Association between serum creatinine level within the normal range and bone mineral density in adolescents

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Research article

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Abstract

Objective: The circulating level of creatinine is a direct, stable indicator of skeletal muscle mass. However, evidence regarding the correlation between serum creatinine (SCre) and bone health is limited. This study aimed to evaluate the association between SCre level within the normal range and bone mineral density (BMD) in adolescents.

Methods: We analyzed data for 3456 adolescents aged 12-19 years from the National Health and Nutrition Examination Survey 2011-2018. Weighted multiple linear regression was conducted to assess the association between SCre and BMD. Weighted generalised additive models and smooth curve fittings were performed to address the nonlinearity of them.

Results: After controlling for potential confounding factors, we found that higher SCre levels were associated with higher total BMD in adolescents. This association remained positive in the subgroup analyses stratified by age, gender, or race. Furthermore, this positive association was more prominent in boys than in girls in adolescents aged 12-15 years.

Conclusions: These findings indicate that higher SCre levels within the normal range in adolescents aged 12-19 years were associated with higher total BMDs, suggesting that SCre may be a candidate biomarker for bone health in adolescents.

Introduction

Osteoporosis has been recognized as a disease during the aging process, but it is now widely accepted that it begins from childhood and adolescence by lack of bone mineral density (BMD) built during these periods[1]. Bone mass reaches the maximum of 90% at adolescence and slightly increases after this period[2, 3]. Therefore, it is critical to acquire a higher BMD during adolescence and thus prevent osteoporosis and osteoporosis-associated fractures in older age.

To better understand the pathogenesis of osteoporosis, ongoing studies are exploring the associations between bone health and some novel or less studied markers[4]. In clinical practice, creatinine-based estimated glomerular filtration rate is widely used as a measure of renal function[5]. Creatine is a naturally occurring guanidino compound composed of arginine and glycine, with > 90% of total body creatine being stored within skeletal muscle[6]. The irreversible process that creatinine is non-enzymatically converted from creatine results in a turnover of ≈ 1.7% of the total creatine daily[7]. The circulating level of creatinine is a direct, stable indicator of skeletal muscle mass because its generation is proportional to muscle mass[8]. However, evidence regarding the correlation between serum creatinine (SCre) and bone health is limited. A recent general population-based study revealed that low SCre was independently associated with low BMD in participants aged 45–95 years with normal renal function[9]. However, to our knowledge no previous studies have examined the association between SCre and BMD in adolescents. Therefore, we conducted a cross-sectional study of a subsample of 3456 adolescents aged 12–19 years participating in the National Health and Nutrition Examination Survey (NHANES) from 2011

to 2018. In our analysis, we considered and tested potential confounding factors, including age, gender, and race.

Methods

Study population

NHANES is a program of studies that is designed to assess the health and nutrition status of US population. We utilized data from NHANES collected from 2011 to 2018. Based on age, gender, and race, NHANES uses a complex, stratified, multistage probability sampling designed to be representative of the civilian, non-institutionalized US population. The ethics review board of the National Center for Health Statistics (NCHS) approved all NHANES protocols. Participants aged ≥ 18 years provided informed consent, and for participants aged < 18 years, their parents/guardians provided informed consent.

Our sample included adolescents aged 12–19 years with complete data for SCre and total BMD (n = 3749). Additionally, we further excluded 293 subjects whose SCre levels were not within the normal range[10], resulting in 3456 subjects remained for the final analysis (Fig. 1).

Study variables

The concentration of SCre was determined on the Beckman DXC800 analyzer using the Jaffe rate method (kinetic alkaline picrate). According to the laboratory procedure manual, the normal range was 0.3-1.0 mg/dL for adolescents aged 12–15 years, 0.7–1.3 mg/dL for boys aged 16–19 years, and 0.6–1.1 mg/dL for girls aged 16–19 years (we used the International System of Units in this study, and converted mg/dL to umol/L by multiplying by 88.4)[10]. The whole body scans were acquired on the Hologic Discovery model A densitometers, using software version Apex 3.2. To verify the accuracy and consistency of the results, expert review was conducted on 100% of analyzed participant scans[11].

