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Age and Association of Body Mass Index with Loss of Kidney Function and Mortality

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Abstract

Background—Obesity may be associated with worse clinical outcomes, including chronic kidney disease. It is unclear if this association is modified by age.

Methods—In a national cohort of over 3·3 million (n=3,376,187) US veterans with estimated glomerular filtration rate (eGFR) >60ml/min/1·73m^2, we examined the association of body mass index (BMI) in patients of different age (<40, 40–<50, 50–<60, 60–<70, 70–<80, and ≥80 years old) with loss of kidney function and with all-cause mortality in logistic regression models and proportional hazards models adjusted for race, gender, comorbidities, medications, and baseline eGFR.

Findings—A U-shaped association between BMI and loss of kidney function was somewhat consistent and more prominent with advancing age, except in the patients ≤40 years old, in whom BMI did not appear to predict renal function impairment. The lowest risk for loss of kidney function was observed in patients with BMI 25– <30 kg/m^2. BMI also displayed a U-shaped association with mortality, which was similar in all age groups.

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CONFLICT OF INTEREST STATEMENT

The other authors report no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: JLL, MZM, KKZ and CPK.

Literature search: JLL and AN.

Acquisition of data: CPK, JLL, MZM.

Analysis and interpretation of data: JLL, MZM, AN, MKM, KKZ and CPK.

Drafting of the manuscript and approval of the final version: JLL, MKM and CPK.

Critical revision of the manuscript for important intellectual content and approval of the final version: MZM, AN and KKZ.

Interpretation—BMI ≥30 kg/m^2 is associated with rapid loss of kidney function in patients with eGFR ≥60 ml/min/1·73m^2, and BMI ≥35 kg/m^2 is also associated with high mortality. The former association is accentuated in older patients. A BMI of 25– <30 kg/m^2 is associated with optimal clinical outcomes.

Keywords

Body Mass Index; Chronic Kidney Disease; Age

INTRODUCTION

Obesity is associated with increased risk of incident chronic kidney disease (CKD),[1,2] end stage renal disease (ESRD),[3,4] and mortality,[5,6] according to some but not all studies. In past decades, many observational studies examined the associations with BMI in individuals of different age[7] and with various clinical conditions.[8] Paradoxical associations were observed in persons with pre-existing chronic illnesses.[9–11] The optimal BMI for survival has also varied from study to study.[5,12] Besides obesity, very low BMI levels have been consistently associated with high all-cause mortality.[6,13] Some, but not all clinical trials reported improved kidney function after intentional weight loss in obese individuals.[14,15]

Obesity is a chronic condition which could persist for decades in most affected individuals. Older age is associated with a higher prevalence of comorbid conditions and a high short-term mortality, and it is therefore possible that age may modify the association of BMI with outcomes such as kidney disease. The heterogeneity of the study populations in most previous studies, in which subjects were different not only by age but also by their comorbidities, makes it difficult to determine the independent effect of age on the risk imparted by obesity. In order to determine whether the risk of adverse clinical outcomes in relation to obesity would differ by age, we examined the association of BMI with progressive loss of kidney function and with all-cause mortality in a large national cohort of US veterans with estimated glomerular filtration rate (eGFR) of ≥60 ml/min/1·73m^2 grouped by age. We hypothesized that the association of BMI with clinical outcomes will be attenuated in older patients, especially in individuals with a high chronic comorbidity burden.

METHODS

Study Population

Data was extracted from a historic cohort study (Racial and Cardiovascular Risk Anomalies in CKD (RCAV) study), as previously described.[16,17] Briefly, the cohort consisted of 3,582,478 US veterans, selected from among all veterans who received clinical care in any of the VA healthcare facilities, and who had an eGFR >60 ml/min/1·73m^2 recorded during October 1, 2004–September 30, 2006, calculated by using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.[18] After excluding patients with no available weight and height measurement, those starting renal replacement therapy before the cohort entry, and those with extreme BMI values, our final study population included 3,376,187 individuals. Cohort entry was defined as the first date of eGFR ≥60 ml/min/

1·73m^2. Information about baseline demographic characteristics, vital signs, comorbid conditions (defined based on ICD9 codes recorded during October 1, 2004–September 30, 2006) and medication usage was extracted from various national VA research databases, as previously described.[19–21] Information about race was cross referenced with data obtained from Medicare through the VA-Medicare data merge project.[22] Baseline blood pressure was defined as the mean of all measurements performed in the first 90 days after cohort entry. Medication usage was examined both at cohort entry and throughout the follow-up period.

