Low Socioeconomic Status Associates with Higher Serum Phosphate Irrespective of Race

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ABSTRACT

Hyperphosphatemia, which associates with adverse outcomes in CKD, is more common among blacks than whites for unclear reasons. Low socioeconomic status may explain this association because poverty both disproportionately affects racial and ethnic minorities and promotes excess intake of relatively inexpensive processed and fast foods enriched with highly absorbable phosphorus additives. We performed a cross-sectional analysis of race, socioeconomic status, and serum phosphate among 2879 participants in the Chronic Renal Insufficiency Cohort Study. Participants with the lowest incomes or who were unemployed had higher serum phosphate concentrations than participants with the highest incomes or who were employed ($P < 0.001$). Although we also observed differences in serum phosphate levels by race, income modified this relationship: Blacks had 0.11 to 0.13 mg/dl higher serum phosphate than whites in the highest income groups but there was no difference by race in the lowest income group. In addition, compared with whites with the highest income, both blacks and whites with the lowest incomes had more than twice the likelihood of hyperphosphatemia in multivariable-adjusted analysis. In conclusion, low socioeconomic status associates with higher serum phosphate concentrations irrespective of race. Given the association between higher levels of serum phosphate and cardiovascular disease, further studies will need to determine whether excess serum phosphate may explain disparities in kidney disease outcomes among minority populations and the poor.

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Racial disparities in kidney disease outcomes are among the most glaring inequities in the United States health care system.[1–5] Despite a similar prevalence of early-stage chronic kidney disease (CKD), blacks are up to 4 times more likely to progress to ESRD than whites.[1–4] In addition, compared with whites, blacks have higher rates of cardiovascular disease and mortality in early CKD.[6,7] Although these differences have largely been attributed to socioeconomic inequalities leading to inadequate access to medical care among minority populations,[5,8] increasing evidence suggests that biologic factors, such as disorders of mineral metabolism, also contribute to racial disparities in CKD outcomes.[9,10]

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Increased serum phosphate is associated with cardiovascular disease, kidney disease progression, and death.[11–15] Although the mechanisms for these relationships are unclear, experimental data showing that excess phosphate promotes vascular calcification, endothelial dysfunction, and renal injury suggest a causal link between an elevated serum phosphate and adverse health outcomes.[16–19] Large cohort studies have shown that hyperphosphatemia is more common and more severe in blacks than in whites, both among patients with CKD and among individuals with normal kidney function.[20–22] Given the emerging connections between increased serum phosphate and accelerated cardiovascular and kidney disease progression, understanding the mechanisms underlying the excess prevalence of hyperphosphatemia among blacks may elucidate novel approaches for reducing racial disparities in CKD outcomes.

Racial and ethnic minorities disproportionately reside in low-income neighborhoods that have limited access to healthy food choices, resulting in the overconsumption of inexpensive processed and fast foods that are rich in highly absorbable phosphorus additives.[23–27] High intake of these foods has been associated with increased serum phosphate in CKD,[25] and dietary counseling aimed at reducing the consumption of these foods lowered serum phosphate in hemodialysis patients.[28] Furthermore, increasing poverty was independently associated with higher serum phosphate levels and greater likelihood of hyperphosphatemia in a cohort of over 14,000 adults with largely preserved kidney function in the Third National Health and Nutrition Examination Survey.[29] Collectively, these observations suggest that lower socioeconomic status may contribute to elevated serum phosphate concentrations by promoting excess dietary phosphorus intake. Whether this accounts for higher serum phosphate concentrations among blacks compared with whites with CKD is unclear. We examined the associations between race, socioeconomic status, and serum phosphate concentrations among participants in the Chronic Renal Insufficiency Cohort (CRIC) Study.

