volunteers analyzed were also required to have data on body mass index (BMI). Obesity data was obtained at the first home physical exam; no data was collected on history of obesity and no further measurements of height and weight were obtained. Data on calculated BMI was missing for 202 volunteers. For 87 of these volunteers, data were present on both height and weight and BMI was then calculated using the standard formula: BMI= (weight in kg) / (height in meters)^2. All volunteers included in analysis who weighed

more than 350 pounds had BMIs which were calculated separately. The remaining volunteers were either missing height or weight data or had implausible values for these measurements.

Finally, 509 volunteers were omitted due to missing information on their last date of follow-up. This left 9,131volunteers for study analysis. Volunteers were not excluded for any other comorbid conditions, and were censored only by their most recent date of follow-up in the REGARDS Study. A description of the baseline characteristics of the 9,131volunteers included in analysis is detailed in Table 1.

Remaining volunteers ranged in age from 45 years to 59 years at their entrance into the REGARDS study. For these individuals, three primary measurements for analysis were calculated: time lived "disease free" (defined as no diagnosis of ESRD), time lived with ESRD, and total survival time. Hazard ratios were calculated to compare obese to non-obese individuals with respect to risk of developing ESRD, risk of overall mortality, and risk of mortality after ESRD. As volunteer age was reported in years and date of birth was not available, exact volunteer age was estimated: volunteers were assumed to be at their reported age plus six months at the baseline visit. For an individual, time lived disease free represented the number of days between their entrance into the study (defined as the date of in home visit) and the date of their ESRD diagnosis, or for individuals without ESRD, either their date of death or last follow-up date. Time lived with ESRD was defined as the number of days between ESRD diagnosis and the last follow-up date, or date of death (0, for those who died without ESRD). Total survival time was the number of days between study entrance and their date of death, or last follow-up date for individuals still alive. Proc phregin SAS 9.3 was used to obtain the

hazard ratios for all BMI categories, accounting for censoring by age 60 years. Disease-free time and total survival time were measured over the observed age range (45 to 60 years). Survival time with ESRD was measured as years lived after diagnosis of ESRD. All analyses controlled for participant race, gender, and smoking status (current vs. never smoker).

For the purpose of comparing hazard ratios, all individuals were categorized by Body Mass Index (BMI) classifications, based on WHO guidelines: "underweight": BMI >18.5; "normal weight": $18.5 \leq \text{BMI} < 25.0$; "overweight": $25.0 \leq \text{BMI} < 30.0$; and "obese": $30 \leq \text{BMI}$. In addition to the hazard ratios described above, the overall risk of developing ESRD by BMI classification was also computed, defined as the number of cases observed per person years. All comparisons made between groups considered the "normal weight" group as the reference category. While underweight individuals were included in certain risk calculations, they were omitted from comparison survival analyses. There were two primary reasons for this omission: first, underweight individuals were a small proportion of the overall study population, and therefore yielded fairly sparse data (importantly, no underweight individuals developed ESRD by age 60); second, underweight persons often have additional health problems that may have led them to be underweight, and therefore comparisons may be biased. Since the primary focus of the study was to compare survival among obese to survival among non-obese persons, excluding underweight individuals made for a clearer comparison. To assess differences between groups, Kaplan-Meier curves were plotted and a log rank test was performed.

A survival analysis was then also conducted in the "traditional" manner, controlling for age, for comparison purposes. Although the original intent was to compare obese and non-obese on selected outcomes defined so that they could be estimated and potentially avoid the collider-biases noted above, preliminary analyses indicated that within the analyzed population, obese persons appeared to have lower overall disease survival, after ESRD onset. However, the hazard for ESRD onset was lower for the obese than the non-obese. As the all the expected associations were not observed, this demonstration was omitted.

Results

Baseline Demographics of Study Population

Participant demographics are described in Table 1. Of the 9,131 participants, 93 were underweight, 1,922 were normal weight, 2,992 were overweight, and 4,124 were obese. The mean age of all participants was 54.81 years. Mean age varied little across BMI categories: BMI-specific mean ages at baseline were 54.99 years for underweight persons, 54.56 years for normal weight persons, 54.85 years for overweight persons, and 54.90 years for obese persons.