We calculated the BMI of every subject as the weight in kilograms divided by the height in meters squared. BMI levels were stable over time, with baseline BMI (29.1±5.6 kg/m^2) and the mean of all intra-individual BMI measurements throughout the entire follow-up period (29.1±5.6 kg/m^2) being similar; the average change in BMI over time was −0.0518 kg/m^2/year (95% confidence interval: −0.0524, −0.0512). Therefore, in order to minimize the effects of random variations and erroneous entries, in primary analyses we used the mean of all available BMI measurements collected for each patient between cohort entry and the end of follow-up, and excluded extreme values over 55 or lower than 15 kg/m^2 (a total of 7,800 patients were excluded due to extreme BMI values). We used baseline BMI as predictor in sensitivity analyses. BMI was divided into 6 a-priori defined categories: <20, 20–<25, 25–<30, 30–<35, 35–<40, and ≥40 kg/m^2. We used this categorization instead of the standard classification[23] in order to allow for the examination of more granular associations with extremely elevated BMI values, which is justified by the steady elevation of mean BMI levels observed in recent years.[24] Age at baseline was stratified into six groups with ten-year increments starting from <40 years old to >80 years old. In order to examine the independent effects of both age and BMI on the studied outcomes, we constructed joint categories based on all possible one-to-one combinations of BMI categories and age groups, using patients with BMI <20 kg/m^2 and age<40 years old as referent in all analyses. In sensitivity analyses we examined the association of BMI with the studied end points in separate subgroups of age, using BMI 20–<25 kg/m^2 as referent within each subgroup.

Outcomes

Our co-primary outcomes were rapid decline of kidney function and all-cause mortality. Rapid decline in kidney function was defined as the presence of an average decrease (slope) in eGFR of more than 5 ml/min/1·73m^2/year during the follow-up period.[25] Slopes were calculated from minimum 3 available serum creatinine measurements by using least square regression. All-cause mortality was ascertained from the VA Vital Status Files[22] which record dates of death or dates of last encounter based on all available sources in the VA system. Using the US National Death index as referent gold standard, the sensitivity and specificity of the VA Vital Status Files were shown to be 98·3% and 99·8% respectively.[22]

Statistical Analysis

Descriptive analyses were performed by using means ± standard deviation (SD), medians (interquartile range, IQR) and proportions as appropriate. The association of mutually exclusive categories of BMI-age combinations with the presence of rapid loss of kidney function and with mortality was examined in logistic regression models, and in Cox proportional hazards models, respectively. Patients were followed in survival analyses from

the date of the baseline eGFR until the first occurrence of death and were censored at the date of last healthcare service, or on July 31, 2013.

The effect of potential confounders was analyzed by constructing multivariable adjusted models. Our main multivariable model included gender, race, baseline eGFR, median income, marital status, comorbidities (coronary heart disease, cerebrovascular disease, congestive heart failure (CHF), peripheral artery disease, rheumatologic disease, malignancy, depression, liver disease, chronic lung disease, HIV, and the Deyo-modified Charlson comorbidity index (CCI)),[26] and baseline medication use (angiotensin-converting-enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), statins, and the use of any antihypertensive medications). Models were also adjusted for urine albumin-creatinine ratio (UACR) in subgroup analyses of patients with available measurements for this variable. Diabetes mellitus (DM) and blood pressure were not included in these models because these are likely effect mediators of obesity, rather than confounders. In order to examine whether DM and/or blood pressure have an effect on the association of BMI with progressive loss of kidney function, we constructed an additional model adjusting for these two variables in addition to all the other ones. In order to clarify the effect of pre-existing chronic illness on the association of BMI with progressive loss of kidney function, a subgroup analysis was conducted in patients lacking comorbid conditions (defined as CCI=0),in patients with and without hypertension. The effect of albuminuria on the association of BMI with both outcomes was examined in the subset of patients (29% of the total cohort) with available UACR, by adjusting for UACR level in addition to the other covariates.

Data points were missing for race (8·7%), marital status (3·6%), income (6·1%), and comorbidities (0·2%). 87·5% (for slopes of eGFR) and 86·6% (for mortality) of the patients included in crude models had complete data for multivariable analysis. Missing values were not imputed in primary analyses, and were substituted by using multiple imputation procedures in sensitivity analyses. Missing values were replaced by multiple imputations with a multivariate normal regression method using data augmentation with an iterative Markov chain Monte Carlo procedure.[27,28] Five imputed datasets were generated, primary analyses were performed on each imputed dataset and Rubin's combination rules were used to form one set of results.[29]

Statistical analyses were performed using Stata MP Version 12 (Stata Corporation, College Station, TX).

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RESULTS

The mean age of the cohort was 60·0±14·0 years, 72% were white and the mean baseline eGFR was 83·8±15·6 ml/min/1·73m^2. The mean of the intra-individual mean BMI was

29·1±5·6 kg/m^2, and BMI was measured a median of 18 (IQR: 10–30) times/patient. Baseline characteristics of patients categorized by their BMI and age are described in Tables 1a and 1b. Younger patients were more likely to be female and to be unmarried. Systolic blood pressure was incrementally higher with increasing BMI and age, but diastolic blood pressure increased with higher BMI but decreased with age. Older patients with higher BMI had higher medication use, higher prevalence of CHF, cardiovascular disease, DM, and hypertension. Depression was more common in younger and more obese individuals, and lung disease, malignancies, and cerebrovascular disease were more prevalent in slimmer and older patients.