Table 1. Demographic, clinical, and laboratory characteristics of CRIC study participants stratified by race

	Black (n = 1347)	White (n = 1532)	P
Age	58 ± 11	59 ± 11	0.21
Female gender (%)	51	40	<0.001
eGFR (ml/min per 1.73 m^2)	43 ± 14	43 ± 13	0.67
Body mass index (kg/m^2)	34 ± 8	31 ± 7	<0.001
Diabetes (%)	52	42	<0.001
Medications (%)			
phosphorus binders	11	14	0.02
activated vitamin D	4	2	0.03
Annual income (%)			<0.001
≤$20,000	48	21	
$20,001 to $50,000	31	29	
>$50,000	21	50	
Educational attainment (%)			<0.001
less than high school degree	25	8	
high school graduate	21	18	
greater than high school degree	54	74	
Employment status (%)			<0.001
employed	29	48	
unemployed[a]	33	15	
retired	34	32	
other[b]	4	5	
Laboratory values			
creatinine (mg/dl)	1.9 ± 0.6	1.6 ± 0.5	<0.001
albumin (g/dl)	3.9 ± 0.5	4.0 ± 0.4	<0.001
calcium (mg/dl)	9.2 ± 0.5	9.2 ± 0.5	0.84
parathyroid hormone (pg/ml)	67 (41, 115)	45 (31, 72)	<0.001

Results are presented as mean ± SD, median (interquartile range), or frequencies.
[a]Includes medically disabled.
[b]Includes homemakers and students.

RESULTS

Population Characteristics

Table 1 depicts the demographic, clinical, and laboratory characteristics of participants according to race. Compared with whites, blacks had higher body mass index and were more likely to be women and diabetic. In addition, blacks were more likely to be unemployed and have lower annual family income and lower educational achievement than whites.

Table 2 depicts estimates of dietary characteristics of participants in whom complete dietary data were available, stratified by race. Although there were significant racial differences in total energy, protein, calcium, and phosphorus intake, the absolute differences were small. Of note, blacks had lower estimated dietary phosphorus intake than whites. Table 3 depicts dietary characteristics stratified by annual family income. There were no significant differences in total caloric intake or phosphorus intake across strata of income.

Serum Phosphate and Race

In the crude analysis, black race was associated with 0.16 mg/dl higher serum phosphate concentrations than white race ($P < 0.001$). After adjustment for age, gender, estimated GFR (eGFR), diabetes, hemoglobin A1c, and activated vitamin D and phosphorus binder use, serum phosphate remained 0.10 mg/dl higher in blacks than in whites ($P < 0.001$). Adjusting for parathyroid hormone (PTH) concentrations did not

Table 2. Diet characteristics of study participants with complete data (n = 2279) stratified by race

	Black (n = 975)	White (n = 1304)	P
Total caloric intake (kcal/d)	1866 ± 896	1813 ± 761	0.14
% from carbohydrates (mean)	53 ± 11	48 ± 10	<0.001
% from protein (mean)	15 ± 4	16 ± 4	<0.001
Carbohydrates (g/d)	213 (152, 309)	199 (147, 270)	<0.001
Protein (g/d)	59 (41, 85)	66 (49, 91)	<0.001
Calcium (mg/d)	566 (392, 826)	648 (456, 912)	<0.001
Phosphorus (mg/d)	1095 ± 543	1196 ± 530	<0.001

Results are presented as mean ± SD or median (interquartile range).

change the results. Further adjustment for dietary phosphorus intake in the subset of participants with available dietary data did not substantially affect the magnitude or strength of the relationship (0.09 mg/dl higher serum phosphate in blacks than in whites, $P < 0.001$). Although blacks had 30% higher odds of hyperphosphatemia than whites (odds ratio [OR] 1.3, 95% confidence interval [CI] 1.05, 1.7), this association was attenuated after multivariable adjustment (OR 1.1, 95% CI 0.9, 1.5).