Certain participant demographics differed noticeably by BMI category. Males comprised 39.95% of the overall study population. However, by BMI category, males were more highly represented among the overweight; they comprised 26.88% of those underweight, 37.51% of those normal weight, 49.10% of those overweight, and 34.75% of obese individuals. Compared to whites, blacks were most highly represented among the obese category; blacks made up 45.13 % of the overall study population, but they comprised 54.19% of all obese participants. Overall, 36.66% of volunteers resided in the stroke belt region, and 22.54% resided in the stroke buckle. Underweight persons were most likely to live in the stroke belt (45.16%) and obese persons were most likely to live in the stroke buckle (22.96%), but overall, region of residence did not differ greatly by BMI category.

Smoking status differed significantly by BMI category, and prevalence of current participant smoking had an inverse relationship with BMI category. Those classified as underweight had more than double the prevalence of current smoking of those who were

normal weight (53.76% for underweight vs. 24.93% for normal weight persons), and more than three times the prevalence of current smoking of those who were obese (prevalence of 17.30%). Underweight persons were the least likely to be former smokers (13.98%) and obese persons were the most likely to be former smokers (32.54%). Obese persons were the most likely to have never smoked at all (50.16%).

Prevalence of diabetes, self-reported chronic kidney disease, and systolic and diastolic blood pressure all had a positive relationship with BMI status. Those classified as obese were most likely to have diabetes and chronic kidney disease, and had, on average, the highest systolic and diastolic blood pressures among the four categories. A total of 90 of the participants entered the study with self-reported CKD: 0 of underweight, 10 (0.52%) of normal weight, 29 (0.98%) of overweight, and 51 (1.25%) of obese participants.

History of cancer and myocardial infarction, as well as family history of ESRD differed inconsistently between categories. Prevalence of patient cancer history ranged from 6.46% among obese volunteers to 9.16% among normal weight volunteers. History of myocardial infarction ranged from 6.37% among normal weight volunteers 10.87% among underweight volunteers. Family history of ESRD ranged from 6.72% among normal weight volunteers to 14.00% among obese volunteers.

Glomerular filtration rates (GFR) and serum creatinine levels differed slightly and inconsistently between groups. Mean GFRs (in mL/min/1.73 m^2) were as follows: 102.10 (SD=24.84) for underweight; 93.27 (SD=22.08) for normal weight; 93.20 (SD=21.62) for overweight; and 94.65 (SD=24.37) for obese persons. Creatinine levels (in mg/dL) were:

0.7426 (SD=0.2109) for underweight; 0.8155 (SD=0.3723) for normal weight; 0.8482 (SD=0.2510) for overweight; and 0.8405 (SD=0.3170) for obese persons.

Risk of Developing ESRD

In the study population, the overall unadjusted risk of developing end-stage renal disease by age 60 years (measured in cases per 100,000 person years) was 105.7 for normal weight persons, 90.0 for overweight persons, and 118.8 for obese persons (Figure 2). The unadjusted odds ratios of developing ESRD were 0.83 (95% CI: 0.31, 2.22) (comparing overweight vs. normal weight persons) and 1.07 (95% CI: 0.44, 2.59) (comparing obese vs. normal weight persons). After adjusting for age, the odds ratios for developing ESRD by age 60 were 0.83 (95% CI: 0.31, 2.24) (comparing overweight vs. normal weight persons), and 1.08 (95% CI: 0.44, 2.63) (comparing obese vs. normal weight persons).

Survival Analyses

All calculations are limited to the observed data, concluding with the most recent follow-up dates of volunteers or up to age 60, whichever came first. The maximum follow-up time in the study to date is 7.63 years. Patients were enrolled in the study up through October 2007, and while only data up until March 2012 is included in the analysis, follow-up is still ongoing and is planned to continue for many years.

Hazard of Developing ESRD

Hazard ratios (HR) of developing ESRD were not significant for overweight vs. normal weight individuals (HR of 0.77 (95% CI: 0.28, 2.06)), and or for obese vs. normal weight individuals (HR of 0.89 (95% CI: 0.36, 2.20)) (Table 2). When adjusting for age,

results did not change: overweight individuals still had a non-significant hazard ratio of developing ESRD of 0.77 (95% CI: 0.29, 2.07), compared to normal weight individuals. Obese individuals still had a non-significant hazard ratio of 0.88 (95% CI: 0.36, 2.19) after age-adjustment. In this study population, overweight and obese persons did not have a significantly different risk of developing ESRD as compared to normal weight individuals, regardless of whether the analysis controlled for age.