Additionally, we included following covariates: age, gender, race, body mass index (BMI), ratio of family income to poverty, vigorous recreational activities, total cholesterol, total protein, blood urea nitrogen (BUN), serum glycohemoglobin, alkaline phosphatase (ALP), alanine amino transferase (ALT), aspartic acid transferase (AST), gamma-glutamyl transpeptidase (GGT), serum uric acid (sUA), serum phosphorus, and serum calcium were adjusted. Details of the acquisition process of SCre, total BMD and other covariate are available at www.cdc.gov/nchs/nhanes/.

Statistical analysis

To account for the probabilities of selection and response as well as total US population, all estimates were calculated using sampling weights as recommended by NCHS. Weighted multiple regression analysis was conducted to evaluate the independent association between SCre and BMD. Following the STROBE guidelines[12], three weighted multivariate linear regression models were constructed: model 0: not adjusted; model 1: age, gender, race were adjusted; model 2: the covariates presented in Table 1 were

adjusted. Weighted generalised additive models and smooth curve fittings were performed to address the nonlinearity of SCre and BMD. All analyses were done by using EmpowerStats software and R version 3.4.3. $P < 0.05$ was considered statistically significant.

Table 1
Weighted characteristic of study sample.

	Boys (n = 1882)	Girls (n = 1574)	P value
Age (years)	15.36 ± 2.30	15.28 ± 2.21	0.319
Age groups (%)			0.570
12–15 years	53.55	54.52	
16–19 years	46.45	45.48	
Race (%)			0.447
Non-Hispanic White	54.99	56.73	
Non-Hispanic Black	12.83	12.81	
Mexican American	15.65	13.72	
Other Race	16.53	16.74	
Body mass index (kg/m2)	23.61 ± 5.76	24.31 ± 6.06	< 0.001
Ratio of family income to poverty	2.51 ± 1.60	2.47 ± 1.62	0.528
Vigorous recreational activities (%)			< 0.001
Yes	58.79	41.70	
No	24.42	41.23	
Not recorded	16.79	17.07	
Blood urea nitrogen ((mmol/L)	4.30 ± 1.24	3.73 ± 1.06	< 0.001
Total protein (g/L)	72.47 ± 4.12	72.01 ± 4.04	< 0.001
Total cholesterol ((mmol/L)	3.94 ± 0.72	4.12 ± 0.78	< 0.001
Serum glycohemoglobin (%)	5.23 ± 0.34	5.23 ± 0.36	0.860
Alkaline phosphatase (U/L)	174.68 ± 106.68	101.28 ± 62.65	< 0.001
Alanine amino transferase (IU/L)	20.94 ± 13.58	15.89 ± 12.94	< 0.001
Aspartic acid transferase (IU/L)	25.35 ± 13.26	20.82 ± 7.44	< 0.001
Gamma-glutamyl transpeptidase (IU/L)	15.95 ± 9.54	12.32 ± 5.66	< 0.001
Serum uric acid(umol/L)	333.50 ± 68.54	266.81 ± 58.30	< 0.001

Mean ± SD for continuous variables: P value was calculated by weighted linear regression model.

% for categorical variables: P value was calculated by weighted chi-square test.

	Boys (n = 1882)	Girls (n = 1574)	P value
Serum phosphorus (mmol/L)	1.44 ± 0.23	1.35 ± 0.18	< 0.001
Serum calcium (mmol/L)	2.41 ± 0.07	2.38 ± 0.08	< 0.001
Serum creatinine (umol/L)	69.02 ± 15.37	59.23 ± 10.40	< 0.001
Total bone mineral density (g/cm^2)	1.04 ± 0.14	1.02 ± 0.10	< 0.001
Mean ± SD for continuous variables: P value was calculated by weighted linear regression model.			
% for categorical variables: P value was calculated by weighted chi-square test.			