Loss of Kidney Function

274,764 (8·8%) veterans in this cohort had steeper slopes (≤−5 ml/min/1·73m^2). Figure 1 and supplemental Table 1 illustrates the multivariable-adjusted odds ratios (95%CI) of progressive loss of kidney function associated with the various combined age-BMI groups. Older patients had a higher risk of progressive loss of kidney function, independent of BMI levels. The association between BMI and faster decline of kidney function was U-shaped in patients older than 40 years old, with a marked accentuation of the risk associated with higher BMI as age increased. In those younger than 40 years old there was no association between BMI and progressive loss of kidney function. The lowest risk of kidney function deterioration was seen in individuals with a BMI of 25–30 kg/m^2. The observed associations were consistent in various sensitivity analyses; such as after multiple imputations to account for missing covariates (supplemental Figure 1), when adjusting for DM and blood pressure in addition to other covariates (supplemental Figure 2), in subgroup analyses of individuals without chronic medical conditions (Figure 3) or history of hypertension (supplemental Figure 3), in patients with available UACR adjusted for UACR levels (supplemental Figure 4), when using baseline BMI as predictor (supplemental Figure 5), and when examining the associations in separate subgroups of age (supplemental Figure 6). Adjustment for DM and baseline blood pressure did not change the nature of the observed associations (supplemental Figure 2).

Mortality

A total of 672,341 patients died (mortality rate: 28·7/1000 patient years (PY), 95% CI: 28·6–28·7) over a median follow-up time of 6·8±1·6 years. Both BMI <20 kg/m^2 and BMI >35 kg/m^2 were associated with higher mortality (Figure 2 and supplemental Table 2), and these associations were similar for patients in all age groups. The results were qualitatively unchanged in various sensitivity analyses, except for an attenuation of the association between elevated BMI and mortality in older age groups after adjustment for UACR (supplemental Figures 7–10).

DISCUSSION

In this large national cohort of veterans with eGFR ≥60 ml/min/1·73m^2, we describe an incrementally accentuated U-shaped association of BMI with progressive loss of kidney function in patients older than 40 years old. Patients younger than 40 years old showed no

detrimental association between BMI and loss of kidney function over this relatively short follow-up period of approximately 7 years. A similar marked U-shaped association was present between BMI and all-cause mortality, with an especially high mortality seen in patients with BMI <20 kg/m^2 in all age groups, and with an attenuated association with higher BMI in older patients after adjustment for UACR. Optimal outcomes were associated with overweight-to-mild obesity status.

Our study supports earlier findings of associations between obesity and higher prevalence of metabolic syndrome[30] and CKD.[31] Other measures of obesity such as the Waist-Hip-Ratio (WHR) have also been associated with renal impairment independent of BMI.[32] However, few studies have examined the effect of age on the association of obesity with renal outcomes. In a cross sectional analysis from Turkey, ageing strengthened the association between BMI and CKD,[33] but to the best of our knowledge there are no studies examining the association of BMI with future loss of kidney function in patients of different ages.

Our findings pertaining to mortality should be interpreted in the context of general population cohorts showing a higher risk of mortality and cardiovascular outcomes associated with obesity,[34] and studies done in patients with severe chronic comorbidities indicating paradoxically lower mortality associated with obesity.[9,35–37] The effect of age on the BMI-mortality relationship has been examined in previous studies, indicating that obesity was associated with a higher mortality rate in healthy non-smoking young persons than in sicker smoking old individuals.[30] In our study, only 19% of the subjects did not have major chronic illnesses and only 20% were younger than 50 years old, so the entire cohort was a relatively sicker and older. Furthermore, even patients without measured comorbidities might have suffered from unmeasured illnesses, since our cohort was recruited from patients who received medical care in the VA system. It is therefore possible that the high mortality associated with the lowest BMI levels is due to measured and unmeasured disease states associated with malnutrition in all age categories, as previously described in other observational studies.[5,38] Another possible explanation for the high mortality seen in patients with low BMI is the presence of the metabolically obese normal weight (MONW)[39] status in some of them. Relatively weaker associations between BMI and mortality in older patients have also been described in other observational studies.[7,40] These latter observations could be explained by short term survival benefits of high muscle mass or even body fat in individuals with elevated BMI.[41]

The accentuation of the association between high BMI and faster decline in kidney function in older individuals could have several explanations. There is strong evidence that obesity exerts negative effects through various mechanisms, either directly (increased renal sinus fat,[42,43] focal or segmental glomerulosclerosis,[44] glomerulomegaly,[45] and glomerular hypertension or increased glomerular permeability caused by hyperfiltration related glomerular filtration barrier (GFB) injury[46]), or indirectly (obesity related hypertension[47] or diabetes[48]). The glomerular hyperfiltration characteristic of higher BMI typically starts at a young age,[49] and in stages of pre-hypertension or pre-diabetes.[50] However, significant physiological and structural changes in nephrons resulting from obesity may only occur after a longer exposure,[48,51,52] followed by irreversible pathological changes after even longer time.[53] It is thus possible that progressive loss of kidney function becomes most obvious in

individuals who were exposed to the effects of obesity for the longest time, which could explain the accentuation of this association with older age in our study. Another potential explanation for our findings is that the effects of aging and obesity on kidney function may conspire and accentuate each other. Aging itself causes increased glomerular permeability, decreased individual glomerular volume, glomerular sclerosis, and decreased nephron numbers.[54] These effects could superimpose on the changes induced by obesity and result in a more marked effect on kidney function in older individuals. The observation that older age was independently associated with higher risk of progressive loss of kidney function in our cohort also supports this hypothesis.

