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Original Investigation

Body Mass Index and Early Kidney Function Decline in Young Adults: A Longitudinal Analysis of the CARDIA (Coronary Artery Risk Development in Young Adults) Study

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Background: Identifying potentially modifiable risk factors is critically important for reducing the burden of chronic kidney disease. We sought to examine the association of body mass index (BMI) with kidney function decline in a cohort of young adults with preserved glomerular filtration at baseline.

Study Design: Longitudinal cohort.

Setting & Participants: 2,839 black and white young adults with cystatin C–based estimated glomerular filtration rate ($eGFR_{cys}$) > 90 mL/min/1.73 m^2 taking part in the year-10 examination (in 1995-1996) of the Coronary Artery Risk Development in Young Adults (CARDIA) Study.

Predictor: BMI, categorized as 18.5-24.9 (reference), 25.0-29.9, 30.0-39.9, and ≥40.0 kg/m^2.

Outcomes: Trajectory of kidney function decline, rapid decline (>3% per year), and incident $eGFR_{cys}$ < 60 mL/min/1.73 m^2 over 10 years of follow-up.

Measurements: GFR_{cys} estimated from the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation for calibrated cystatin C at CARDIA years 10, 15, and 20.

Results: At year 10, participants had a mean age of 35.1 years, median $eGFR_{cys}$ of 114 mL/min/1.73 m^2, and 24.5% had BMI ≥ 30.0 kg/m^2. After age 30 years, average $eGFR_{cys}$ was progressively lower with each increment in BMI after adjustment for baseline age, race, sex, hyperlipidemia, smoking status, and physical activity. Higher BMI category was associated with successively higher odds of rapid decline (for 25.0-29.9, 30.0-39.9, and ≥40.0 kg/m^2, adjusted ORs were 1.50 [95% CI, 1.21-1.87], 2.01 [95% CI, 1.57-2.87], and 2.57 [95% CI, 1.67-3.94], respectively). 18 participants (0.6%) had incident $eGFR_{cys}$ < 60 mL/min/1.73 m^2. In unadjusted analysis, higher BMI category was associated with incident $eGFR_{cys}$ < 60 mL/min/1.73 m^2 (for 25.0-29.9, 30.0-39.9, and ≥40.0 kg/m^2, ORs were 5.17 [95% CI, 1.10-25.38], 7.44 [95% CI, 1.54-35.95], and 5.55 [95% CI, 0.50-61.81], respectively); adjusted associations were no longer significant.

Limitations: Inability to describe kidney function before differences by BMI category were already evident. Absence of data for measured GFR or GFR estimated from serum creatinine level.

Conclusions: Higher BMI categories are associated with greater declines in kidney function in a cohort of young adults with preserved GFR at baseline. Clinicians should vigilantly monitor overweight and obese patients for evidence of early kidney function decline.

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INDEX WORDS: Kidney function decline; obesity; risk factor.

Chronic kidney disease (CKD) affects an estimated 14% of US adults and is associated with significant morbidity and mortality.[1] Identification of potentially modifiable risk factors for CKD is essential for reducing its burden.

Although several longitudinal studies have demonstrated an association between obesity and incident CKD, these observations have been made primarily in cohorts of older individuals[2-4] or among individuals with established kidney disease.[2,4] Because obesity affects an estimated 17% of children and adolescents, nearly triple its prevalence in the 1980s,[5,6] determining the association of obesity with declining kidney function in younger populations, as well as understanding the association of obesity on the continuum of incipient kidney disease throughout the life course, is critical.

Within a cohort of young adults with preserved glomerular filtration at baseline, we examined the association of body mass index (BMI) categories with kidney function decline as measured by cystatin C, an alternative biomarker used to estimate glomerular filtration rate (GFR) and thought to be particularly useful for detecting reductions in kidney function at

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earlier stages (estimated GFR [eGFR] > 60 mL/min/1.73 m^2).[7] We hypothesized that individuals with higher BMI would have a faster decline in kidney function and more progression to eGFR < 60 mL/min/1.73 m^2 than their counterparts with normal BMI.

METHODS

Study Design and Population

We conducted a longitudinal analysis of CARDIA (Coronary Artery Risk Development in Young Adults) Study participants. CARDIA is a multicenter cohort study to evaluate the development and determinants of cardiovascular risk factors and disease in young adults. From 1985 to 1986, a total of 5,115 asymptomatic young adults aged 18-30 years were recruited from 4 US cities (Birmingham, AL; Chicago, IL; Minneapolis, MN; and Oakland, CA). The study design, protocol, and recruitment process have been described previously in detail.[8] The institutional review boards at each site approved the examination protocol, and written informed consent was obtained at every examination. The cohort was designed for balance by race (black and white), sex, age, and education. There were 52% black participants, 55% women, and 40% with 12 or fewer years of formal education. Follow-up examinations were completed at study years 2, 5, 7, 10, 15, 20, and 25. The retention rate of the surviving cohort was 79% at year 10, 74% at year 15, and 72% at year 20. All measurements were obtained for all available participants at every study visit except for cystatin C, which was measured as part of an ancillary study to CARDIA on all available stored plasma samples from participants attending the year-10, -15, and -20 examinations.