Results

The weighted characteristics of the participants are presented in Table 1. A total of 1882 boys and 1574 girls were included in this study. Among different gender groups, BMI, vigorous recreational activities, BUN, total protein, total cholesterol, ALP, ALT, AST, GGT, sUA, serum phosphorus, serum calcium, SCre, and total BMD were significantly different.

In the weighted multiple regression (Table 2), higher SCre levels were associated with higher total BMDs in each model [model 0: 0.0052 (0.0050, 0.0054); model 1: 0.0036 (0.0033, 0.0039); model 2: 0.0029 (0.0026, 0.0032)].

Table 2

Association between serum creatinine (umol/L) and total bone mineral density (g/cm^2).

	Model 0	Model 1	Model 2
	β (95% CI)	β (95% CI)	β (95% CI)
Serum creatinine	0.0052 (0.0050, 0.0054)	0.0036 (0.0033, 0.0039)	0.0029 (0.0026, 0.0032)
12–15 years			
Boys	0.0057 (0.0052, 0.0061)	0.0043 (0.0038, 0.0048)	0.0037 (0.0032, 0.0043)
Girls	0.0043 (0.0037, 0.0049)	0.0029 (0.0023, 0.0036)	0.0021 (0.0015, 0.0027)
16–19 years			
Boys	0.0027 (0.0021, 0.0033)	0.0023 (0.0017, 0.0029)	0.0020 (0.0014, 0.0026)
Girls	0.0022 (0.0014, 0.0030)	0.0019 (0.0011, 0.0027)	0.0020 (0.0012, 0.0027)
Model 0: no covariates were adjusted.			
Model 1: age, gender, race were adjusted.			
Model 2: age, gender, race, body mass index, ratio of family income to poverty, vigorous recreational activities, blood urea nitrogen, total protein, total cholesterol, serum glycohemoglobin, alkaline phosphatase, alanine amino transferase, aspartic acid transferase, gamma-glutamyl transpeptidase, serum uric acid, serum phosphorus, and serum calcium were adjusted.			

In the subgroup analyses stratified by age and gender (Table 2), the positive association between SCre and total BMD remained in each group after controling for potential confounders [boys aged 12–15 years: 0.0037 (0.0032, 0.0043); girls aged 12–15 years: 0.0021 (0.0015, 0.0027); boys aged 16–19 years: 0.0020 (0.0014, 0.0026); girls aged 16–19 years: 0.0020 (0.0012, 0.0027)].

In the subgroup analyses stratified by age and race (Table 3), this association remained positive in each model of all groups.

Table 3

Associations between serum creatinine (umol/L) and total bone mineral density (g/cm^2), stratified by race.

	Model 0 β (95% CI)	Model 1 β (95% CI)	Model 2 β (95% CI)
12–15 years			
Non-Hispanic White	0.0048 (0.0040, 0.0055)	0.0038 (0.0030, 0.0046)	0.0034 (0.0026, 0.0042)
Non-Hispanic Black	0.0046 (0.0038, 0.0054)	0.0037 (0.0029, 0.0045)	0.0026 (0.0017, 0.0034)
Mexican American	0.0046 (0.0038, 0.0054)	0.0037 (0.0027, 0.0046)	0.0036 (0.0027, 0.0046)
Other Race	0.0047 (0.0041, 0.0054)	0.0037 (0.0031, 0.0044)	0.0028 (0.0021, 0.0035)
16–19 years			
Non-Hispanic White	0.0028 (0.0021, 0.0034)	0.0020 (0.0012, 0.0028)	0.0020 (0.0012, 0.0028)
Non-Hispanic Black	0.0031 (0.0024, 0.0038)	0.0024 (0.0015, 0.0034)	0.0015 (0.0005, 0.0025)
Mexican American	0.0029 (0.0020, 0.0039)	0.0018 (0.0007, 0.0030)	0.0020 (0.0009, 0.0031)
Other Race	0.0035 (0.0027, 0.0043)	0.0030 (0.0019, 0.0040)	0.0025 (0.0015, 0.0036)
Model 0: no covariates were adjusted.			
Model 1: age, gender, were adjusted.			
Model 2: age, gender, body mass index, ratio of family income to poverty, vigorous recreational activities, blood urea nitrogen, total protein, total cholesterol, serum glycohemoglobin, alkaline phosphatase, alanine amino transferase, aspartic acid transferase, gamma-glutamyl transpeptidase, serum uric acid, serum phosphorus, and serum calcium were adjusted.			