Hazard of Mortality, Overall

Hazard ratios (HR) of dying by age 60 were not significant for either overweight vs. normal weight individuals (HR of 0.77 (95% CI: 0.57, 1.04) or for obese vs. normal weight individuals (HR of 1.08 (95% CI: 0.82, 1.42)). After controlling for age, results changed negligibly and were still not significant: the HR for overweight vs. normal weight individuals was 0.77 (95% CI: 0.57, 1.04) and the HR for obese vs. normal weight individuals was 1.08 (95% CI: 0.82, 1.42).

Hazard of Mortality, After Developing ESRD

Hazard ratios (HR) of dying by age 60 after a diagnosis of ESRD were non-significant both for overweight vs. normal persons (HR: 0.58 (95% CI: 0.11, 2.97) and obese vs. normal weight persons (HR: 0.75 (95% CI: 0.20, 2.84). Again, controlling for age did not change the direction or significance of the results: for overweight vs. normal weight persons, the HR was 0.70 (95% CI: 0.14, 3.48), and for obese vs. normal weight persons, it was 0.88 (0.23, 3.43) (Table 2).

Sensitivity Analysis

Sensitivity analyses were also conducted, excluding individuals with reporting chronic kidney disease at baseline from the dataset. These individuals were not excluded from the primary dataset, as disease-free time was defined as time from study entry until time of ESRD onset; time with chronic kidney disease is still included as disease-free time, and therefore these individuals fit the criteria of being alive and disease-free at the start of the study. However, under ideal analysis conditions, all individuals would be free of both CKD and ESRD at the start of follow-up. This would allow for fuller observation of the risk period, and therefore the effect of including patients with existing CKD in the analysis was further examined.

However, the analyses indicated that the inclusion of these patients had little effect on the study results. When including patients with pre-existing CKD, very little to no impact was seen on the overall risk of ESRD, or the direction and significance of the hazard ratios.

Discussion

Summary of Findings

After adjusting for gender, race and smoking status, obese persons had, on average, slightly lower hazard of developing ESRD and dying after ESRD diagnosis, but a slightly higher hazard of all-cause mortality, compared to normal weight persons; however, these results were not statistically significant. Overall, differences in hazard ratios for developing ESRD, overall death, and death after ESRD between normal weight, overweight, and obese persons did not differ meaningfully in our analyses. Our findings were not affected by excluding those with chronic kidney disease at baseline, and were impacted only mildly by adjusting for age. These results are surprising, and somewhat inconsistent with our expectations based upon the existing literature and our original hypotheses.

Comparison of Analysis to Literature and Expected Results

In the literature, obese persons are shown, on average, to be at higher risk for developing chronic disease (including ESRD), death at a younger age, and earlier development of chronic disease, as compared to normal weight persons (28, 29, 32). While our results were not statistically significant, it is somewhat puzzling as to why obese persons in our analyses had a lower hazard of developing ESRD.

There are several possible explanations for our results. If our original hypothesis holds true, our findings could be a result of the small number of volunteers that developed end-stage renal disease; it is possible that we did not have enough data in our analysis to observe the true relationships between obesity, ESRD, and mortality.

A possible explanation for the lower mortality of obese people after ESRD onset is that normal weight individuals developing ESRD are more likely to have a more serious etiology to their disease than do obese persons, caused by factors that are unknown and therefore cannot be accounted for in analysis. These unknown factors could lead to early death as well as the early onset of ESRD, and could potentially result in higher death rates from ESRD than obesity-induced ESRD (Figure 1). Such factors could include, for example, certain genes or viruses, or unmeasured environmental exposures. Another explanation is the likelihood of collider biases. We expected that, via our alternative analyses that omitted control for age, we could have decreased collider biases. However, we did not include them, as the expected association between obesity and ESRD occurrence was not seen. Additionally, it is possible that the treatments given to persons with ESRD may work better for obesity induced ESRD than for ESRD induced by other causes. For example, controlling blood pressure and taking medications for diabetes may improve disease prognosis for persons who also have high blood pressure and diabetes, but will not affect persons without those health issues. Notably, our data also showed that those with the longest overall survival times (by a small margin) were those who were overweight, rather than the obese. Some research has shown that those in the "overweight" category may have a survival advantage, although the reasons for this are unclear (41).

Effect of Controlling for Age

Controlling for age had only a small effect on the outcome of our analysis (Table 2). Regardless of whether we controlled for age, obese persons did not differ significantly

from normal weight persons with respect to disease-free, overall, or with-ESRD survival time. Controlling for age did bring the hazard ratio for death after ESRD diagnosis closer to the null value, decreasing the observed (though non-significant) association.