Serum Phosphate and Socioeconomic Status

In the overall study sample, mean serum phosphate concentrations significantly increased with decreasing levels of annual income (>$50,000, reference; $20,001 to 50,000, 0.14 mg/dl higher serum phosphate concentrations; ≤$20,000, 0.28 mg/dl higher, P for trend <0.001). The monotonic association between decreasing income and increasing serum phosphate remained significant after adjustment for age, gender, eGFR, diabetes, hemoglobin A1c, and phosphorus binder and vitamin D use (P for trend <0.001). Further adjustment for fasting status, timing of blood collection, or dietary phosphorus intake did not alter these relationships. Compared with employed participants, serum phosphate concentrations were 0.23 mg/dl higher in unemployed participants in unadjusted analysis ($P < 0.001$) and 0.07 mg/dl higher in multivariable analyses adjusted for age, gender, race, diabetes, and eGFR ($P = 0.02$). Lower educational attainment was similarly associated with increased serum phosphate in unadjusted ($P < 0.001$) but not in multivariable-adjusted analyses ($P = 0.07$).

Lower levels of family income were strongly associated with increasing odds of hyperphosphatemia (>$50,000, reference; $20,001 to 50,000, OR 1.9, 95% CI 1.3, 2.7; ≤$20,000, OR 3.6, 95% CI 2.6, 5.1). After multivariable adjustment, odds of hyperphosphatemia remained twofold higher among participants in the lowest income level as compared with participants in the highest income level (OR 2.1, 95% CI 1.5, 3.0). Similarly, odds of hyperphosphatemia were significantly higher in unemployed *versus* employed participants in unadjusted (OR 3.0, 95% CI 2.1, 4.1) and multivariable-adjusted analyses (OR 1.9, 95% CI 1.4, 2.8).

Effect of Socioeconomic Status on the Relationship between Race and Phosphate

The effect of race on serum phosphate concentrations was modified by income level (P for interaction =0.01). As depicted in Figure 1, mean serum phosphate concentrations were significantly higher in blacks than in whites in the two highest levels of income. In contrast, with the focus exclusively on the lowest level of income (≤$20,000 per year), there were no racial differences in serum phosphate. After multivariable adjustment, serum phosphate was 0.11 mg/dl higher in blacks than in whites among participants earning $20,001 to 50,000 per year ($P = 0.007$) and 0.13 mg/dl higher in blacks than in whites among participants earning >$50,000 per year ($P < 0.001$), whereas there remained no racial difference in serum phosphate in the lowest income group.

Figure 2 depicts odds ratio of hyperphosphatemia in logistic regression models stratified by race and income. The prevalence of hyperphosphatemia significantly increased with decreasing income tertiles in both black and whites (P for trend <0.001 for both). Compared with white participants in the highest income group, black and white participants in the lowest income group had significantly higher odds of hyperphosphatemia in both unadjusted and multivariable-adjusted analyses.

Table 3. Dietary characteristics of study participants with complete data (n = 2279) stratified by income level

	≤$20,000	$20,001 to $50,000	>$50,000	P
N	711	678	890	
Total caloric intake (kcal/d)	1894 ± 895	1781 ± 834	1830 ± 745	0.13
% from carbohydrates (mean)	53 ± 11	51 ± 10	48 ± 9	<0.001
% from protein (mean)	15 ± 4	15 ± 4	16 ± 4	<0.001
Carbohydrates (g/d)	218 (153, 320)	197 (146, 271)	199 (151, 270)	<0.001
Protein (g/d)	62 (42, 91)	59 (42, 83)	68 (51, 91)	<0.001
Calcium (mg/d)	605 (411, 920)	585 (404, 817)	638 (457, 874)	0.01
Phosphorus (mg/d)	1156 ± 573	1099 ± 516	1190 ± 522	0.20

Results are presented as mean ± SD or median (interquartile range).

