Published in final edited form as:
Am J Kidney Dis. 2008 July ; 52(1): 39–48. doi:10.1053/j.ajkd.2008.03.003.

Overweight, Obesity, and the Development of Stage 3 CKD: The Framingham Heart Study

Meredith C. Foster, BA, **Shih-Jen Hwang, PhD**, **Martin G. Larson, ScD**, **Judith H. Lichtman, PhD MPH**, **Nisha I. Parikh, MD MPH**, **Ramachandran S. Vasan, MD**, **Daniel Levy, MD**, and **Caroline S. Fox, MD MPH**

National Heart, Lung, and Blood Institute's Framingham Heart Study (MCF, SJH, DL, CSF); Boston University Department of Mathematics and Statistics, Boston MA (MGL); Yale School of Public Health Division of Chronic Disease Epidemiology (JHL); Boston University School of Medicine (NIP, RSV), Boston, MA; Framingham, MA; the Department of Endocrinology, Diabetes, and Hypertension, the Brigham and Women's Hospital, Harvard Medical School, Boston, MA (CSF); and the National Heart, Lung, and Blood Institute, National Institutes of Health (MCF, CSF, SJH, DL), Bethesda, MD

Abstract

Background—Prior research has yielded conflicting results on the magnitude of the association between body mass index (BMI) and chronic kidney disease (CKD).

Study Design—Prospective cohort study.

Settings and Participants—Framingham Offspring participants (n=2676; 52% women; mean age 43 years) free of stage 3 CKD at baseline who participated in examination cycles 2 (1978-1981) and 7 (1998-2001).

Predictor—Body Mass Index.

Outcome—Stage 3 CKD (estimated glomerular filtration rate<59mL/min/1.73m^2 [<0.98 mL/sec/1.73m^2, women] and <64mL/min/1.73m^2 [<1.07 mL/sec/1.73m^2, men]).

Measurements—Age- sex- and multivariable-adjusted (diabetes, systolic blood pressure, hypertension treatment, current smoking status, high-density lipoprotein cholesterol) logistic regression models were used to examine the relationship between BMI at baseline and incident stage 3 CKD and incident dipstick proteinuria (>= trace).

Results—At baseline, 36% of the sample was overweight and 12% was obese; 7.9% (n=212) developed stage 3 CKD over 18.5 years of follow-up. Relative to participants with normal BMI, there was no association between overweight individuals and stage 3 CKD incidence in age- and sex-adjusted models (OR 1.29, 95%CI 0.93-1.81, p=0.13) or multivariable models (OR 1.06, 95%CI 0.75-1.50, p=0.75). Obese individuals had a 68% increased odds of developing stage 3 CKD (OR 1.68, 95%CI 1.10-2.57, p=0.02), which became non-significant in multivariable models (OR 1.09, 95%CI 0.69-1.73, p=0.70). Similar findings were observed when BMI was modeled as a continuous variable or as quartiles. Incident proteinuria occurred in 14.4%; overweight and obese individuals

Corresponding Author: Caroline S. Fox MD MPH, Framingham Heart Study, 73 Mt Wayte Ave Suite #2, Framingham, MA 01702, (508) 935-3447, foxca@nhlbi.nih.gov.

Financial Disclosure: None.

were at increased odds of proteinuria in multivariable models [(OR 1.43, 95% CI 1.09-1.88) and (OR 1.56 1.08-2.26), respectively].

Limitations—BMI is measure of generalized obesity and not abdominal obesity. Participants are predominantly white, and these findings may not apply to different ethnic groups.

Conclusions—Obesity is associated with increased risk of developing stage 3 CKD, which was no longer significant after adjustment for known CVD risk factors. The relationship between obesity and stage 3 CKD may be mediated through CVD risk factors.

Keywords

chronic kidney disease; chronic kidney disease risk factors; Framingham Heart Study; obesity; epidemiology; cardiovascular disease risk factors

Introduction

Chronic kidney disease (CKD) affects 19 million adults in the United States.[1] CKD is a risk factor for cardiovascular disease (CVD),[2; 3] and this association is partly mediated through the association between CKD and diabetes, hypertension, dyslipidemia, smoking, and obesity.[4-7]

Obesity is a major global health concern, and it precedes the development of many CVD risk factors, including diabetes[9; 10] hypertension,[11; 12] and dyslipidemia.[13; 14] Therefore, obesity may mediate the association with CKD through these risk factors. In addition, biologic pathways have been identified as potential mechanisms leading from obesity to kidney damage, such as hormonal factors, inflammation, oxidative stress, and endothelial dysfunction.[15; 16]

Prospective observational studies investigating the longitudinal relation of body mass index (BMI) to end-stage renal disease (ESRD) have yielded conflicting results. Increased risk for ESRD was associated with increasing BMI in patients from the Kaiser Permanente of Northern California health care system[17] and in a sample of men from Okinawa, Japan,[18] but no association was observed among male veterans in the Hypertension Screening and Treatment Program.[19] Limited data are available on the relation between body weight and moderate CKD incidence. Higher BMI at baseline was associated with increased CKD risk among men in the Physician's Health Study,[20] but findings were limited due to the inclusion of prevalent CKD at baseline. We have previously demonstrated a positive association between BMI and the onset of stage 3 CKD.[6] However, these models did not account for measures of blood pressure, nor did we examine relations between clinically relevant BMI categories and incident stage 3 CKD.

