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Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease

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Abstract

Background. Elevations in serum phosphorus are associated with renal decline in animal models and progression of established chronic kidney disease (CKD) in human observational studies. We examined whether serum phosphorus levels increase the risk of incident CKD or end-stage renal disease (ESRD) in two population-based prospective cohort studies.

Methods. Overall, 2269 participants free of CKD [estimated glomerular filtration rate (eGFR) <60 mL/min/1.73^2] from the Framingham Heart Study (FHS; mean age 42 years; 53% women) and 13 372 participants from the Third National Health and Nutrition Examination Survey (NHANES III; mean age 44.3 years, 52% women) contributed to the present study. In the FHS, we evaluated the relationship between baseline phosphorus category (<2.5 mg/dL, 2.5–3.49 mg/dL, 3.5–3.99 mg/dL and ≥4 mg/dL) and incident CKD ($n = 267$). In NHANES, we examined the relationship between phosphorus below and above 4 mg/dL in relation to incident ESRD ($n = 65$).

Results. FHS participants in the highest phosphorus category had an increased risk of CKD [odds ratio 2.14; 95% confidence interval (CI), 1.07–4.28; P = 0.03] in multivariable-adjusted models when compared to the referent group (2.5–3.49 mg/dL). Similarly, NHANES III participants with phosphorus levels ≥4 mg/dL demonstrated an increased risk of incident ESRD compared to those <4 mg/dL (relative risk 1.90; 95% CI 1.03–3.53; P = 0.04).

Conclusions. In prospective studies of the general population, serum phosphorus levels in the upper-normal range were associated with a doubling in the risk of developing incident CKD and ESRD.

Keywords: CKD; ESRD; phosphorus

Introduction

Chronic kidney disease (CKD) is a major worldwide health problem associated with substantial morbidity, including hypertension, metabolic abnormalities [1], anemia [2], bone disease [3], cardiovascular disease (CVD), stroke [4], end-stage renal disease (ESRD) and death [5]. ESRD carries substantial economic burden, with a cost of $24 billion per year in the USA, a figure that is increasing annually [6]. Despite this, our understanding of the causes of kidney disease is limited.

In animal models of CKD, serum phosphorus concentration is directly associated with renal structural changes and functional decline [7]. In humans, hyperphosphatemia is associated with rapid progression of established CKD [8–10] and the development of ESRD [8, 10]. Hyperphosphatemia as observed in advanced kidney disease [11] or tumoral calcinosis [12] is associated with accelerated vascular calcification and the development of arteriosclerosis in humans.

In light of these observations, we sought to determine whether serum phosphorus is associated with incident CKD in the Offspring cohort of the Framingham Heart Study (FHS). In a complementary analysis, we further assessed whether serum phosphorus is associated with incident ESRD in the Third National Health and Nutrition Examination Survey (NHANES III), a nationally representative study in the USA.

Materials and methods

FHS sample

The design of the Framingham Offspring Study is detailed elsewhere [13]. For the present analysis, participants who had serum phosphorus measured at the second examination cycle (1978–81), who also attended the eighth

exam cycle (2005–08), were included. Overall, 2275 participants attended both examinations and also had serum creatinine measured at baseline and follow-up and 6 were excluded due to missing covariates, resulting in a final study sample of 2269 for the analysis. The median follow-up was 25.1 years. All participants provided written informed consent, and the institutional review board of the Boston Medical Center, Boston, Massachusetts approved the study.

National Health and Nutrition Examination Survey

A full description of NHANES III is available elsewhere [14]. Briefly, NHANES III was a national probability sample of US non-institutionalized civilians conducted between 1988 and 1994. Analyses were restricted to adults ≥18 years of age who underwent a baseline physical examination and laboratory testing, had vital status information available at follow-up and available linkage to Medicare and Medicaid files ($n = 13\ 372$). The median follow-up of participants included in the present analysis was 9.1 years. NHANES III was approved by the institutional review board of the National Center for Health Statistics and each participant signed an informed consent. The institutional review board at the Albert Einstein College of Medicine determined the current NHANES analysis to be exempt.