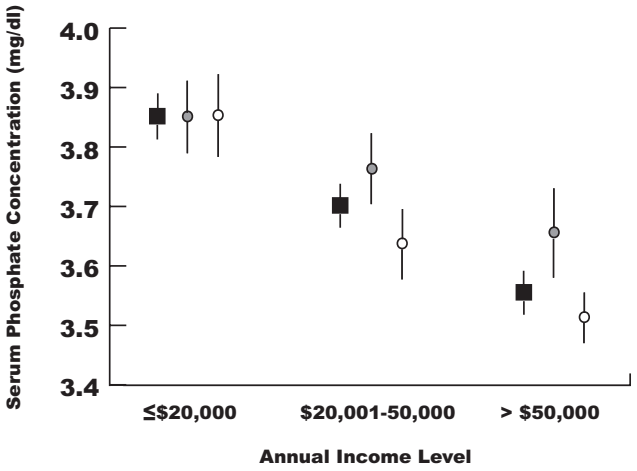

Figure 1. Relationship between race and serum phosphate is modified by income. Black boxes represent mean values for the overall sample within each stratum of income, filled circles represent mean values for blacks, and open circles represent mean values for whites. Vertical lines represent SD.

The effect of race on serum phosphate was similarly modified by education level (P for interaction = 0.01)—whereas blacks had significantly higher serum phosphate than whites in the highest education group in both unadjusted (by 0.17 mg/dl, $P < 0.001$) and multivariable-adjusted analyses (by 0.13 mg/dl, $P < 0.001$), there were no differences in serum phosphate by race among participants who had a high school education or lower.

DISCUSSION

Lower socioeconomic status was independently associated with higher serum phosphate concentrations and higher likelihood of hyperphosphatemia among a diverse cohort of individuals participating in the CRIC Study. Although small differences in serum phosphate concentrations were also noted by race, this relationship was modified by income, such that blacks had higher serum phosphate levels than whites in the two highest strata of income, but among the lowest income participants, there were no differences in serum phosphate by race. In addition, both blacks and whites with the lowest income had more than twice the likelihood of hyperphosphatemia compared with whites with the highest income. Although previous studies have consistently demonstrated higher serum phosphate levels among blacks compared with whites, these results suggest that socioeconomic disparities play a predominant role in explaining these differences. Perhaps more importantly, these data suggest that low socioeconomic status is a novel risk factor for increased serum phosphate concentrations in CKD irrespective of race.