The identification of an association between obesity and moderate CKD may help guide targeted interventions and treatment with the goal of ultimately preventing CKD progression. Thus, the purpose of this study is to characterize the relation between overweight and obesity and the development of stage 3 CKD in the Framingham Heart Study.

Methods

Study sample

The Framingham Offspring Study cohort was established in 1971, and includes 5124 men and women who were children and spouses of children of the original Framingham cohort. Examinations for participants in the Offspring Cohort occurred approximately every four years, and the design and methodology of these examinations are described elsewhere.[21] Members of the Offspring Cohort who attended the second (1978-1982) and seventh (1998-2001)

examination cycles were included in this analysis. The study was approved by the Boston University Medical Center institutional review boards, and all subjects provided written informed consent.

Of individuals who attended the second examination cycle (n=3825), 808 individuals were excluded in this analysis because they did not attend the seventh examination cycle, 159 individuals were excluded due to missing serum creatinine at Exam 7, 127 individuals due to the presence of stage 3 CKD at Exam 2, 38 individuals due to a BMI less than 18.5 kg/m^2, and 17 individuals due to missing covariate data, resulting in a final study sample of 2676 individuals.

Measurements and definitions

Kidney function was estimated using the glomerular filtration rate (GFR), and the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation was used to estimate the GFR (eGFR).[22-24] According to the National Kidney Foundation Disease Outcome Quality Initiative working group, stage 3 CKD is defined as the presence of kidney damage or the presence of a GFR<60 mL/min/1.73m^2 (<1.00 mL/s/1.73m^2) with or without kidney damage for three or more months.[22] Because the use of this GFR cut point classified 50% more women than men as having stage 3 CKD, our definition of stage 3 CKD was modified to include sex-specific GFR cut points for stage 3 CKD (eGFR < 59 mL/min/1.73m^2 [<0.98 mL/s/1.73m^2]in women or < 64 mL/min/1.73 m^2 in men [<1.07 mL/s/1.73m^2]).[6]

Serum creatinine was measured from a fasting blood sample collected during a participant's examination at both the second and seventh examination cycles using the modified Jaffe method. Due to variations that can occur in serum creatinine measurements across laboratories, a 2-step process was used to calibrate these measurements. The first step involved calibrating serum creatinine values from the National Health and Nutritional Examination Survey III (NHANES III) to the Cleveland Clinic Laboratory by utilizing a correction factor of 0.23 mg/dl (20.3 μmol/L).[25] The serum creatinine values from our study sample were calibrated by aligning our values to the age- and sex- specific means from NHANES III by age and sex. This process has been described elsewhere.[6]

Body mass index (BMI) was defined as an individual's weight in kilograms divided by the square of height in meters (kg/m^2). Weight was measured to the nearest pound during the examination while the participant stood in the middle of the scale (Detecto scale; Worcester Scale Co Inc, Worcester, Massachusetts). The participant wore a gown and was barefoot during the measurement. The scale is calibrated with a 22.5-kilogram weight on a monthly basis, and is calibrated professionally each year. Height was measured to the nearest 0.25 of an inch using a standardized protocol. Normal weight was defined as a BMI greater or equal to 18.5 kg/m^2 and less than 25.0 kg/m^2. Overweight was defined as a BMI greater than or equal to 25.0 kg/m^2 and less than 30.0 kg/m^2. Obesity was defined as a BMI greater or equal to 30.0 kg/m^2. Class I obesity was defined as a BMI greater or equal to 30.0 kg/m^2 and less than 35.0 kg/m^2. Class II obesity was defined as a BMI greater than or equal to 35.0 kg/m^2.

The presence of proteinuria at Exams 2 and 7 was determined based on urine dipstick tests (Ames Labstix, Elkhardt, Indiana) dipped for 1 minute in spot urine samples collected during the clinic visit.[26] Exam 2 protein measurements were classified as none or trace amounts or above; Exam 7 protein measurements were classified as none, trace, small, moderate, and large amounts. In the present analysis, proteinuria was defined as a dipstick protein measure of trace or above.

Covariate assessment

Individuals in the Offspring cohort had fasting morning blood samples collected and tested during each examination. All covariates adjusted for in our models were collected at the baseline examination. Hypertension was defined as a systolic blood pressure greater than or equal to 140 mm Hg, a diastolic blood pressure greater than or equal to 90 mm Hg, or as being prescribed medication for hypertension treatment. Diabetes was defined as a fasting blood glucose greater than or equal to 126 mg/dL (7.0 mmol/L) or a prescription for hypoglycemic medications. Current smoking was defined as at least one cigarette per day on average in the year prior to the examination. Prevalent CVD was identified based on a three-physician adjudication panel for CVD endpoints; diagnosis criteria for prevalent CVD and coronary heart disease events have been described previously.[27]