Study Design Limitations

Strengths

The greatest strength of this study is its use of the well-established REGARDS dataset. As REGARDS is a population based cohort study, consisting of randomly selected individuals across the United States, it provides a wealth of information on chronic disease risk factors which have been uniformly collected and used for a variety of research studies. As individuals were excluded from the existing dataset for our analysis only for missing or implausible data, pre-existing ESRD, or having surpassed the age cutoff (60 years) of our survival analysis (and not for any other pre-existing conditions), we decreased the likelihood of selection bias.

Additionally, use of the US Renal Data System for ESRD diagnosis dates provided highly accurate information on the exact date of ESRD diagnosis for volunteers. As data is collected nationally and includes all reported cases of ESRD in the United States, this information could easily be integrated with information from the REGARDS dataset.

Finally, by conducting sensitivity analyses which looked at the impact of controlling for existing CKD and patient age, we were able to compare our results and examine the impact of these factors on the obesity-ESRD relationship. Somewhat surprisingly, these analyses indicated little impact of either existing CKD or age on the overall study results.

Weaknesses

Our study also had several limitations. ESRD was a fairly rare disease in this population (32 diagnosed cases among 9,131 volunteers), and therefore data on age group and BMI-specific risks of developing ESRD were limited. For underweight individuals, estimated risks were unstable and could not be reliably included in the analysis, as no one in this BMI category developed the disease over time.

We also lacked information regarding patient history of obesity, as well as obesity status over time in the study. As we only had BMI information from one specific time point (baseline in-home visit), we do not know if those classified within a given BMI category had a lifetime history of obesity, nor would we know if their weight or BMI category changed over the course of the study. We were required to assume that their baseline body mass index was a good representation of their lifetime BMI "exposure." Additionally, our use of BMI as a measurement of obesity can be considered problematic. BMI does not take into account body composition (fat vs. muscle) or where the weight is carried (abdominal fat vs. lower body fat – research has shown that abdominal fat can be more detrimental to health than fat carried in other parts of the body (41)). While our dataset includes information on abdominal obesity (through measurements of waist circumference), it does not include information on body composition (body fat percentage). We justify our use of BMI as a measurement of obesity for its simplicity and common use in the literature, as well as through evidence that it does provide a reasonable approximation of obesity and weight related health complications (43).

Our analysis is also limited by the number of years of follow-up present in our dataset. Ideally, we would be able to follow all members of our cohort from study entry

until death. While this will be plausible once the REGARDS study has completed, it is not possible for an ongoing study. The maximum number of years of follow-up to age 60 is currently 7.63 years, and 1,363 living volunteers had follow-up times of less than 1 year. Mean follow-up time to age 60 among volunteers still living was 3.33 years. Among the 32 volunteers developing ESRD over the course of the study, 15 died before the most recent follow-up time period (46.88%), compared to 1.70% of those not developing ESRD during the study.

Finally, our analysis did not control for the effect of diabetes or hypertension, the two primary risk factors for the development of ESRD, and potential confounders of the ESRD-mortality relationship. As described in Table 1, these two factors (particularly the presence of diabetes) differed by BMI category. We also do not have data on the cause of death for individuals – while we know that persons died after diagnosis of ESRD, we do not know if ESRD was the primary cause of death. However, as the purpose of this simple analysis was to show the impact of obesity on the development of ESRD and mortality not controlling for age, the sparse data present meant that controlling for diabetes and hypertension would lower statistical power. Additionally, preliminary sensitivity analyses controlling for diabetes indicated that, as expected, hazard ratios did not change direction and rather were only strengthened.

Impact of Study Results

Our results contribute to the understanding of the impact of obesity on mortality, the development of End-Stage Renal Disease, and subsequent mortality. While we did not find statistically significant associations between obesity and either ESRD or mortality (all-cause or after ESRD), our results appear to conform observations in the

literature that obese individuals survive longer than do normal weight individuals after diagnosis of ESRD. We note that analyses which do not control for age like those proposed by Flanders et al, as most such analyses do, would be a way to reduce the previously-noted collider biases (35, 36). We did not conduct them here as all the expected association of obesity with higher risk of ESRD was not observed. However, we may pursue them in future work as a way to illustrate analyses than can avoid the suspected biases, such as the association of obesity with improved survival after ESRD onset.