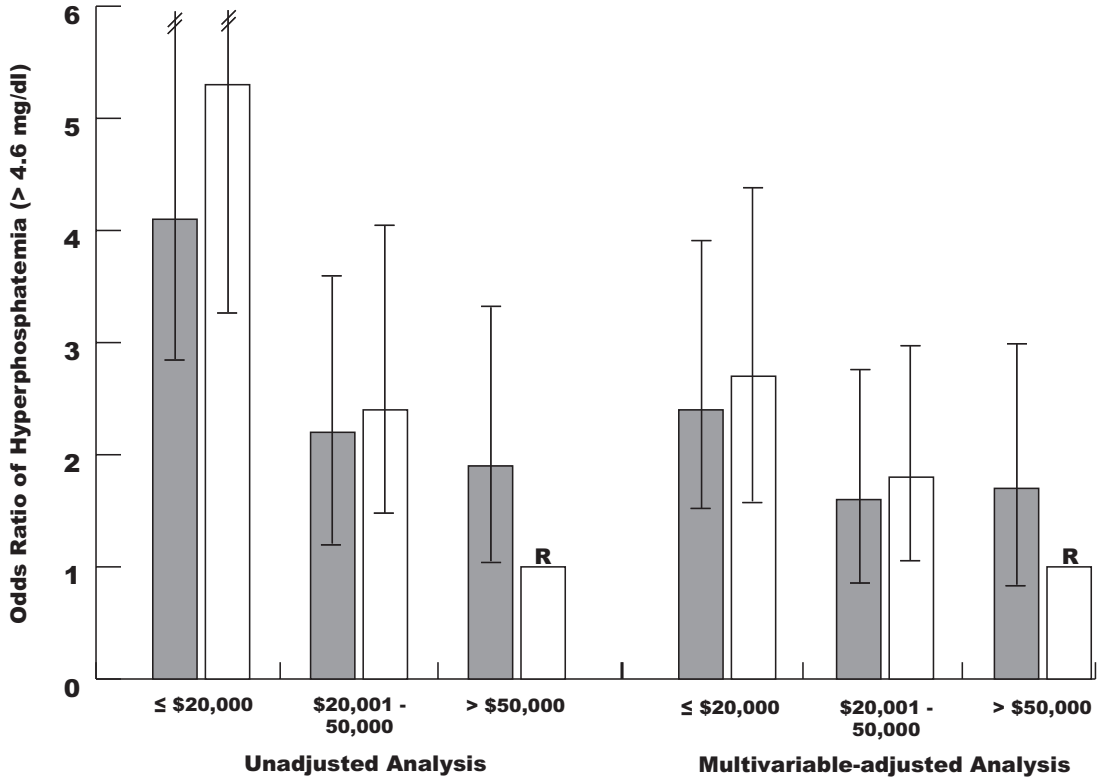

Figure 2. Odds of hyperphosphatemia (>4.6 mg/dl) increase in blacks and whites with decreasing income. Filled bars represent blacks and open bars represent whites. Vertical lines represent 95% confidence intervals. Whites in the highest income level are the referent group in both models. The multivariable model was adjusted for age, gender, diabetes, eGFR, and activated vitamin D and phosphorus binder use.

Poverty has been linked with a number of chronic disease conditions, including CKD. The prevalence of CKD among impoverished individuals is disproportionately high and steadily rising,[30] and incidence rates of ESRD in the United States are inversely correlated with socioeconomic status.[30] Although these associations are largely attributable to known associations between poverty and established CKD risk factors, such as diabetes, hypertension, and smoking, the results of this study suggest that an elevated serum phosphate may be an additional mechanism linking poverty and poor outcomes related to CKD. Despite the relatively small absolute differences in serum phosphate by strata of socioeconomic status in this study, prior studies have reported an elevated risk of adverse renal and cardiovascular outcomes in association with differences in serum phosphate as small as 0.3 mg/dl.[12–15,31,32] More importantly, the high odds ratios for overt hyperphosphatemia that we observed in low-income and unemployed groups support the clinical relevance of these findings. Thus, it is intriguing to speculate whether, in addition to addressing known risk factors for CKD, interventions aimed at treating or preventing elevated serum phosphate levels may improve CKD outcomes among the very poor.

It is unclear why participants with the lowest socioeconomic status had the highest serum phosphate concentrations and the greatest likelihood of hyperphosphatemia. However, given the very low probability that higher serum phosphate levels among lower income participants could be explained by biologic differences in phosphorus metabolism that are somehow intrinsic to being poor, cultural or environmental factors likely play a predominant role. For example, excess dietary phosphorus intake among less affluent participants could explain these findings. Although the lack of differences in estimated phosphorus intake across income levels would be inconsistent with this hypothesis, it is likely that there was incomplete ascertainment of total phosphorus intake by the Dietary History Questionnaire (DHQ), which does not fully account for phosphorus additives in inexpensive convenience and fast foods disproportionately consumed by low-income individuals.[23,24] Such additives are rarely captured by food frequency questionnaires because manufacturers are not required to quantify their amount in product labels.[33–36] As a result, calculated phosphorus intake may underestimate actual intake by as much as 1000 mg/d.[36] Moreover, additive-based phosphorus is more readily absorbed in the gastrointestinal tract than organified phosphorus in meats and dairy, or plant-based phosphorus such as in phytate-rich foods.[36] Thus, it is possible that participants in lower income strata preferentially consumed foods with highly absorbable and largely unaccounted phosphorus additives, explaining their higher likelihood of hyperphosphatemia compared with more affluent participants despite no differences in estimated phosphorus intake by income level. In support of this hypothesis are previous studies that have shown that diets rich in additive-containing foods increase serum phosphate levels;[37] greater fast food consumption is associated with higher serum phosphate despite negligible effects on estimated phosphorus intake;[25] and reduction in the consumption of these foods can significantly reduce serum phosphate.[28]