Statistical Methods

Statistical analyses were performed using SAS Version 9.1.3 for Windows. For comparisons of covariates among BMI groups, we used age- sex-adjusted analysis of variance (ANCOVA) for continuous data, and age- sex-adjusted logistic regression for dichotomous variables. Logistic regression models for the dichotomous stage 3 CKD outcome as a function of BMI were performed and initially adjusted for age at baseline and sex using BMI in the following ways: 1) BMI category (normal weight, overweight, obese); 2) BMI by sex-specific quartiles; 3) BMI as a continuous variable. These models were additionally adjusted for diabetes, systolic blood pressure, hypertension treatment, current smoking status and HDL level at baseline. The normal weight BMI group was used as the reference for odds ratios in the categorical analyses and the lowest BMI quartile was used as the reference for odds ratios in the quartile analyses. The categorical BMI logistic regression models were additionally performed using a cut point of eGFR <60 mL/min/1.73m^2 (<1.00 mL/s/1.73m^2). In secondary analyses, logistic regression models were performed using additional BMI categories for class I and class II obesity. Age-sex- and multivariable-adjusted models were also secondarily adjusted for baseline eGFR, weight change during follow-up, or length of follow-up. Additional analyses restricted the sample to participants free of hypertension, diabetes, or prevalent CVD at baseline. A test for nonlinearity of BMI was conducted by modeling log-odds of developing stage 3 CKD with continuous BMI centered on the mean and the square of the centered BMI added to models. Logistic regression models for the development of proteinuria at Exam 7 as a function of baseline BMI category were performed excluding individuals with stage 3 CKD. Model assumptions of linearity and binomial variability were assessed through index plots of the Pearson residuals and the deviate residuals for all observations were used to check assumption of linearity between the independent predictors and the log odds of developing stage 3 CKD and by calculating the Pearson chi-square statistic and the deviance and dividing by their respective degrees of freedom. A two-tailed p-value of less than 0.05 was considered statistically significant.

Results

The average follow-up time was 18.5 years (range 15.9-21.9 years), Overall, 7.9% (n=212) participants developed stage 3 CKD. At baseline 51.8% (n=1387) participants were normal weight, 36.0% (n=964) were overweight, and 12.1% (n=325) were obese (Table 1). Mean eGFR at baseline was slightly higher among normal weight and obese individuals than among overweight individuals (p=0.006).

Clinical BMI Categories

Relative to normal weight individuals, there was no statistically significant association between overweight individuals and stage 3 CKD in either age- sex- adjusted models (OR 1.29, 95% CI 0.93-1.81, p=0.1) or multivariable models (OR 1.06, 95% CI 0.75-1.50, p=0.8) (Table 2).

Obese individuals had a 68% increased odds of developing stage 3 CKD (OR 1.68, 95% CI 1.10-2.57, p=0.02), which was no longer observed in multivariable models (OR 1.09, 95% CI 0.69-1.73, p=0.7). In analyses limited to those free of either HTN or DM, point estimates were similar, although statistical significance was not achieved (Table 2). The overall multivariable model indicates that the addition of diabetes, systolic blood pressure, and HDL-cholesterol were influential in changing the point estimates. Significant trends were observed in age- sex-adjusted models for the overall (p=0.01) and prevalent CVD-free (p=0.009) groups, but these trends were no longer observed after multivariable adjustment (p=0.7 and p=0.7, respectively).

In a secondary analysis, we examined individuals with Stage II obesity (BMI≥35.0kg/m^2). Overall, 80 participants (3.0%) were categorized in this group. Stage II obesity was associated with a non-significant 64% increase in odds of developing stage 3 CKD (OR 1.64, 95% CI 0.75-3.62, p=0.2) in age- sex-adjusted models, and was not associated with stage 3 CKD in multivariable models (OR 0.93 95% CI 0.40-2.13, p=0.9).

Age- sex- and multivariable-adjusted models were also adjusted for baseline eGFR and weight change during follow-up. The odds of developing stage 3 CKD associated with obesity and overweight were not materially different from the odds observed in the primary analysis when considering either baseline eGFR or weight change (data not shown).

BMI Quartile Analysis

Relative to participants in the lowest BMI quartile, individuals in the highest BMI quartile had a 67% increased odds of developing stage 3 CKD (OR 1.67, 95% CI 1.09-2.56, p=0.02); which was rendered non-significant in multivariable models (OR 1.19, 95% CI 0.75-1.87, p=0.5) (Table 3). When the sample was limited to those free of either hypertension or diabetes, significance in either age- sex- or multivariable models was not observed.

BMI as a Continuous Exposure

When analyzed as a continuous exposure, a one-unit increase in BMI was associated with a 5% increase in the odds of stage 3 CKD (p=0.005; Table 4). This association was rendered non-significant in multivariable models (OR 1.01, 95% CI 0.97-1.05, p-value=0.6). When the sample was limited to those free of diabetes at baseline, no significance in age- sex- or multivariable models was observed. In a secondary analysis, the addition of BMI-squared did not materially change the observed effects (data not shown).

Proteinuria Analysis

Overall, among those without CKD (n=347), 14.4% developed proteinuria. Relative to individuals with normal weight, both overweight and obese individuals were at a statistically significant increased odds of developing proteinuria in the age- sex- and multivariable-adjusted models (Table 5). Associations of similar magnitude were observed among the diabetes-free and prevalent CVD-free at baseline subgroups.

Secondary Analyses

Similar results were obtained when the categorical BMI models were performed using a cut point of eGFR <60 mL/min/1.73m^2 (<1 mL/s/1.73m^2) for stage 3 CKD (data not shown). The addition of length of follow-up time as an additional covariate to the models with categorical BMI as the main response did not materially change the observed effect estimates, indicating that differing follow-up times did not have a significant impact on the BMI and stage 3 CKD association (data not shown).