From a grander public health perspective, this lack of understanding of the improved survival of obese people after ESRD onset is an important issue to consider. Obesity is viewed as one of the largest threats to public health in the United States. Government programs, ranging from local efforts to ban trans-fats and large soft drink sizes to White House initiatives to combat childhood obesity through the First Lady's "Let's Move!" campaign, target the reduction of obesity levels among Americans of all ages. However, while US obesity rates have leveled off in the last decade and there is some evidence to show a reduction in childhood obesity rates in certain areas, there are very few prescriptions for individual weight reduction that prove effective long-term (44, 45). Therefore, if weight loss is still to be recommended by a clinician to a patient, there should be compelling evidence of its benefit. Evidence of this benefit certainly exists in the literature; however, it is important to weigh this recommendation against both the magnitude of its predicted benefits as well as the likelihood of its success. If weight loss is an ideal – but, unlikely to succeed – treatment option for those already presenting with chronic illness, analyses such as ours lend credence to the idea that clinicians may do

better focusing on other health goals. To put it simply: obesity is a risk, but it may not be the important risk.

Finally, though there is clear evidence that obesity raises the risk of many chronic diseases as well as the risk of mortality, results such as ours indicate that there are likely other factors at play. Obesity could, for instance, lead to higher prevalence of more treatable forms of chronic illness. On the other hand, obesity may be harmful and its association with better survival a consequence of collider biases (12, 35, 36). This results in an increasing burden of morbidity, but less of an impact on mortality; or, larger numbers of sicker people living for a longer period of time. In a country with skyrocketing health care costs and high obesity levels, this is an important point to consider. It is also important to weight the impact that increasing chronic disease burden has on patients' quality of life. The goal of public health is not only to increase longevity, but also to improve health standards of the populace. For patients with ESRD, quality of life is particularly relevant. As ESRD is an incurable disease which is typically treated with frequent, extended visits to an outpatient dialysis clinic, development of the disease has a severe impact on a patient's daily life.

These issues underscore the importance of prevention efforts, particularly with respect to obesity. Provisions aimed at reducing childhood obesity rates are likely to be the most effective long-term. Preventing childhood obesity decreases the likelihood of developing chronic diseases as an adult, and helps to avoid the greater difficulties of losing weight in adulthood.

Conclusion

This analysis of the impact of obesity on the development of end-stage renal disease and mortality yielded results, although not statistically significant, which suggested a harmful overall effect of obesity on mortality. However, the association with ESRD onset was in the opposite direction, but statistically unstable. In the literature, obesity is generally found to increase the risk of developing ESRD and all-cause mortality, and increase the length of time lived with ESRD. Our findings highlight the need for greater understanding of the complicated relationship between obesity and both the development and the progression of chronic disease. With respect to ESRD, further study among a cohort focused upon kidney disease risk factors would provide greater insight into important factors involved in this relationship.

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Table 1. Baseline demographics and clinical characteristics of patients analyzed from REGARDS Study, by BMI category, United States, 2003 - 2007.

	All Study Participants n= 9,131 n (%) or Mean (SD)	n	BMI <18.5 n = 93 n (%) or Mean (SD)	n
Sex (Male)	3,648 (39.95%)	9,131	25 (26.88%)	93
Age (in years)		9,131		93
45-49	1,467 (16.07%)		16 (17.02%)	
50-54	2,188 (23.96%)		14 (15.05%)	
55-59	5,476 (59.97%)		63 (67.74%)	
Race		9,131		93
White	5,010 (54.87%)		54 (58.06%)	
Black	4,121 (45.13%)		39 (41.94%)	
Region		9,131		93
Stroke Belt[1]	3,347 (36.66%)		42 (45.16%)	
Stroke Buckle[2]	2,058 (22.54%)		17 (18.28%)	
Smoking Status		9,095		93
Current Smoker	1,857 (20.42%)		50 (53.76%)	
Former Smoker	2,813 (30.93%)		13 (13.98%)	
	1,587 (18.00%)	8,817	2 (2.27%)	88
History of Cancer[4]	341 (7.49%)	4,554	3 (8.11%)	37
History of Myocardial Infarction[5]	662 (7.39%)	8,956	10 (10.87%)	92
Self-Reported Chronic Kidney Disease	90 (1.00%)	8,948	0 (0.00%)	92