Based on these competing hypotheses, it is unclear whether weight-reduction strategies aimed at renoprotection should start in younger vs. older age. This, and the optimal target BMI for interventions, will need further evaluation by clinical trials. Considering the effects of obesity on both kidney function and mortality (with the latter being most accentuated in younger patients), it is plausible to hypothesize that weight reduction in very obese individuals should be implemented at an early age, and maintained for a prolonged duration of time (potentially for several decades) in order to reap optimal benefits. Inadequate duration of weight-loss intervention may be one of the explanations why previous studies of intentional weight management[14,15,55] did not universally improve mortality or comorbidity conditions. Conversely, it is also possible that obese older individuals could experience renoprotection from weight-loss interventions, by alleviating the burden of obesity on the ageing kidneys. However, any weight-reducing intervention (regardless of patients' age) would have to be implemented cautiously, due to the uncertainty of the ideal therapeutic target, and the possibility of higher mortality associated with low BMI levels.

Our study has limitations. Most individuals in our cohort were male US veterans and suffered from a high prevalence of comorbid conditions, which limits the generalizability of our findings to women, the general population, or to individuals from other geographic regions of the world. We adjusted for multiple potential confounders, but we cannot rule out the effect of unmeasured confounders. We defined CKD using the CKD-EPI equation as it is more accurate than other estimating equations (such as the Modification of Diet in renal Disease (MDRD) equation) in patients with normal and mildly decreased GFR. The CKD-EPI equation was, however, meant to be used with serum creatinine measured by the IDMS-traceable method, which was not ubiquitous at the time when our cohort was defined (2005–2006), and hence it is unclear how accurate the estimation of GFR in our cohort was. BMI is not an ideal marker of obesity. A study from Taiwan used body fat as predictor of outcomes instead of BMI, since their mean BMIs were closer to the normal range.[56] Indeed, some studies also assessed the WHR or visceral fat and found these to be better associated with kidney function than BMI.[32,57–60] We used estimated GFR to assess kidney function, which could lead to inaccuracies at extreme BMI levels. However, our main renal outcome was intra-individual change in eGFR, which should not have been affected by such inaccuracies assuming stable BMI over time. BMI's association with mortality could affect competing end points such as the development of CKD, but our use of eGFR slopes with sufficient number of measurements over time eliminates such competing risk.

In conclusion, the association between BMI and progressive loss of kidney function in this cohort of patients with normal baseline eGFR is U-shaped. Age had a strong effect on this association, which became more accentuated in older individuals. BMI also had a U-shaped association with mortality, but the association of higher BMI with mortality was attenuated (but not negated) in older individuals. It will be important to study in randomized controlled trials the optimal age when weight-loss interventions should start, and the optimal duration for which such interventions should be maintained in order to achieve the best clinical outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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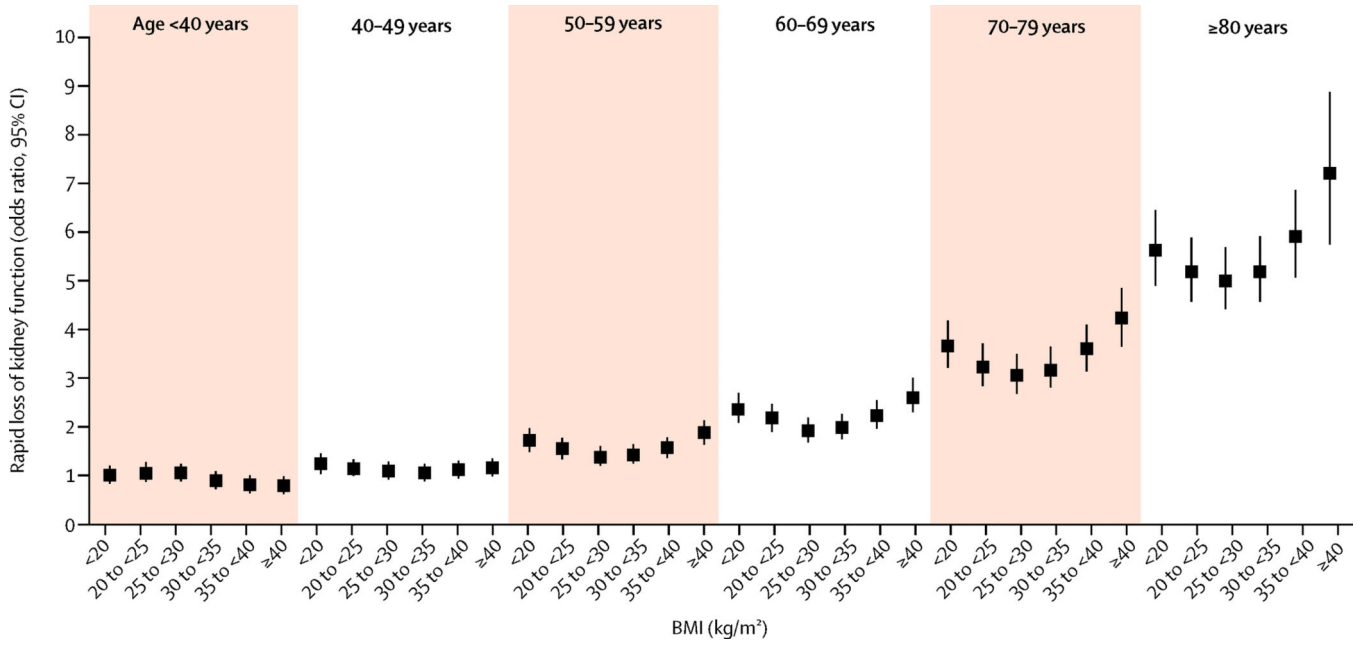

Figure 1.