The weighted generalised additive models and smooth curve fittings were conducted to characterize the non-linear relationship, and the results further confirmed this positive association (Figs. 2–4).

Discussion

In this nationally representative sample study, we found that SCre level within the normal range was independently associated with total BMD among adolescents aged 12–19 years. Additionally, this association remained positive in each subgroup stratified by age, gender, or race, and was more prominent in boys than in girls in adolescents aged 12–15 years.

Muscle is the largest organ in the body that accounts for 40% of body mass[13]. Muscles grow larger and stronger from birth and start to lose its mass from 25 years of age. The loss in muscle mass and consequently its strength results in sarcopenia[14]. Several evidences suggest that individuals with sarcopenia had lower BMD and a higher risk of osteoporosis[15–17]. SCre concentration may be affected by changes in muscle mass[18]. However, evidence regarding the correlation between SCre and bone health is limited.

To evaluate the correlation of SCre with BMD among older adult with normal renal function, Huh et al.[9] conducted a cross-sectional study using the Fourth Korea NHANES data. Their findings provided the first clinical evidence that low SCre level was independently associated with low BMD. Moreover, their data showed that the positive association between SCre and BMD was more prominent in men than in women. In our study, SCre levels differed by gender. It might be explained by the fact that boys have higher muscle mass than girls. However, after controlling for potential confounding factors, SCre level within the normal range was positively associated with total BMD in adolescents in each subgroup stratified by age, gender, or race. Furthermore, this positive association was more prominent in boys than in girls in adolescents aged 12–15 years. These findings were consistent with the previous study focusing on older adults[9].

It is widely accepted that the increase in peak bone mass achieved during adolescence is effective in preventing osteoporosis and osteoporosis-associated fractures[19]. Creatine has been a popular dietary supplement choice of adolescents, and no study has observed any gastro-intestinal discomforts or changes in markers of clinical health and safety following creatine supplement use periods[20]. Thus, adequate creatine supplementation may be a new strategy for adolescents with low SCre.

By our knowledge, this is the first study that evaluated the association between SCre and BMD in adolescents. Additionally, this nationally representative sample makes our conclusions persuasive and highly relevant to the whole population. However, several weaknesses of our study must be acknowledged. First, due to the cross-sectional nature of NHANES data, it is incapable of indicating the causal association between SCre and BMD. Therefore, a longitudinal follow-up study is required to clarificate the role of creatinine metabolism on bone health. Second, we excluded subjects with abnormal SCre levels, because renal dysfunction may influence BMD[21, 22]. Therefore, our conclusions cannot be used for this special population. Third, other potential confounding factors not included in this study may cause some bias. For example, differences in gender and developmental age during pubertal development is a potential confounding factor in the present study. Hence, we conducted subgroup analyses stratified by age and gender to confirm the results.

In conclusion, our findings indicate that higher SCre levels within the normal range in adolescents aged 12–19 years were associated with higher total BMDs, suggesting that SCre may be a candidate biomarker for bone health in adolescents. It is our hope that this study will stimulate future multidisciplinary research on the effect of creatine and creatinine metabolism on bone health in adolescents.