	All Study Participants n= 9,131 n (%) or Mean (SD)	n	BMI <18.5 n = 93 n (%) or Mean (SD)	n
Family History of End-Stage Renal Disease	790 (10.82%)	7,299	6 (7.79%)	77
Systolic Blood Pressure (mm Hg)	123.99 (16.21)	9,121	111.89 (17.96)	93
Diasotlic Blood Pressure (mm Hg)	77.77 (9.85)	9,121	70.73 (10.68)	93
Glomerular Filtration Rate (mL/min/1.73 m^2)	93.96 (23.04)	8,780	102.10 (24.84)	88
Serum Creatinine (mg/dL)	0.8368 (0.3096)	8,780	0.7426 (0.2109)	88
	BMI 18.5-24.9 n = 1,922 n (%) or Mean (SD)	n	BMI 25.0 - 29.9 n = 2,992 n (%) or Mean (SD)	n
Sex (Male)	721 (37.51%)	1,922	1,469 (49.10%)	2,992
Age (in years)		1,922		2,992
45-49	326 (16.96%)		473 (15.81%)	
50-54	491 (25.55%)		728 (24.33%)	
55-59	1,105 57.49%)		1,791 (59.86%)	
Race		1,922		2,992
White	1,301 (67.69%)		1,766 (59.02%)	
Black	621 (32.21%)		1,226 (40.98%)	
Region		1,922		2,992
Stroke Belt[1]	698 (36.32%)		1,119 (37.40%)	
Stroke Buckle[2]	435 (22.63%)		659 (22.03%)	

	BMI 18.5-24.9 n = 1,922 n (%) or Mean (SD)	n	BMI 25.0 - 29.9 n = 2,992 n (%) or Mean (SD)	
Smoking Status		1,917		2,982
Current Smoker	478 (24.93%)		619 (20.76%)	
Former Smoker	507 (26.45%)		958 (32.13%)	
Diabetes[3]	98 (5.28%)	1,856	342 (11.86%)	2,883
History of Cancer[4]	86 (9.16%)	939	121 (7.81%)	1,549
History of Myocardial Infarction[5]	120 (6.37%)	1,885	195 (6.66%)	2,930
Self-Reported Chronic Kidney Disease	10 (0.52%)	1,905	29 (0.98%)	2,968
Family History of End-Stage Renal Disease	106 (6.72%)	1,577	216 (9.22%)	2,344
Systolic Blood Pressure (mm Hg)	117.30 (15.61)	1,921	123.08 (15.29)	2,992
Diasotlic Blood Pressure (mm Hg)	74.03 (9.35)	1,921	77.28 (9.44)	2,992
Glomerular Filtration Rate (mL/min/1.73 m^2)	93.27 (22.08)	1,856	93.20 (21.62)	2,891
Serum Creatinine (mg/dL)	0.8155 (0.3723)	1,856	0.8482 (0.2510)	2,891

	BMI of 30.0 or higher n =4,124 n (%) or Mean (SD)	n
Sex (Male)	1,433 (34.75%)	4,124
Age (in years)		4,124
45-49	652 (15.81%)	
50-54	955 (23.16%)	
55-59	2,517 (61.03%)	
Race		4,124
White	1,889 (45.81%)	
Black	2,235 (54.19%)	
Region		4,124
Stroke Belt[1]	1,488 (36.08%)	
Stroke Buckle[2]	947 (22.96%)	
Smoking Status		4,103
Current Smoker	710 (17.30%)	
Former Smoker	1,335 (32.54%)	
Diabetes[3]	1,145 (28.70%)	3,990
History of Cancer[4]	131 (6.46%)	2,029
History of Myocardial Infarction[5]	337 (8.32%)	4,049
Self-Reported Chronic Kidney Disease	51 (1.25%)	4,073

	BMI of 30.0 or higher	
	n =4,124	
	n (%) or Mean (SD)	n
Family History of End-Stage Renal Disease	462 (14.00%)	3,301
Systolic Blood Pressure (mm Hg)	128.08 (15.80)	4,115
Diasotlic Blood Pressure (mm Hg)	80.04 (9.70)	4,115
Glomerular Filtration Rate (mL/min/1.73 m^2)	94.65 (24.37)	3,945
Serum Creatinine (mg/dL)	0.8405 (0.3170)	3,945

[1] Coastal North Carolina, South Carolina, and Georgia

[2] Remaining areas of North Carolina, South Carolina, and Georgia as well as Tennessee, Mississippi, Alabama, Louisiana, and Arkansas

[3] As defined by self-reported pills or insulin for diabetes or fasting glucose greater than or equal to 126 mg/dL or non-fasting glucose greater than or equal to 200 mg/dL

[4] Self-reported history of cancer

[5] History of MI (self-reported MI OR evidence of MI via ECG (from CATI and ECG))

Table 2. Hazard Ratios (HRs) Comparing Obese vs. Normal Weight Persons for Developing ESRD, All-Cause Mortality, and Mortality After ESRD Diagnosis, REGARDS Study, 2003-2012.