Multivariable adjusted odds ratios (95% confidence intervals) of steeper slopes of estimated GFR vs. time (defined as slopes <−5 ml/min/1.73m^2/year), associated with various BMI-age joint categories in logistic regression models. Model adjusted for gender, race, baseline eGFR, marital and income status, comorbidities, and medications except for diabetes mellitus and baseline blood pressure. Patients with BMI <20 kg/m^2 and age <40yrs served as referent.

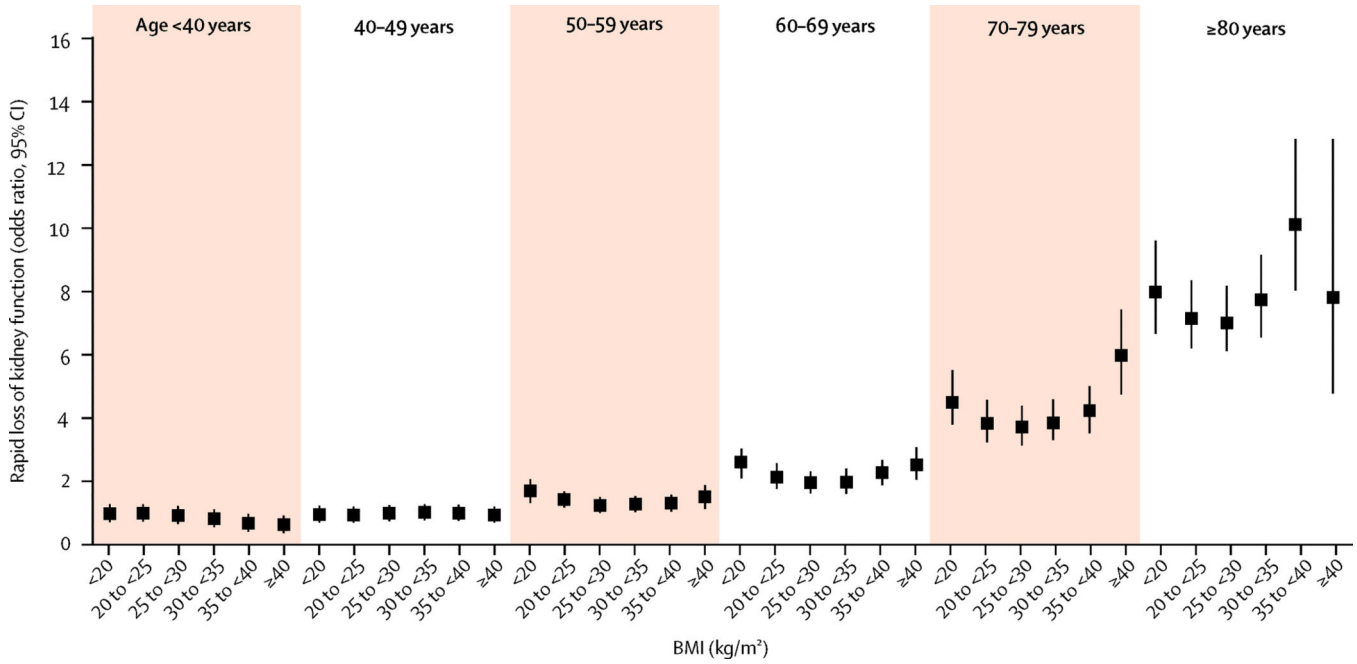

Figure 2.

Multivariable adjusted log-transformed hazard ratios (95% confidence intervals) of all-cause mortality associated with various BMI-age joint categories in Cox models. Model adjusted for gender, race, baseline eGFR, marital and income status, comorbidities, and medications except for diabetes mellitus and baseline blood pressure. Patients with BMI <20 kg/m^2 and age <40yrs served as referent.