The lack of a racial difference in serum phosphate among participants with the lowest income is particularly intriguing. One possible explanation for this finding may be that whereas there are biologic differences in phosphate metabolism—such as lower fibroblast growth factor 23 levels among blacks[38]—or cultural food preferences that predispose blacks to a higher serum phosphate than whites as we observed in the upper two tertiles of income, these differences may be nullified by severe socioeconomic disadvantages such as poor nutrition. Indeed, when compared with whites with the highest income, blacks and whites with the lowest income had virtually equivalent serum phosphate and elevated odds of hyperphosphatemia, although blacks had lower use of oral phosphorus binders and higher use of activated vitamin D. Moreover, low income and unemployment were independently associated with hyperphosphatemia, whereas the association between race and hyperphosphatemia was mitigated after multivariable adjustment. Collectively, these findings suggest that low socioeconomic status is a more robust risk factor for elevated serum phosphate than race.

A number of limitations of this study deserve mention. The cross-sectional design precludes us from drawing definitive conclusions with respect to potential mechanisms that may underlie the association between lower socioeconomic status and higher serum phosphate. Furthermore, we did not have indices of gut phosphorus absorption or urinary phosphate excretion which could be used to estimate net phosphorus absorption, allowing us to draw stronger inferences about a link between "hidden" dietary phosphorus sources and hyperphosphatemia. In addition, the magnitude of the difference in serum phosphate by race was relatively small, and thus, although statistically significant, may have limited clinical significance, especially in light of the more robust association between low socioeconomic status and hyperphosphatemia. Furthermore, as with any observational study, residual confounding from unmeasured factors may have affected the results, particularly with respect to the small differences in serum phosphate by race. Missing dietary data in 21% of the study sample is an additional limitation. However, it is unlikely that this substantially affected the main findings since adjusting for dietary phosphorus intake had virtually no effect on the main results in the large sample of participants with available dietary data. Moreover, if unaccounted additive intake was indeed a mechanism for these results, then having full dietary data would likely not have made a significant difference because additive intake is not accurately captured by conventional food frequency questionnaires.[35,36]

The proportion of the U.S. population living in severe poverty has grown alarmingly over the past decade,[39] particularly in the wake of the recent severe economic recession. Impoverished individuals are at a disproportionately high risk of kidney disease, especially among racial or ethnic minorities,[30] and the widespread lack of health insurance among poor individuals in

the United States[40] makes it likely that this disparity will only grow in the foreseeable future. As a result, the findings of this study may have important implications for efforts to stem the rising prevalence of kidney disease and one of its major complications, hyperphosphatemia, among minorities and the very poor. Novel nutritional assessment instruments specifically designed to more accurately capture true dietary phosphorus intake are urgently needed to support detailed physiologic and population-based studies that explore whether excess intake of phosphorus additives explains the link between poverty and hyperphosphatemia that we observed, and if so, whether nutritional interventions proven to reduce the consumption of additive-rich foods[28] may improve CKD outcomes among minority populations and the very poor.

CONCISE METHODS

Study Population

The CRIC Study is a prospective cohort of patients with mild to moderate kidney disease that was established by the National Institute of Diabetes and Digestive and Kidney Diseases to examine risk factors for kidney and cardiovascular disease progression in CKD.[41,42] A total of 3612 participants aged 21 to 74 years were initially enrolled from seven clinical centers throughout the United States (Ann Arbor, MI; Baltimore, MD; Chicago, IL; Cleveland, OH; New Orleans, LA; Philadelphia, PA; and Oakland, CA). All participants completed a baseline visit, during which socioeconomic characteristics, medical history, diet history, current medications, and anthropomorphic measurements were recorded. In addition, plasma and urine samples were collected for measurement of study variables. Protocols to recruit and study CRIC participants were approved by the local institutional review board at each of the clinical centers, and all participants provided written, informed consent.