HR of Developing ESRD		HR of All-Cause Mortality		HR of Mortality After ESRD Diagnosis	
Unadjusted HR (95% CI)	Age-adjusted HR (95% CI)	Unadjusted HR (95% CI)	Age-adjusted HR (95% CI)	Unadjusted HR (95% CI)	Age-adjusted HR (95% CI)
0.89 (0.36, 2.20)	0.88 (0.36, 2.19)	1.08 (0.82, 1.42)	1.08 (0.82, 1.42)	0.75 (0.20, 2.84)	0.88 (0.23, 3.43)

Figure 1. Directed Acyclic Graph Illustrating Potential Confounding Between Unknown Factors and the ESRD-Obesity-Mortality Relationship.

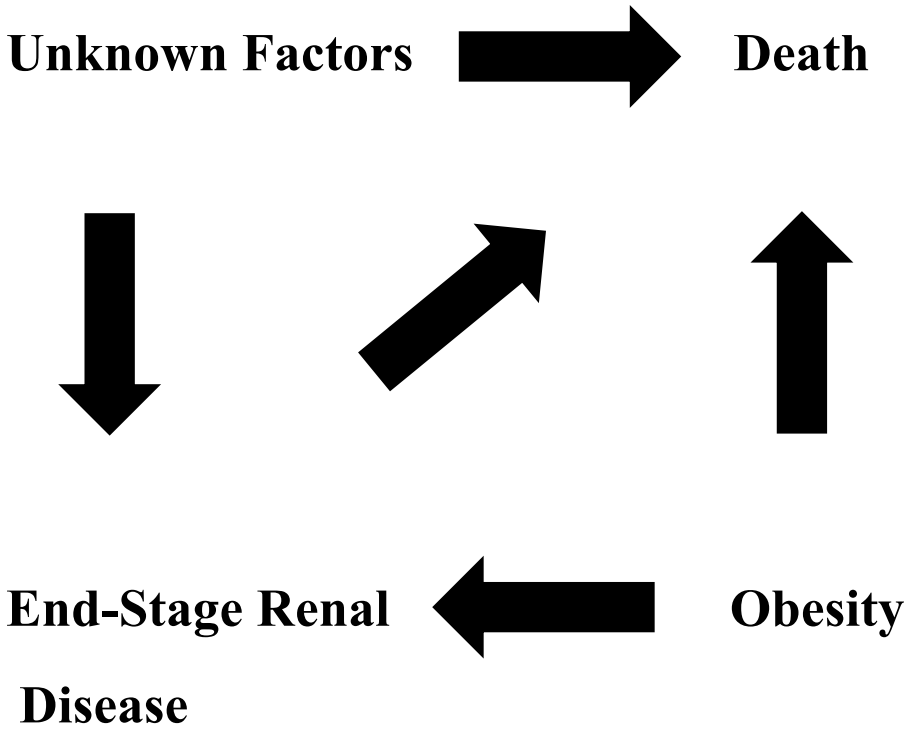
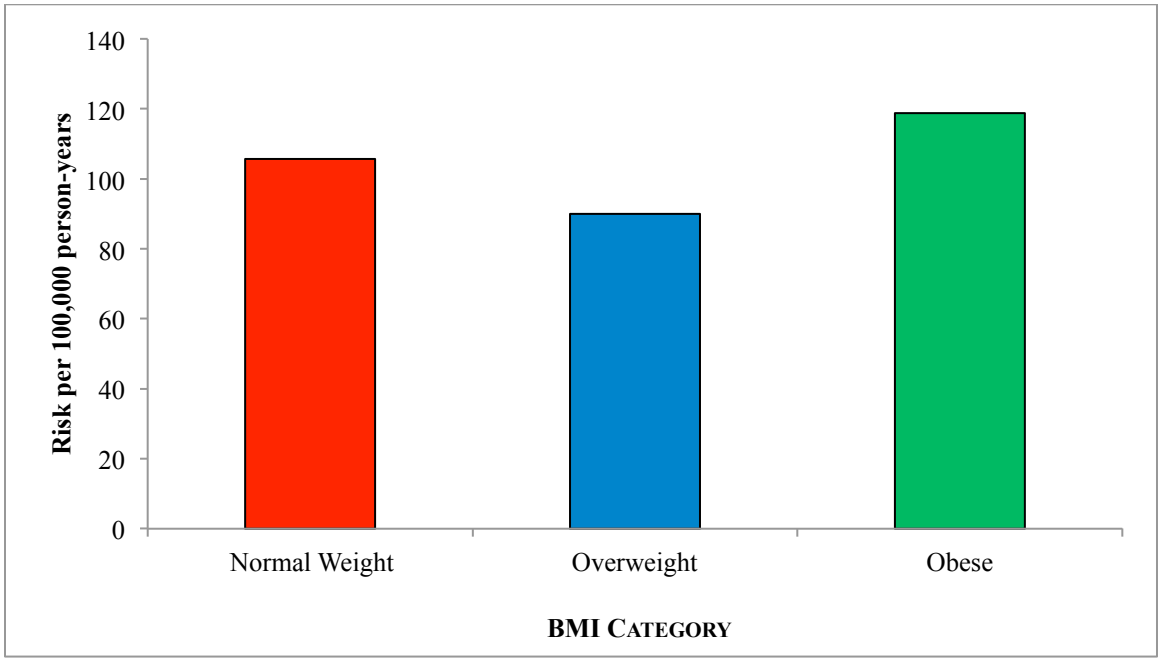