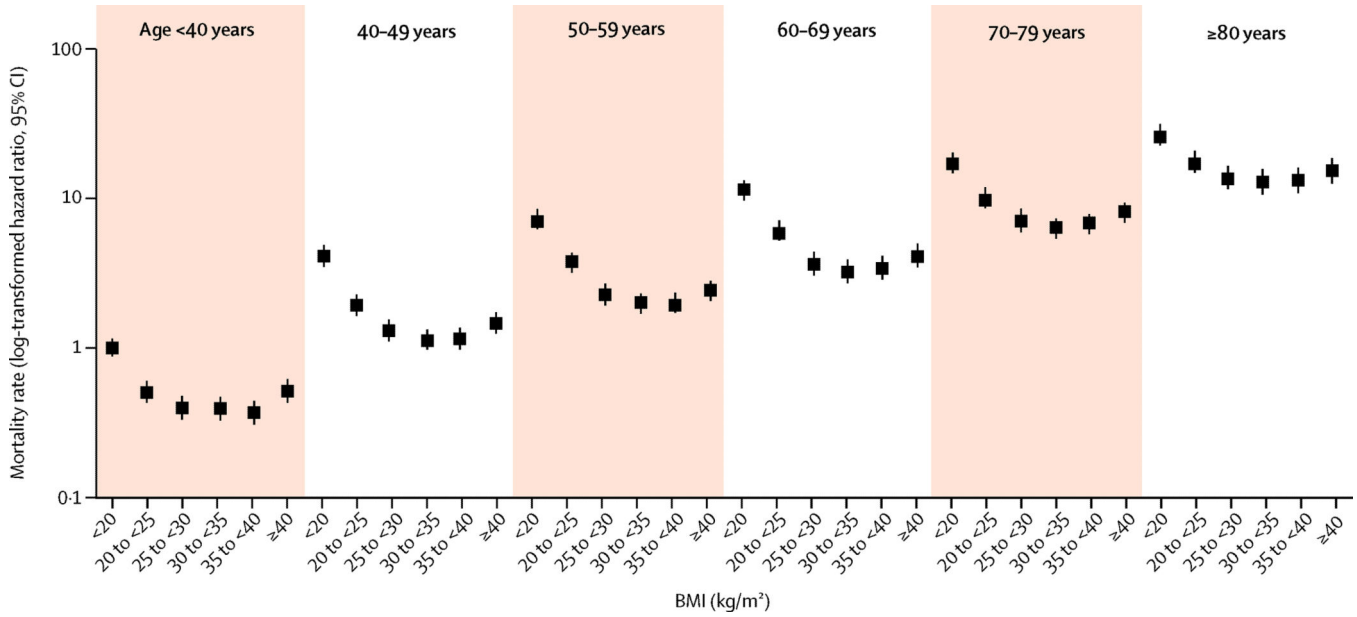

Figure 3.

Multivariable adjusted odds ratios (95% confidence intervals) of steeper slopes of estimated GFR vs. time (defined as slopes <−5 ml/min/1.73m^2/year), associated with various BMI-age joint categories in logistic regression models in subjects with Charlson comorbdity index of 0. Model adjusted for gender, race, baseline eGFR, marital and income status, comorbidities, and medications except for diabetes mellitus and baseline blood pressure. Patients with BMI <20 kg/m^2 and age <40yrs served as referent.

Table 1

a: Baseline characteristics in patients grouped according to mutually exclusive categories of baseline age and body mass index

	BMI (kg/m^2)					
Number of patients	**<20 kg/m^2**	**20–<25 kg/m^2**	**25–<30 kg/m^2**	**30–<35 kg/m^2**	**35–<40 kg/m^2**	**≥40 kg/m^2**
<40	5,284	57,632	107,898	77,030	32,467	14,096
40–<50	8,520	71,687	148,400	117,231	52,143	27,404
50–<60	27,678	173,941	364,094	272,786	118,113	61,920
60–<70	20,528	132,535	299,402	198,035	73,946	31,620
70–<80	22,798	159,263	276,900	127,394	33,770	9,661
≥80	15,844	95,764	104,018	30,084	5,299	1,002
Gender (%Male)						
<40	56.04	69.61	81.50	82.13	79.31	79.21
40–<50	81.12	83.18	87.15	86.49	83.56	82.50
50–<60	94.14	94.10	95.38	94.79	93.29	91.87
60–<70	96.82	97.18	98.04	97.75	96.90	95.53
70–<80	97.66	98.76	99.16	99.05	98.44	97.45
≥80	94.07	97.22	97.94	97.39	96.38	92.81
Race (%black)						
<40	22.90	22.22	22.42	25.64	28.99	31.47
40–<50	35.05	32.21	31.74	32.52	31.67	30.29
50–<60	28.95	23.75	19.25	18.01	16.61	15.67
60–<70	20.73	14.21	10.94	10.71	10.69	11.31
70–<80	19.24	11.15	8.38	8.76	9.97	11.24
≥80	16.54	8.90	6.63	7.41	8.96	13.74
Marital status (%married)						
<40	27.01	30.40	38.56	44.51	46.17	44.78
40–<50	23.94	29.61	39.43	44.58	45.53	43.65
50–<60	28.29	37.61	49.81	55.13	55.90	54.26
60–<70	37.37	51.19	61.93	64.33	63.10	60.02

a: Baseline characteristics in patients grouped according to mutually exclusive categories of baseline age and body mass index