Demographic, Clinical, and Socioeconomic Variables

The CRIC Study was designed to include a racially and ethnically diverse group of patients; thus, blacks were deliberately oversampled during the recruitment process. Participants were asked to classify their race as black ($n = 1658$), white ($n = 1767$), or other ($n = 187$). Given that the analysis was primarily focused on examining differences in serum phosphate in blacks compared with that in whites, participants identified as "other race" were excluded. Diabetes was defined as having an established medical history of diabetes, current or previous use of diabetes medications, or documented laboratory evidence of diabetes (*i.e.*, two episodes of a random plasma glucose >200 mg/dl in conjunction with classic symptoms or a fasting plasma glucose level >126 mg/dl). Annual household income, highest level of education achieved, and employment status were the primary indices of socioeconomic status. Annual income was categorized as $\leq$\$20,000 per year, \$20,001 to \$50,000, or $>$\$50,000; the 546 participants (19% of blacks and 13% of whites) who did not provide their income were excluded from the analysis. Educational attainment was categorized as less than a high school education, high school graduate, or more than a high school education. Employment status was categorized as employed, unemployed (including medically disabled), retired, or other. There were no differences in the characteristics of the 733 excluded participants as compared with the 2879 participants in the final study sample.

Laboratory and Dietary Characteristics

Phosphate, albumin, calcium, creatinine, and hemoglobin A1c levels were measured in a centralized laboratory at the University of Pennsylvania using standard biochemical assays. PTH concentrations were measured using an intact assay (Scantibodies, Santee, CA). Estimated GFR was calculated using the four-variable Modification of Diet in Renal Disease equation [43] after calibrating serum creatinine measurements to Cleveland Clinic Foundation reference values.

Diet was assessed using the National Cancer Institute's Diet History Questionnaire (DHQ). The DHQ is a food frequency questionnaire designed to assess usual dietary intake by recording the frequency of consumption and portion size eaten for 124 food items over the year preceding the baseline visit. The foods listed in the DHQ are based on national dietary intake data from the 1994 through 1996 U.S. Department of Agriculture's Continuing Survey of Food Intake in Individuals. After being manually reviewed for completeness, DHQs were analyzed for daily nutrient intake using the National Cancer Institute's DietCalc software. Six hundred (21%) of the 2879 participants eligible for this study did not complete dietary questionnaires or had questionnaires excluded because of extreme values for total energy intake (*i.e.*, <600 kcal or >4000 kcal for women and <800 kcal or >5000 kcal for men), leaving 2279 participants available for the analyses of dietary data.

Statistical Analyses

Participant characteristics at the time of entry into the CRIC Study were compared across categories of race and income using *t* tests, Wilcoxon rank-sum tests, one-way ANOVA or Kruskal-Wallis tests for continuous variables, and Pearson χ^2 tests for categorical variables. Serum phosphate was analyzed as a continuous variable and dichotomized by presence (>4.6 mg/dl) or absence (≤ 4.6) of hyperphosphatemia. eGFR was analyzed as a continuous variable and categorized by level of kidney function (*i.e.*, >60 ml/min per 1.73 m^2, 45 to 60, 30 to 44, <30).[44]

Linear regression models were fit to examine the association between race and serum phosphate concentrations. Multivariable analyses were used to adjust for potential confounders, including age, gender, eGFR, diabetes, hemoglobin A1c, and vitamin D and phosphorus binder use.[20,22] Further adjustment for PTH was performed to examine whether differences in serum phosphate may be accentuated when accounting for racial differences in PTH concentrations.[22] In addition, adjustment for dietary phosphorus intake was performed in the subset of 2279 patients with available dietary data. Because serum phosphate concentrations vary diurnally and by fasting status,[20] we further adjusted for timing of blood collection and fasting status in the multivariable models. Logistic regression models were fit to examine the relationship between race and odds of hyperphosphatemia, adjusted for the same covariates. The relationships between socioeconomic indices and serum phosphate were examined in linear and logistic regression models using a similar analytical approach. In ad-

dition, we examined whether the effect of race on serum phosphate concentrations was modified by socioeconomic factors by testing the significance of interaction terms (race × income level, race × education level, and race × employment status). When interactions were detected ($P < 0.05$), we analyzed stratified models. Two-tailed P values <0.05 were considered statistically significant in all analyses. SAS version 9.1 statistical software (SAS Institute, Cary, NC) was used to conduct all analyses.

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DISCLOSURES

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