Declarations

Author contributions

KYP, and HYY contributed to data collection, analysis and writing of the manuscript. ZXZ contributed to study design and editing of the manuscript.

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Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Ethical Statement

The ethics review board of the National Center for Health Statistics approved all NHANES protocols. For participants aged < 18 years, their parents/guardians provided informed consent, and participants aged ≥18 years provided informed consent on their own.

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Figures

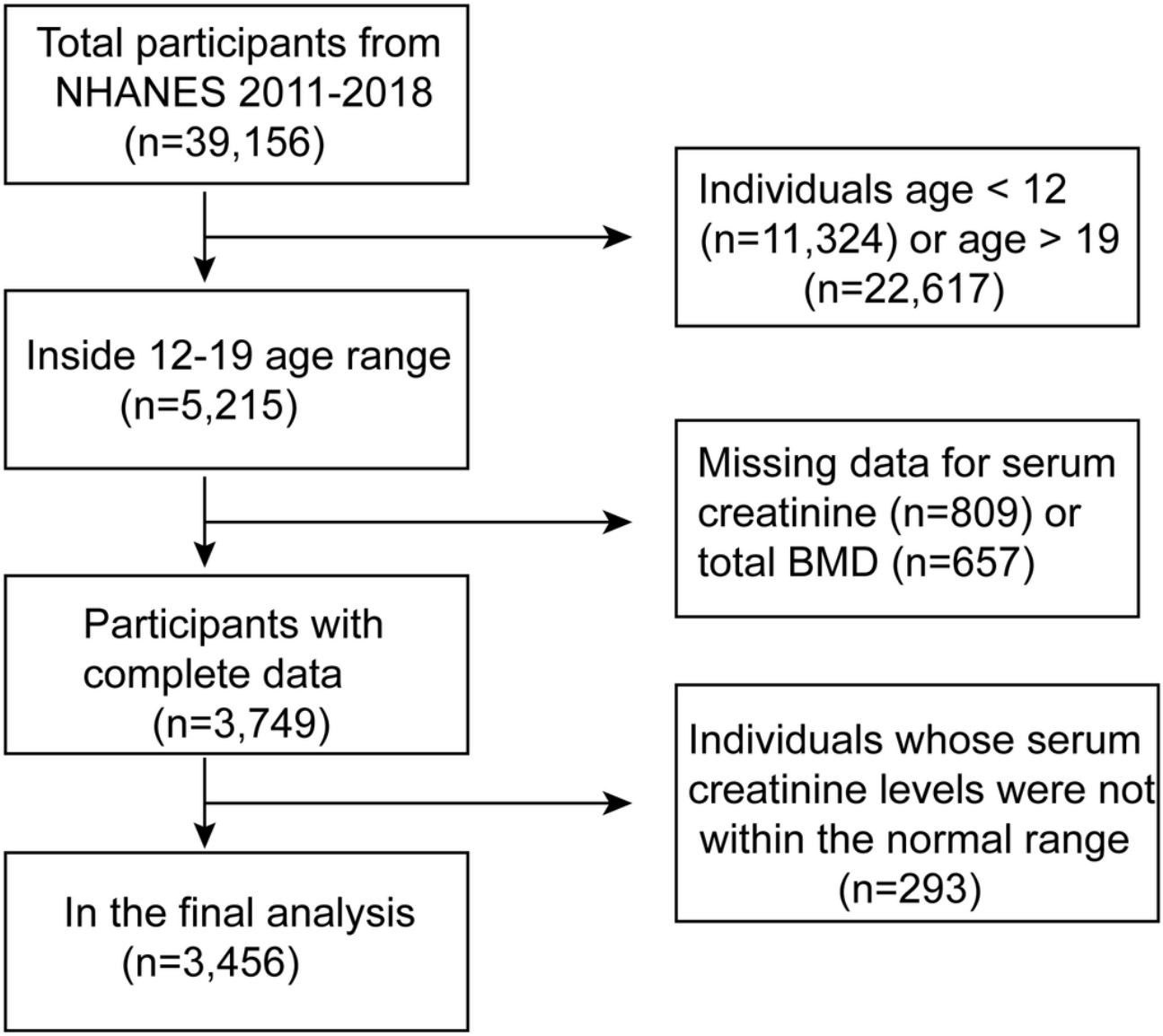

Figure 1

The flow chart of the participants.