	BMI (kg/m^2)					
Number of patients	**<20 kg/m^2**	**20–<25 kg/m^2**	**25–<30 kg/m^2**	**30–<35 kg/m^2**	**35–<40 kg/m^2**	**≥40 kg/m^2**
70–<80	48.46	62.88	69.17	68.58	65.77	62.31
≥80	50.17	59.81	62.33	59.65	56.60	51.90
Median income($)						
<40	17,000	17,967	19,218	19,172	18,849	18,837
40–<50	12,641	14,539	17,387	18,514	18,969	18,383
50–<60	13,719	17,495	22,514	23,895	23,862	22,774
60–<70	15,571	23,059	28,034	28,108	27,193	25,446
70–<80	15,787	24,287	28,404	28,008	25,974	24,159
≥80	16,649	22,535	24,936	23,307	21,994	20,967
eGFR (EPI) (ml/min/1.73m^2)						
<40	108.0±18.0	103.6±17.0	99.8±16.4	98.4±16.5	98.8±16.6	99.8±16.7
40–<50	101.9±17.0	96.8±15.7	93.1±15.4	91.7±15.4	92.0±15.5	93.2±15.8
50–<60	95.6±15.4	90.1±14.6	86.1±13.9	85.0±13.7	85.1±13.9	85.9±14.2
60–<70	87.4±14.0	81.9±12.7	79.3±11.9	78.9±11.9	79.2±12.0	79.9±12.4
70–<80	79.5±11.8	75.8±10.2	74.5±9.7	74.3±9.8	74.4±10.0	74.9±10.4
≥80	73.9±9.9	71.5±8.9	70.6±8.5	70.6±8.6	70.5±8.6	71.4±9.3
SBP (mmHg)						
<40	117±15	122±15	127±15	131±15	133±16	137±17
40–<50	125±20	127±18	130±17	134±17	136±18	139±19
50–<60	130±22	132±20	134±19	137±19	139±19	140±19
60–<70	133±22	135±20	136±19	138±19	140±19	141±19
70–<80	134±22	137±20	138±19	139±19	140±19	140±19
≥80	136±22	138±21	139±20	140±20	140±20	140±21
DBP (mmHg)						
<40	71±11	73±11	76±11	78±11	80±11	81±12
40–<50	77±13	78±12	80±12	82±12	82±12	82±12
50–<60	78±13	79±12	80±11	81±11	81±12	80±12

a: Baseline characteristics in patients grouped according to mutually exclusive categories of baseline age and body mass index

	BMI (kg/m^2)					
Number of patients	**<20 kg/m^2**	**20–<25 kg/m^2**	**25–<30 kg/m^2**	**30–<35 kg/m^2**	**35–<40 kg/m^2**	**≥40 kg/m^2**
60–<70	76±13	76±12	77±11	78±11	78±11	77±12
70–<80	72±12	72±11	73±11	74±11	74±11	74±11
≥80	70±12	71±11	72±11	72±11	72±11	73±12
Statin (%)						
<40	5.19	9.85	19.23	28.54	34.68	40.98
40–<50	22.04	31.98	44.80	53.21	57.97	61.60
50–<60	30.54	46.65	59.92	66.62	69.77	70.51
60–<70	37.29	55.12	64.01	67.66	69.24	68.64
70–<80	38.74	55.43	61.73	63.77	64.85	63.03
≥80	31.79	46.22	53.10	54.98	56.39	48.70
ACEI/ARB (%)						
<40	4.45	6.20	11.88	21.46	31.28	41.95
40–<50	21.40	24.29	33.67	45.77	56.57	66.59
50–<60	34.30	40.74	51.98	64.06	73.21	79.91
60–<70	39.83	48.85	58.94	69.21	76.69	81.42
70–<80	43.81	54.23	61.38	69.28	75.74	80.19
≥80	42.47	52.23	58.43	64.95	70.41	73.15
Anti-hypertensive medication (%)						
<40	21.54	25.13	34.12	46.29	57.69	69.13
40–<50	52.23	54.15	62.07	71.98	80.13	87.38
50–<60	70.97	73.44	79.97	86.92	91.39	94.14
60–<70	76.55	80.06	85.01	89.94	93.09	94.52
70–<80	79.81	84.55	87.95	91.32	93.62	94.72
≥80	78.04	84.06	87.58	90.16	91.77	90.42

b: Baseline characteristics in patients grouped according to mutually exclusive categories of baseline age and body mass index

	BMI (kg/m^2)					
	<20 kg/m^2	20–<25 kg/m^2	25–<30 kg/m^2	30–<35 kg/m^2	35–<40 kg/m^2	≥40 kg/m^2
DM						
<40	2.07	2.10	2.89	5.26	8.51	13.04
40–<50	5.90	6.88	10.38	16.60	23.93	33.00
50–<60	8.49	12.39	20.20	30.96	42.07	52.42
60–<70	9.55	16.97	25.34	36.77	48.26	57.61
70–<80	12.08	21.24	28.16	38.35	48.82	55.96
≥80	12.76	19.71	25.80	34.59	43.89	45.16
Hypertension						
<40	4.64	6.52	13.14	22.20	31.51	42.62
40–<50	23.89	26.08	35.36	47.52	57.49	67.34
50–<60	40.36	45.20	55.94	67.34	75.88	81.28
60–<70	51.25	58.16	67.88	77.17	83.35	86.57
70–<80	58.92	67.74	74.74	81.49	85.94	88.16
≥80	61.87	69.66	75.66	80.61	83.81	83.57
CHF						
<40	0.21	0.17	0.17	0.25	0.46	1.05
40–<50	1.50	1.00	0.96	1.28	2.08	4.27
50–<60	3.49	2.73	2.47	3.33	5.23	9.41
60–<70	5.77	4.25	3.74	5.14	8.02	13.04
70–<80	8.29	6.36	5.60	7.75	12.07	17.51
≥80	11.47	9.43	9.02	12.86	16.82	24.60
Cardiovascular disease						
<40	0.17	0.31	0.48	0.63	0.88	1.34
40–<50	2.47	2.73	3.36	4.26	5.13	5.78
50–<60	7.00	7.86	9.54	11.67	13.47	14.02
60–<70	10.82	12.81	14.51	16.68	18.06	18.28
70–<80	13.78	16.29	17.32	18.65	19.00	18.18
≥80	14.79	17.34	18.12	19.24	18.64	15.12