Discussion

Obesity is associated with an increased risk of developing stage 3 CKD over nearly 20 years of follow-up, which was no longer observed after adjustment for CVD risk factors. These findings suggest that the association of obesity with stage 3 CKD may be mediated by vascular disease risk factors. Additionally, overweight and obesity are associated with increased risk of developing proteinuria.

While our findings highlight the association between obesity and stage 3 CKD, among patients on dialysis, higher body mass index is associated with less adverse outcomes.[28] This "obesity paradox" has been ascribed to the association between higher BMI and better nutrition, less inflammation, and less co-morbidities among dialysis patients with higher BMI levels.[28] Our findings are distinctly different from this, as we studied obesity and stage 3 CKD development among free-living individuals from a community-based population who were free of major co-morbidities.

Using data from over 300000 individuals in the Kaiser Permanente of Northern California health care system, Hsu and colleagues[17] reported a strong, stepwise increase in the relative risk of ESRD among overweight (RR 1.72) and obese individuals (Class I Obesity: RR 2.98; Class II Obesity: RR 4.68; Extreme Obesity: RR 4.99) when compared to normal weight individuals in multivariable models among patients with varying degrees of kidney dysfunction at baseline. These results are significantly stronger and in contrast to what were observed in our study. Factors that may explain the disparate findings include potential ascertainment bias based on the use of a clinical database, and the use of a different endpoint.

In an additional study lending support to the concept that body mass index may be an independent risk factor for CKD, Ejerblad and colleagues observed a significantly increased odds of CKD among men (OR 3.1) and women (OR 3.0) with a BMI in the overweight or greater range at age 20 based on self-reported anthropometrics.[29] However, the overall increased odds ratios were not adjusted for hypertension, diabetes, or HDL cholesterol. Additionally, the CKD observed in this study was more severe than in the present analysis, with median creatinine clearance among cases of 22 mL/min (0.37 mL/s) among men and 19 mL/min (0.32 mL/s) among women. Lastly, the use of self-reported body mass index may have been prone to recall bias.

When examining the relation between BMI and stage 3 CKD, Gelber and colleagues reported an association between higher BMI at baseline and increased risk of stage 3 CKD among 11,104 men in the Physician's Health Study (PHS) after 14 years of follow-up.[20] The highest quintile of BMI (BMI>26.6kg/m^2) was associated with a 26% increase in the odds of developing stage 3 CKD (OR 1.26; p-value for trend = 0.007) when compared to the lowest quintile (BMI<22.7kg/m^2). The confidence limits around our estimate include that of Gelber *et al*, suggesting that we may have been underpowered to detect a modest effect given our sample size. However, the use of self-reported diabetes and hypertension in the PHS sample may have resulted in incomplete adjustment for these covariates and thus may contribute to the disparate findings. An additional reason for the conflicting results may be the inclusion of participants with CKD at baseline in the PHS.

In contrast, only one study published to date has failed to document an independent association between body mass index and ESRD. Iseki and colleagues reported on the relation of BMI and ESRD in a community-based cohort from a voluntary annual health-screening program in Okinawa, Japan.[18] The study (100753 individuals) found that each increase in BMI quartile was associated with a significant increase in the odds of developing ESRD in men (OR 1.27, p-value for trend = 0.0002), but not women. While DM status was only available for about 14% of the sample, additional adjustment for DM in this subgroup completely attenuated the

relation of BMI and odds of ESRD among men (OR 0.99). Limitations of this study include the use of a voluntary and potentially healthier screening cohort, inclusion of CKD cases at baseline, and incomplete ascertainment of kidney disease risk factors. Nonetheless, these findings are similar to ours, and support the notion that the relation between obesity and CKD may be mediated by diabetes.

The association between obesity and CKD may be mediated through multiple biologic mechanisms, including hormonal factors, inflammation, oxidative stress, and endothelial dysfunction.[15; 16] Our results demonstrating the reduction in significance of the odds ratio for obesity as a stage 3 CKD risk factor with CVD risk factor adjustment suggest that the relation of obesity to stage 3 CKD may be mediated by the presence of vascular risk factors, including diabetes, hypertension, and HDL levels.

Excess adipose tissue can lead to the activation of the sympathetic nervous and renin-angiotensin systems, as well as lipid deposition, hyperfiltration, and increased sodium absorption in the kidneys, resulting in a feedback loop where obesity-induced declines in kidney function lead to the development of hypertension, which results in further damage to the kidneys.[33] Pathways leading from obesity to diabetes have also been identified, including the development of insulin resistance through the disruption of insulin signaling pathways due to lipolysis, the release of adipokines,[9] and inflammation,[34] Further research involving these mechanisms could provide a better understanding of the association between obesity, CKD, and potential mediating factors.

The strong association between adiposity and proteinuria suggests that proteinuria may be an important mediator in the pathway between overweight, obesity, and stage 3 CKD. This observation is supported by the previously published finding that weight change is directly associated with changes in urinary albumin excretion while no association was observed for changes in eGFR, as measured as creatinine clearance.[35]

In the present study, the relation between obesity and stage 3 CKD is explained by the presence of concomitant CVD risk factors Future research is necessary in order to develop a clearer picture of the relation of obesity and stage 3 CKD. Obesity itself varies greatly, depending on the distribution of adipose tissue in the body. Different fat depots may be differentially associated with CKD. Specifically, central adiposity has been associated with increased metabolic complications.[38; 39] Therefore, future research should focus on measures of abdominal obesity.