Assessment of serum phosphorus level

Fasting serum phosphate levels were drawn at the baseline visit in FHS. In NHANES, a random subset of approximately one-third of participants was assigned to fast overnight prior to their study visit. The remaining approximately two-thirds of the sample did not fast. In the FHS, serum phosphorus was measured using a standard colorimetric method (Roche Diagnostics, Alameda, CA), and the intra-assay coefficient of variation was 5.6%. In NHANES III, serum phosphorus was measured using a Hitachi model 737 multichannel analyzer (Boehringer Mannheim Diagnostics, Indianapolis, IN). The coefficient of variation was 1.8–2.8%.

Measurement of risk factors in FHS

In FHS, participants underwent examinations approximately every 4 years. Each examination visit comprised a detailed medical history, physical examination including blood pressure (BP) measurements, anthropometry and laboratory assessment of risk factors. Two BP measurements were taken using a mercury sphygmomanometer after 5 min of rest, and the average was used in the analyses. Hypertension was defined as systolic BP ≥ 140 mm Hg, diastolic BP ≥ 90 mm Hg and/or use of antihypertensive medications. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters. Persons who reported having smoked cigarettes during the previous year were classified as current smokers. Fasting levels of high-density lipoprotein (HDL) cholesterol and blood glucose were measured using standardized assays. Diabetes mellitus was defined as a fasting blood glucose level of 126 mg/dL (7 mmol/L) or higher or the use of insulin or any hypoglycemic agents. Proteinuria was assessed using urine dipstick tests (Ames Labstix, Elkhardt, Indiana) dipped for 1 min in spot urine samples collected during the clinic visit [15]. Proteinuria was defined as dipstick protein trace or above.

Prevalent CVD was defined as a history of one or more of the following: non-fatal myocardial infarction, angina pectoris (stable or unstable), stroke or transient ischemic attacks, peripheral vascular disease or congestive heart failure. CVD events were adjudicated by a committee of three experienced investigators.

Measurement of risk factors in NHANES III

In NHANES III, interview questions, physical examination and laboratory values were assessed at baseline and processed per a standardized protocol [14]. BP was measured six times following a standard protocol. Hypertension, diabetes and BMI were defined as in FHS. Participants were considered to have baseline CVD if they reported a history of heart failure, stroke and myocardial infarction or had reported a surgical or percutaneous intervention for any of the above. Participants who reported having smoked ≥100 cigarettes during their lifetime were classified as current smokers if they answered affirmatively to the question 'Do you now smoke cigarettes?' Low socioeconomic status was defined as ≤200% of the poverty index. Urinary albumin-to-creatinine ratio was assessed using a spot urine sample. Albumin-to-creatinine ratio and C-reactive protein (CRP) were log-transformed to achieve normality for statistical analyses.

Assessment of eGFR and incident CKD outcome

In the FHS, the primary outcome studied was the development of incident CKD, defined as eGFR <60 mL/min/1.73^2 using the Modification of Diet in Renal Disease (MDRD) equation [16], by the eighth examination cycle (2005–08). This definition of incident CKD is consistent with our prior work in this area [17]. It has been widely used in prior epidemiological studies, has relatively good agreement with other definitions of incident CKD and demonstrates relatively consistent risk factor associations [18]. Serum creatinine levels were measured using the modified Jaffé method. In NHANES III, ESRD incidence was defined as initiating chronic dialysis. ESRD cases through 1 July 2001 were identified through linkage of the NHANES III database with Medicare files. Specifically, the ESRD Patient Master File and Death Notification (Form 2746) was used to identify participants initiating chronic dialysis therapy following their NHANES III study visit. In both studies, calibration of serum creatinine values to the Cleveland Clinic Laboratory standard was performed using the correction factor of 0.23 mg/dL (20.33 μmol/L) [19].