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b: Baseline characteristics in patients grouped according to mutually exclusive categories of baseline age and body mass index

	BMI (kg/m^2)					
	<20 kg/m^2	20–<25 kg/m^2	25–<30 kg/m^2	30–<35 kg/m^2	35–<40 kg/m^2	≥40 kg/m^2
Cerebrovascular disease						
<40	0.70	0.56	0.47	0.52	0.61	0.60
40–<50	2.87	2.19	1.89	1.90	1.99	2.07
50–<60	6.43	5.37	4.63	4.55	4.57	4.14
60–<70	10.65	8.78	7.16	6.67	6.37	5.66
70–<80	13.67	11.40	9.57	8.88	8.32	7.10
≥80	13.85	13.14	12.02	11.43	10.05	9.38
PAD						
<40	0.65	0.55	0.42	0.39	0.41	0.73
40–<50	2.88	1.89	1.49	1.43	1.64	2.09
50–<60	7.50	5.55	4.30	4.21	4.53	5.47
60–<70	12.32	8.54	6.43	6.21	6.74	7.34
70–<80	13.51	9.49	7.86	7.98	8.81	9.52
≥80	11.67	9.79	9.17	9.80	10.33	9.68
Malignancy						
<40	2.11	1.46	1.30	1.26	1.19	1.33
40–<50	7.85	3.88	2.68	2.55	2.44	2.39
50–<60	15.92	9.02	6.69	5.97	5.58	5.13
60–<70	23.10	15.57	12.15	11.11	10.40	9.15
70–<80	25.25	20.25	17.91	16.85	16.22	14.55
≥80	23.61	21.44	20.73	20.11	19.19	18.65
Depression						
<40	13.49	13.77	13.48	14.45	15.93	17.04
40–<50	14.81	16.89	16.76	16.72	17.73	18.47
50–<60	11.14	12.97	12.86	13.20	13.85	14.05
60–<70	6.58	6.16	5.65	5.94	6.69	7.14
70–<80	3.90	3.30	2.97	2.93	3.37	3.92
≥80	3.12	2.76	2.67	2.97	3.03	4.13

b: Baseline characteristics in patients grouped according to mutually exclusive categories of baseline age and body mass index

	BMI (kg/m^2)					
	<20 kg/m^2	20–<25 kg/m^2	25–<30 kg/m^2	30–<35 kg/m^2	35–<40 kg/m^2	≥40 kg/m^2
Liver disease						
<40	0.23	0.25	0.20	0.22	0.22	0.28
40–<50	2.51	2.02	1.54	1.27	1.12	1.06
50–<60	3.60	3.11	2.12	1.77	1.53	1.30
60–<70	2.19	1.47	0.94	0.86	0.85	0.70
70–<80	0.90	0.70	0.53	0.51	0.62	0.52
≥80	0.39	0.32	0.31	0.31	0.47	0.30
Rheumatologic disease						
<40	0.67	0.56	0.53	0.49	0.65	0.53
40–<50	1.30	1.14	1.03	0.93	1.02	1.08
50–<60	1.89	1.45	1.31	1.27	1.27	1.21
60–<70	2.09	1.93	1.53	1.40	1.23	1.27
70–<80	2.54	2.38	1.79	1.53	1.28	1.45
≥80	2.35	2.15	1.82	1.55	1.78	2.12
Lung disease						
<40	7.35	7.22	8.07	9.81	11.30	13.94
40–<50	21.47	14.44	12.09	13.03	15.40	19.04
50–<60	37.22	21.78	15.81	15.92	18.49	22.65
60–<70	50.39	26.75	17.99	17.93	20.88	25.17
70–<80	50.36	26.08	18.54	19.38	22.98	26.62
≥80	39.47	22.73	18.63	21.29	25.05	29.44
HIV						
<40	2.45	1.72	1.05	0.51	0.40	0.29
40–<50	6.45	3.90	1.92	0.88	0.55	0.37
50–<60	3.07	1.94	0.74	0.30	0.18	0.15
60–<70	1.23	0.64	0.20	0.09	0.06	0.05
70–<80	0.33	0.13	0.05	0.02	0.01	0
≥80	0.06	0.02	0.01	0.01	0.02	0