Findings from the current study enhance the current literature in several ways. In the present study, we were able to exclude individuals with stage 3 CKD as defined by estimated GFR at our baseline examination due to the collection of serum creatinine measurements. We were also able to assess the association of obesity and overweight with the development of proteinuria. Strengths associated with this study include the continued follow-up of the Framingham Offspring cohort and the routine ascertainment of CVD risk factors during each examination cycle. We did not rely upon self-report of hypertension, diabetes, or obesity, which results in underestimation of these conditions. Our cohort was not selected specifically for CKD outcomes, which limits potential referral or selection bias. Additionally, CKD is our sample is predominately stage 3 CKD, while other studies have published on BMI and CKD in populations with more severe CKD.

There are limitations associated with the study sample and variable definitions. We only examined generalized obesity and not abdominal obesity, as measures of central obesity were not available at the baseline examination. We did not have a reliable measure of proteinuria at either baseline or follow-up, so stage 3 CKD classification was based on eGFR alone. Our sample is predominantly white, and these findings may not apply to different ethnic groups.

Creatinine is derived from muscle and the amount produced is proportional to muscle mass;[41] obese individuals are likely to have more muscle mass. While this may have lead to higher creatinine values (and lower eGFR values) among obese individuals, it is unlikely to explain why our findings were significant in age- sex-adjusted models but not multivariable models. GFR was estimated using the MDRD Study equation instead of a direct measure of GFR. A recent study has indicated that the MDRD Study equation underestimates GFR in healthy individuals without CKD.[42] This study, however, compared eGFR to GFR measured as a continuous measure, and it is unclear how this underestimation would affect stage 3 CKD classification when used as a dichotomous variable. Finally, we may have been underpowered to detect modest effect sizes.

In conclusion, obesity is associated with significantly increased odds of developing stage 3 CKD, but this association is not observed after adjustment for known CVD risk factors. The relationship between obesity and stage 3 CKD may be mediated through the presence of known CVD risk factors, including hypertension, diabetes, and low HDL-cholesterol.

Acknowledgements

The Framingham Heart Study is supported by the National Heart, Lung and Blood Institute (N01-HC-25195).

References

1. Coresh J, Astor BC, Greene T, et al. Prevalence of chronic kidney disease and decreased kidney function in the adult US population: Third National Health and Nutrition Examination Survey. Am J Kidney Dis 2003;41:1–12. [PubMed: 12500213]
2. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med 2004;351:1296–1305. [PubMed: 15385656]
3. Anavekar NS, McMurray JJ, Velazquez EJ, et al. Relation between renal dysfunction and cardiovascular outcomes after myocardial infarction. N Engl J Med 2004;351:1285–1295. [PubMed: 15385655]
4. Longenecker JC, Coresh J, Powe NR, et al. Traditional cardiovascular disease risk factors in dialysis patients compared with the general population: the CHOICE Study. J Am Soc Nephrol 2002;13:1918–1927. [PubMed: 12089389]
5. Wheeler DC, Townend JN, Landray MJ. Cardiovascular risk factors in predialysis patients: baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study. Kidney Int 2003:S201–S203.
6. Fox CS, Larson MG, Leip EP, et al. Predictors of new-onset kidney disease in a community-based population. JAMA 2004;291:844–850. [PubMed: 14970063]
7. Yamagata K, Ishida K, Sairenchi T, et al. Risk factors for chronic kidney disease in a community-based population: a 10-year follow-up study. Kidney Int 2007;71:159–166. [PubMed: 17136030]
8. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 2006;295:1549–1555. [PubMed: 16595758]
9. Rosenberg DE, Jabbour SA, Goldstein BJ. Insulin resistance, diabetes and cardiovascular risk: approaches to treatment. Diabetes Obes Metab 2005;7:642–653. [PubMed: 16219008]
10. Weinstein AR, Sesso HD, Lee IM, et al. Relationship of physical activity vs body mass index with type 2 diabetes in women. JAMA 2004;292:1188–1194. [PubMed: 15353531]
11. Wilsgaard T, Schirmer H, Arnesen E. Impact of body weight on blood pressure with a focus on sex differences: the Tromso Study, 1986-1995. Arch Intern Med 2000;160:2847–2853. [PubMed: 11025795]
12. Vasan RS, Larson MG, Leip EP, et al. Assessment of frequency of progression to hypertension in non-hypertensive participants in the Framingham Heart Study: a cohort study. Lancet 2001;358:1682–1686. [PubMed: 11728544]
13. Folsom AR, Burke GL, Ballew C, et al. Relation of body fatness and its distribution to cardiovascular risk factors in young blacks and whites. The role of insulin. Am J Epidemiol 1989;130:911–924. [PubMed: 2683750]