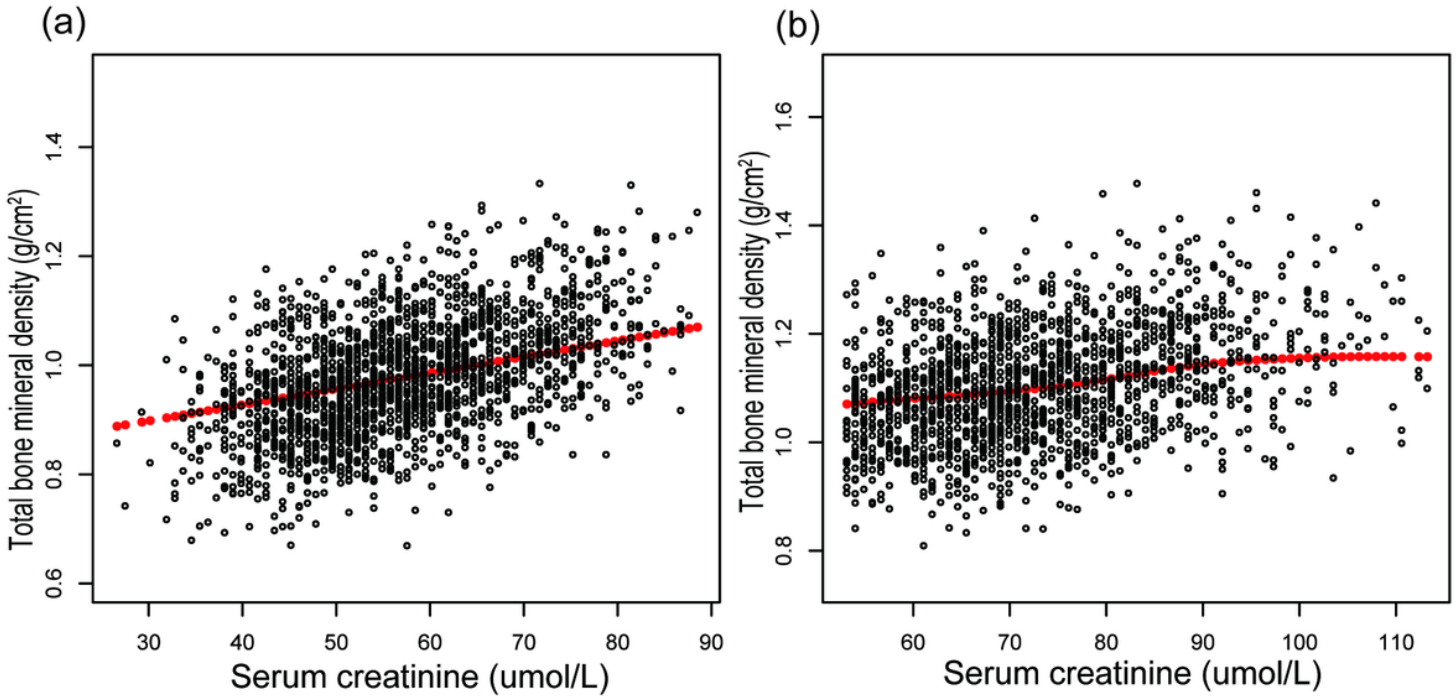

Figure 2

Association between serum creatinine and total bone mineral density. (a) 12-15 years (b)16-19 years Circles represent individual data points. Sample weighted regressions were adjusted for age, gender, race, body mass index, ratio of family income to poverty, vigorous recreational activities, blood urea nitrogen, total protein, total cholesterol, serum glycohemoglobin, alkaline phosphatase, alanine amino transferase, aspartic acid transferase, gamma-glutamyl transpeptidase, serum uric acid, serum phosphorus, and serum calcium.