Of 3,944 participants who completed the year-10 study visit, we excluded 58 without a year-10 BMI measurement, 76 with BMI < 18.5 kg/m^2 at year 10, and 118 without a cystatin C measurement at year 10. We excluded 295 participants with eGFR estimated from cystatin C level ($eGFR_{cys}$) < 90 mL/min/1.73 m^2 at year 10 in order to examine the cohort with preserved kidney function at baseline (year 10). We excluded 558 additional participants with no year-15 cystatin C measurement because consecutive kidney function measurements were required for our rapid $eGFR_{cys}$ decline and incident CKD outcomes. The participants excluded because of missing year-15 cystatin C values had similar BMI subgroup prevalences compared with the 2,839 participants with available data who were included in this study ($P = 0.09$).

Predictor

Our primary predictor was BMI (in kilograms per meter squared), which we categorized as 18.5-24.9 (reference, normal weight), 25.0-29.9 (overweight), 30.0-39.9 (obese), or ≥40.0 kg/m^2 (extremely obese).[9] BMI was calculated from body weight measured with light clothing to the nearest 0.2 lb and body height without shoes to the nearest 0.5 cm.

Main Outcome

Our outcome of interest was kidney function decline, which we evaluated in 3 ways: (1) trajectory of $eGFR_{cys}$ (in milliliters per minute per 1.73 m^2) using repeated $eGFR_{cys}$ measurements at study years 10, 15, and 20; (2) rapid $eGFR_{cys}$ decline (>3% per year in the intervals between years 10, 15, and 20); and (3) incident $eGFR_{cys}$ < 60 mL/min/1.73 m^2 at study years 15 or 20. Our definition of rapid decline represents a magnitude of change 3 times the expected rate previously described in aging population studies[10] and has been used in several studies.[11-13] Serum creatinine also was measured at all study years for all available participants; however, as in prior CARDIA Study analyses, we estimated kidney function using cystatin C level because it has been shown to perform better in evaluating kidney function for persons at higher eGFR ranges[7,14,15] and may detect changes in kidney function earlier than creatinine level.[16] Furthermore, creatinine values in the CARDIA Study have been measured using different assays over time, thus rendering examination of trajectories in kidney function uninterpretable.

Cystatin C was measured as part of an ancillary study on all stored frozen plasma from study years 10, 15, and 20 by nephelometry using the N Latex Cystatin C kit (Dade Behring) and later calibrated to most recent cystatin C standardization. Kidney function (eGFR in milliliters per minute per 1.73 m^2) then was estimated by the 2012 CKD-EPI (CKD Epidemiology Collaboration) cystatin C equation, which is for use with calibrated cystatin C.[17]

Covariates

Age, race, sex, smoking status, and hyperlipidemia were defined using year-10 data and were measured on all available CARDIA participants. Age, race (white or black), sex, and smoking status were obtained by self-report. We defined smoking status as never, past, or current use. Hyperlipidemia was defined by low-density lipoprotein cholesterol (derived by the Friedewald equation)[18] level > 130 mg/dL or self-reported lipid-lowering medication use.

We defined diabetes as fasting serum glucose level ≥ 126 mg/dL or self-reported hypoglycemic medication use using data collected at the year-10, -15, and -20 examinations. Serum glucose was measured using hexokinase coupled to glucose-6-phosphate dehydrogenase by Linco Research (St Louis, MO). Three seated systolic and diastolic blood pressure measurements were performed with a random-zero sphygmomanometer. We used the mean of the second and third readings at the year-10, -15, and -20 examinations and considered systolic and diastolic blood pressures separately as continuous variables.

Albuminuria was determined from a single untimed (spot) urine sample collected at the year-10, -15 and -20 examinations.[19] Urine albumin was measured using a nephelometric procedure with a specific anti-albumin monoclonal antibody, and creatinine was assessed using the Jaffé method.[19] Urine albumin-creatinine ratios were standardized to sex and race and expressed in milligrams per gram of creatinine.[20] Albuminuria was defined as urine albumin-creatinine ratio > 30 mg/g.

Serum high-sensitivity C-reactive protein (CRP; in milligrams per liter) was measured at the year-7, -15, and -20 examinations with a BNII nephelometer (Dade Behring). Because CRP was not measured at year 10, we used the year-7 data as the baseline measurement. Because values were not normally distributed, we $\log_2$ transformed them to downweight noisier values in the higher ranges.

Physical activity was defined by an interviewer-administered questionnaire at each CARDIA examination. This validated questionnaire asked about frequency of participation in 13 categories of moderate and vigorous recreational sports, exercise, leisure, and occupational activities during the previous 12 months.[21] We used log-transformed physical activity scores, which were calculated in exercise units based on frequency and intensity of each activity.

Statistical Analyses

We estimated the trajectory of population mean $eGFR_{cys}$ values across the entire age spectrum from 30-50 years, using linear mixed models in which age effects were captured using 5-knot restricted cubic splines, specific to each BMI group. Individual departures from the trajectory of the population mean were modeled using random intercepts and cubic spline components. We examined population mean $eGFR_{cys}$ graphically by age for each BMI group separately, which included a total of 8,146 $eGFR_{cys}$ measurements over 26,535 person-years. We tested for differences in slopes across BMI categories of $eGFR_{cys}$ trajectories