14. Hu D, Hannah J, Gray RS, et al. Effects of obesity and body fat distribution on lipids and lipoproteins in nondiabetic American Indians: The Strong Heart Study. Obes Res 2000;8:411–421. [PubMed: 11011907]
15. de Jong PE, Verhave JC, Pinto-Sietsma SJ, et al. Obesity and target organ damage: the kidney. Int J Obes Relat Metab Disord 2002;26:S21–S24. [PubMed: 12457295]
16. Wu Y, Liu Z, Xiang Z, et al. Obesity-related glomerulopathy: insights from gene expression profiles of the glomeruli derived from renal biopsy samples. Endocrinology 2006;147:44–50. [PubMed: 16210374]
17. Hsu CY, McCulloch CE, Iribarren C, et al. Body mass index and risk for end-stage renal disease. Ann Intern Med 2006;144:21–28. [PubMed: 16389251]
18. Iseki K, Ikemiya Y, Kinjo K, et al. Body mass index and the risk of development of end-stage renal disease in a screened cohort. Kidney Int 2004;65:1870–1876. [PubMed: 15086929]
19. Perry HM Jr, Miller JP, Fornoff JR, et al. Early predictors of 15-year end-stage renal disease in hypertensive patients. Hypertension 1995;25:587–594. [PubMed: 7721402]
20. Gelber RP, Kurth T, Kausz AT, et al. Association between body mass index and CKD in apparently healthy men. Am J Kidney Dis 2005;46:871–880. [PubMed: 16253727]
21. Kannel WB, Feinleib M, McNamara PM, et al. An investigation of coronary heart disease in families. The Framingham offspring study. Am J Epidemiol 1979;110:281–290. [PubMed: 474565]
22. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2):S1–266. [PubMed: 11904577]
23. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–470. [PubMed: 10075613]
24. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med 2006;145:247–254. [PubMed: 16908915]
25. Coresh J, Astor BC, McQuillan G, et al. Calibration and random variation of the serum creatinine assay as critical elements of using equations to estimate glomerular filtration rate. Am J Kidney Dis 2002;39:920–929. [PubMed: 11979335]
26. Culleton BF, Larson MG, Parfrey PS, et al. Proteinuria as a risk factor for cardiovascular disease and mortality in older people: a prospective study. Am J Med 2000;109:1–8. [PubMed: 10936471]
27. Cupples, LA.; D'Agostino, RB. Some risk factors related to the annual incidence of cardiovascular disease and death using pooled repeated biennial measurements: Framingham Study, 30-year follow-up. In: Kannel, WB.; Garrison, RJ., editors. NIH Publication 87-203, section 34. Washington, DC: Government Printing Office; 1987.
28. Kalantar-Zadeh K, Abbott KC, Salahudeen AK, et al. Survival advantages of obesity in dialysis patients. Am J Clin Nutr 2005;81:543–554. [PubMed: 15755821]
29. Ejerblad E, Fored CM, Lindblad P, et al. Obesity and risk for chronic renal failure. J Am Soc Nephrol 2006;17:1695–1702. [PubMed: 16641153]
30. U.S.Renal Data System. USRDS 2006 Annual Data Report: Atlas of End-Stage Renal Disease in the United States. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; Bethesda, MD: 2006.
31. Kronenberg F, Lingenhel A, Neyer U, et al. Prevalence of dyslipidemic risk factors in hemodialysis and CAPD patients. Kidney Int 2003:S113–S116.
32. Parikh NI, Hwang SJ, Larson MG, et al. Cardiovascular disease risk factors in chronic kidney disease: overall burden and rates of treatment and control. Arch Intern Med 2006;166:1884–1891. [PubMed: 17000946]
33. Aneja A, El-Atat F, McFarlane SI, et al. Hypertension and obesity. Recent Prog Horm Res 2004;59:169–205. [PubMed: 14749502]
34. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911–919. [PubMed: 15867843]
35. Bello AK, de Z D, El NM, et al. Impact of weight change on albuminuria in the general population. Nephrol Dial Transplant 2007;22:1619–1627. [PubMed: 17360767]

36. Fox CS, Pencina MJ, Meigs JB, et al. Trends in the incidence of type 2 diabetes mellitus from the 1970s to the 1990s: the Framingham Heart Study. Circulation 2006;113:2914–2918. [PubMed: 16785337]

37. Coresh J, Selvin E, Stevens LA, et al. Prevalence of chronic kidney disease in the United States. JAMA 2007;298:2038–2047. [PubMed: 17986697]

38. Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature 2006;444:881–887. [PubMed: 17167477]

39. Hutley L, Prins JB. Fat as an endocrine organ: relationship to the metabolic syndrome. Am J Med Sci 2005;330:280–289. [PubMed: 16355012]

40. Foster MC, Hwang SJ, Larson MG, et al. Cross-classification of microalbuminuria and reduced glomerular filtration rate: associations between cardiovascular disease risk factors and clinical outcomes. Arch Intern Med 2007;167:1386–1392. [PubMed: 17620532]

41. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem 1992;38:1933–1953. [PubMed: 1394976]

42. Rule AD, Larson TS, Bergstralh EJ, et al. Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med 2004;141:929–937. [PubMed: 15611490]

Table 1

Baseline characteristics of study sample, separated by BMI category, among participants free of kidney disease at baseline. Data are presented as mean (standard deviation) for continuous variables* and % (n) for dichotomous variables**.