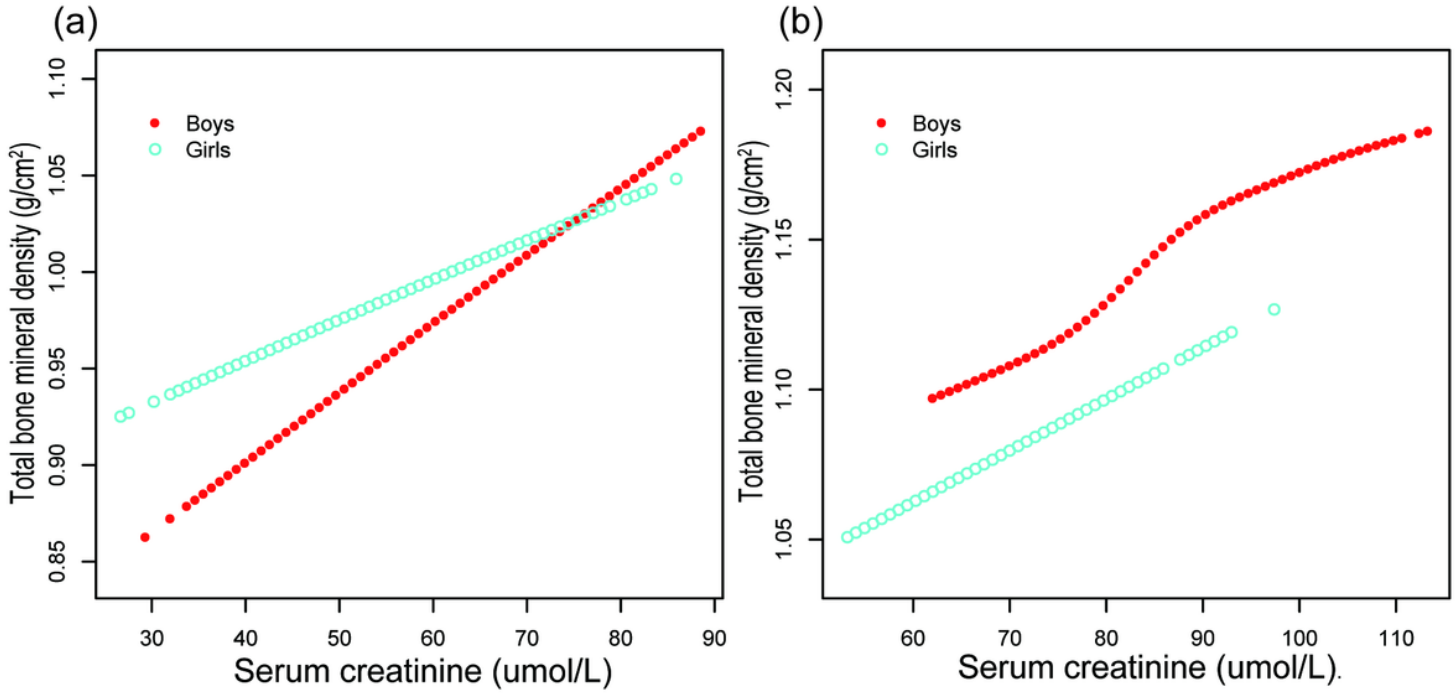

Figure 3

Association between serum creatinine and total bone mineral density, stratified by gender. (a) 12-15 years (b)16-19 years Sample weighted regressions were adjusted for age, race, body mass index, ratio of family income to poverty, vigorous recreational activities, blood urea nitrogen, total protein, total cholesterol, serum glycohemoglobin, alkaline phosphatase, alanine amino transferase, aspartic acid transferase, gamma-glutamyl transpeptidase, serum uric acid, serum phosphorus, and serum calcium.