Figure 2. Unadjusted Risk (per 100,000 person-years) of Developing End-Stage Renal Disease, by BMI Category, REGARDS Study, 2003-2013.



Underweight*: BMI < 18.5 kg/m^2

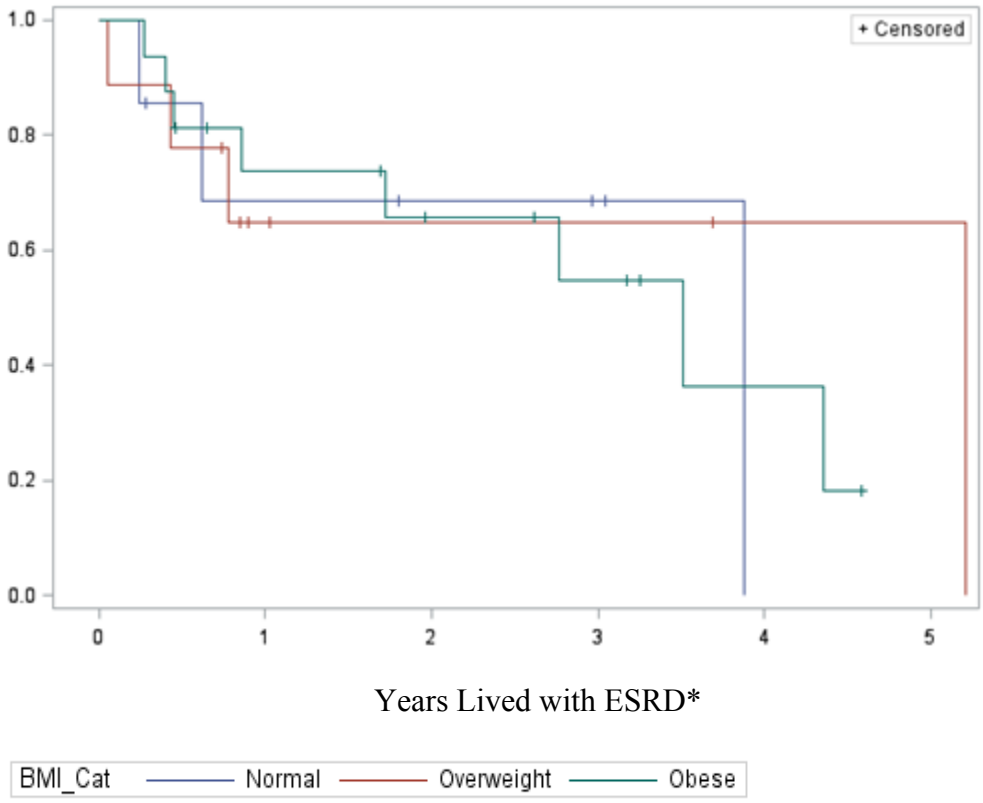
Normal Weight: 18.5 ≤ BMI < 25 kg/m^2

Overweight: 25 ≤ BMI < 30 kg/m^2

Obese: BMI ≥ 30 kg/m^2

*Rate based on small numbers, with no observed cases; therefore rate not pictured

Figure 3. Kaplan-Meier Plot of Proportion of Subjects Surviving After Diagnosis of End-Stage Renal Disease, by BMI Category.



*Before Death or Censor