	Normal Weight (N=1387)	Overweight (N=964)	Obese (N=325)	Age- sex-adjusted p-value***
Age (years)	41 (9)	44 (9)	44 (9)	<0. 001
Sex (% women)	67.4 (935)	32.6 (314)	46.2 (150)	<0. 001
BMI (kg/m^2)	22.3 (1.7)	27.1 (1.4)	33.5 (3.4)	<0. 001
1979****	22.3 (1.8)	26.6(1.3)	33.4 (5.4)	<0.001
1980	22.3(1.7)	27.1(1.4)	33.3 (2.9)	<0.001
1981	22.3(1.6)	27.1(1.4)	33.4 (3.1)	<0.001
1982	22.3(1.7)	27.2 (1.3)	33.6 (3.8)	<0.001
Serum creatinine (mg/dL)	1.1 (0.22)	1.2 (0.22)	1.1 (0.23)	0.5
eGFR (mL/min/1.73m^2)	108 (36)	103 (33)	107 (38)	0.006
Smoking (%)	35.6 (494)	30.0 (289)	34.2 (111)	0.3
Hypertension (%)	10.8 (150)	26.2 (253)	38.8 (126)	<0. 001
Hypertension Rx (%)	4.0 (56)	10.0 (96)	14.5 (47)	<0. 001
Systolic Blood Pressure (mm Hg)	116 (14)	124 (15)	130 (15)	<0. 001
Diabetes (%)	0.6 (9)	2.1 (20)	4.6 (15)	<0. 001
HDL cholesterol (mg/dL)	53 (13)	45 (12)	43 (12)	<0. 001
Triglycerides (mg/dL)	102 (55)	141 (76)	162 (87)	<0. 001
Prevalent CVD (%)	1.6 (22)	2.5 (24)	1.2 (4)	0.4

Abbreviations: BMI = body mass index; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; CVD = cardiovascular disease.

Note: To convert serum creatinine in mg/dL to mol/L, multiply by 88.4; eGFR in mL/min/1.73m^2 to mL/s/1.73m^2, multiply by 0.01667; HDL cholesterol in mg/dL to mmol/L, multiply by 0.02586; triglycerides in mg/dL to mmol/L, multiply by 0.01129.

* ANOVA used to test for differences in means of continuous variables across the BMI categories.

** Logistic regression used to test for differences in categorical variables across the BMI categories.

*** Age is sex-adjusted; sex is age-adjusted.

**** Mean BMI and standard deviation by year of cohort accrual during examination cycle 2.

Table 2

Age- sex- and multivariable odds ratios for the development of CKD among individuals free of CKD at baseline in the overall sample, hypertension-free, diabetes-free, and prevalent CVD-free at baseline subgroups.

Model	Sample size/# CKD cases	BMI category	Odds Ratio (95% CI)	p-value	p-value for trend
Overall	2676/212				
Age- sex-adjusted*		Overweight	1.29 (0.93, 1.81)	0.1	0.01
		Obese	1.68 (1.10, 2.57)	0.02	
Multivariable-adjusted**		Overweight	1.06 (0.75, 1.50)	0.8	0.7
		Obese	1.09 (0.69, 1.73)	0.7	
Hypertension-free	2147/126				
Age- sex-adjusted		Overweight	1.09 (0.72, 1.67)	0.7	0.1
		Obese	1.70 (0.95, 3.03)	0.07	
Multivariable-adjusted		Overweight	0.91 (0.59, 1.41)	0.7	0.7
		Obese	1.10 (0.59, 2.06)	0.8	
Diabetes-free	2632/196				
Age- sex-adjusted		Overweight	1.31 (0.93, 1.84)	0.1	0.2
		Obese	1.25 (0.78, 2.01)	0.4	
Multivariable-adjusted		Overweight	1.10 (0.77, 1.56)	0.6	0.8
		Obese	0.87 (0.53, 1.44)	0.6	
Free of prevalent CVD	2626/197				
Age- sex-adjusted		Overweight	1.32 (0.93, 1.86)	0.1	0.009
		Obese	1.77 (1.15, 2.73)	0.01	
Multivariable-adjusted		Overweight	1.05 (0.73, 1.52)	0.8	0.7
		Obese	1.10 (0.69, 1.77)	0.7	

Abbreviations: BMI = Body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease.

Note: The normal BMI category (18.5 kg/m^2-<25.0kg/m^2) is the reference group (Odds Ratio = 1.0) for these models.

*Age- sex- models adjusted for age at Exam 2 and sex.

**Multivariable models adjusted for age at Exam 2, sex, diabetes, systolic blood pressure, hypertension treatment, current smoking status and high-density lipoprotein level at baseline.

Table 3

Age- sex-, multivariable model odds ratio for the development of CKD among individuals free of CKD at baseline in the overall sample, hypertension-free, diabetes-free, and prevalent CVD-free at baseline subgroups using sex-specific BMI quartiles.

Model	Sample size/# CKD cases	BMI Quartile*	Odds Ratio (95% CI)	p-value
Overall	2676/212			
Age- sex-adjusted**		Q2	0.94 (0.58, 1.52)	0.8
		Q3	1.15 (0.73, 1.81)	0.5
		Q4	1.67 (1.09, 2.56)	0.02
Multivariable-adjusted***		Q2	0.91 (0.56, 1.47)	0.7
		Q3	1.01 (0.63, 1.60)	0.9
		Q4	1.19 (0.75, 1.87)	0.5
Hypertension-free	2147/126			
Age- sex-adjusted		Q2	1.04 (0.57, 1.92)	0.9
		Q3	1.44 (0.81, 2.55)	0.2
		Q4	1.66 (0.95, 2.90)	0.08
Multivariable-adjusted		Q2	0.90 (0.49, 1.68)	0.8
		Q3	1.24 (0.69, 2.22)	0.5
		Q4	1.18 (0.66, 2.13)	0.6
Diabetes-free	2632/196			
Age- sex-adjusted		Q2	0.94 (0.58, 1.53)	0.8
		Q3	1.11 (0.70, 1.77)	0.6
		Q4	1.48 (0.95, 2.31)	0.08
Multivariable-adjusted		Q2	0.91 (0.56, 1.49)	0.7
		Q3	1.00 (0.62, 1.60)	0.9
		Q4	1.12 (0.70, 1.78)	0.6
Free of prevalent CVD	2626/197			
Age- sex-adjusted		Q2	0.87 (0.53, 1.45)	0.6
		Q3	1.21 (0.76, 1.92)	0.4
		Q4	1.70 (1.09, 2.66)	0.02
Multivariable-adjusted		Q2	0.82 (0.49, 1.36)	0.4
		Q3	1.02 (0.63, 1.64)	0.9
		Q4	1.16 (0.72, 1.86)	0.6