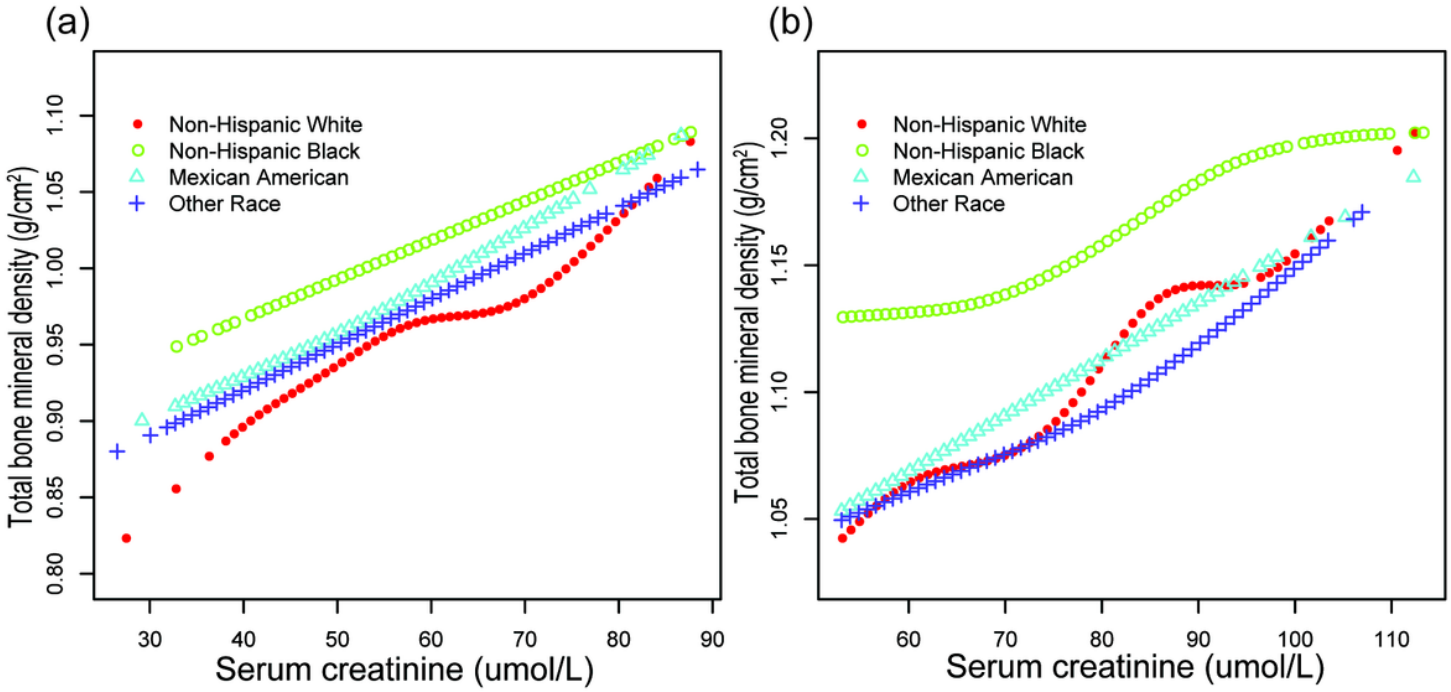

Figure 4

Association between serum creatinine and total bone mineral density, stratified by race. (a) 12-15 years (b)16-19 years Sample weighted regressions were adjusted for age, gender, body mass index, ratio of family income to poverty, vigorous recreational activities, blood urea nitrogen, total protein, total cholesterol, serum glycohemoglobin, alkaline phosphatase, alanine amino transferase, aspartic acid transferase, gamma-glutamyl transpeptidase, serum uric acid, serum phosphorus, and serum calcium.