BMI = Body mass index; CKD = chronic kidney disease; CVD = cardiovascular disease.

Note: The lowest sex-specific BMI quartile (Q1: 18.50-<21.30 for women and 18.50-<24.10 for men) is the reference group (Odds Ratio=1.0) for these models.

* Sex-specific BMI (kg/m^2) quartiles used in overall sample as well as for each subgroup analysis. Among women: Q1 18.50-<21.30; Q2: 21.30-<23.26; Q3: 23.26-<26.06; Q4: >26.06. Among men: Q1: 18.50-<24.10; Q2: 24.10- <26.20; Q3: 26.20-<28.40; Q4: >28.40

** Age- sex- models adjusted for age at Exam 2 and sex.

*** Multivariable models adjusted for age at Exam 2, sex, diabetes, systolic blood pressure, hypertension treatment, current smoking status and high-density lipoprotein level at baseline.

Table 4

Age- sex-, multivariable model odds ratio for the development of CKD among individuals free of CKD at baseline in the overall sample, hypertension-free, diabetes-free, and prevalent CVD-free at baseline subgroups using BMI as a continuous variable.

Model	Sample size/# CKD cases	Odds Ratio (95% CI)	p-value
Overall	2676/212		
Age- sex-adjusted*		1.05 (1.02, 1.09)	0.005
Multivariable-adjusted**		1.01 (0.97, 1.05)	0.6
Hypertension-free	2147/126		
Age- sex-adjusted		1.05 (1.004, 1.10)	0.03
Multivariable-adjusted		1.01 (0.96, 1.07)	0.6
Diabetes-free	2632/196		
Age- sex-adjusted		1.03 (0.99, 1.07)	0.1
Multivariable-adjusted		1.00 (0.96, 1.04)	0.9
Free of prevalent CVD	2626/197		
Age- sex-adjusted		1.05 (1.02, 1.09)	0.003
Multivariable-adjusted		1.01 (0.97, 1.05)	0.7

Abbreviations: CKD = chronic kidney disease; CVD = cardiovascular disease.

* Age- sex- models adjusted for age at Exam 2 and sex.

** Multivariable models adjusted for age at Exam 2, sex, diabetes, systolic blood pressure, hypertension treatment, current smoking status and high-density lipoprotein level at baseline.

Table 5

Age- sex- and multivariable odds ratios for the development of proteinuria by urinary dipstick test among individuals free of Stage 3 CKD or proteinuria by dipstick at Exam 2 and Stage 3 CKD at Exam 7 in the overall sample, hypertension-free, diabetes-free, and prevalent CVD-free at baseline subgroups.

Model	Sample Size (Overall/# ≥ trace proteinuria)	BMI category	Odds Ratio (95% CI)	p-value
Overall	2413/347			
Age- sex-adjusted*		Overweight	1.52 (1.16, 1.98)	0.002
		Obese	1.80 (1.27, 2.55)	<0.001
Multivariable-adjusted**		Overweight	1.43 (1.09, 1.88)	0.01
		Obese	1.56 (1.08, 2.26)	0.02
Hypertension-free	1976/243			
Age- sex-adjusted		Overweight	1.44 (1.07, 1.95)	0.02
		Obese	1.14 (0.70, 1.87)	0.6
Multivariable-adjusted		Overweight	1.43 (1.05, 1.94)	0.02
		Obese	1.10 (0.67, 1.81)	0.7
Diabetes-free	2392/341			
Age- sex-adjusted		Overweight	1.55 (1.18, 2.02)	0.001
		Obese	1.83 (1.29, 2.60)	<0.001
Multivariable-adjusted		Overweight	1.46 (1.11, 1.92)	0.007
		Obese	1.56 (1.07, 2.26)	0.02
Free of prevalent CVD	2378/336			
Age- sex-adjusted		Overweight	1.52 (1.16, 1.99)	0.002
		Obese	1.88 (1.32, 2.66)	<0.001
Multivariable-adjusted		Overweight	1.44 (1.09, 1.89)	0.01
		Obese	1.62 (1.12, 2.36)	0.01

Abbreviations: CKD = chronic kidney disease; BMI = body mass index; CVD = cardiovascular disease.

Note: The normal BMI category (18.5 kg/m^2-<25.0kg/m^2) is the reference group (OR=1.0) for these models.

*Age- sex- models adjusted for age at Exam 2 and sex.

**Multivariable models adjusted for age at Exam 2, sex, diabetes, systolic blood pressure, hypertension treatment, current smoking status and high-density lipoprotein level at baseline.