Statistical analyses

Framingham Heart Study. Baseline characteristics of study participants were calculated by phosphorus category and the statistical significance of differences compared using χ^2 tests for categorical and one-way analysis of variance for continuous variables. Correlation between serum phosphorus values and CKD risk factors were evaluated using Pearson's correlation test. Baseline phosphorus was considered both in categories (<2.5 mg/dL, 2.5–3.49 mg/dL, 3.5–3.99 mg/dL and ≥4 mg/dL) and as a continuous variable (per 1 mg/dL higher phosphorus level). The association between phosphorus category and risk of CKD was tested using logistic regression models. Two sets of regression models were constructed: (i) adjusting for age, sex and eGFR, (ii) a multivariable model adjusting for age, sex, eGFR, BMI, diabetes mellitus, systolic BP, treatment for hypertension, smoking and HDL cholesterol. In these regression models, the reference category for the phosphorus levels was 2.5–3.49 mg/dL, which contained the highest number of individuals. A linear trend in odds ratios (ORs) was calculated across categories.

As serum phosphorus is associated with CVD risk and cardiovascular mortality [20, 21], and because CKD and CVD may be causally linked [22], we performed a sensitivity analysis. Specifically, we repeated the logistic regression analyses after excluding individuals with prevalent CVD in a secondary analysis. We performed two additional sensitivity analyses, adjusting for serum calcium and dipstick proteinuria.

Third National Health and Nutrition Examination Survey. As in FHS, baseline phosphorus was considered as both a categorical and continuous variable in NHANES III. However, there were insufficient ESRD cases in NHANES III ($n = 65$) to perform an analysis using four baseline phosphorus categories. As the risk for kidney disease appeared to increase in participants with serum phosphorus ≥4 mg/dL in FHS, we categorized NHANES III participants as having serum phosphorus ≥4 mg/dL or <4 mg/dL in the categorical analyses. In sensitivity analyses, we also evaluated levels above and below 3.5 mg/dL and 4.5 mg/dL, separately. Baseline characteristics of the study participants were calculated by phosphorus level (<4 mg/dL and ≥4 mg/dL). Poisson regression models were used to calculate the relative risk (RR) for incident ESRD associated with serum phosphorus. Follow-up time for each individual was calculated as the number of days between their baseline visit and the incidence of ESRD, death or 31 December 2000, whichever occurred first. Due to the small number of events, statistical adjustment was made using propensity score analysis. The propensity for having phosphorus levels ≥4 mg/dL was determined using a logistic regression model with age, sex, race/ethnicity, hypertension, history of CVD, diabetes mellitus, BMI, HDL cholesterol, use of cholesterol-lowering medications, CKD, serum albumin, log urinary albumin-creatinine ratio, log CRP and low socio-economic status as the covariable vector. In addition, serum phosphorus was also modeled as a continuous variable. As in the FHS analysis, secondary analyses were conducted for participants without CVD at baseline.

Analyses of FHS were performed using SAS, version 9.1 (SAS Institute, Cary, NC). NHANES analyses were performed using Stata version 10 (Stata Corp., College Station, TX), accounting for its complex survey design. Also, to account for the over-sampling of subgroups and participant non-response, all NHANES III analyses incorporated sampling weights. A two-tailed $P < 0.05$ was considered statistically significant.

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Statistics (NCHS). The NCHS had no role in the design, conduct, reporting or the decision to submit for publication.

Results

Cross-sectional correlates of serum phosphorus level in FHS

The demographic characteristics of the FHS participants are shown in Table 1. The mean age was 42 years and 53.2% were women. Serum phosphorus levels were higher in women ($P < 0.0001$) and current smokers ($P < 0.001$) and those with a lower BMI ($P = 0.04$). A negative correlation was observed between phosphorus levels and BMI, systolic BP, serum glucose and HDL cholesterol, whereas a direct correlation with eGFR was observed ($r = 0.06$, $P = 0.002$).

Association between serum phosphorus level and incident CKD in FHS

Incident CKD developed in 267 FHS participants (11.7%) during follow-up. Participants in the highest phosphorus category (≥4 mg/dL) demonstrated an increased risk of incident CKD compared to the referent group in age, sex and eGFR-adjusted analyses (OR for CKD 2.15, 95% confidence interval (CI) 1.10–4.22, $P = 0.026$, Table 2). Results were not materially different after multivariable adjustment for CKD risk factors (OR 2.14, 95% CI 1.07–4.28, $P = 0.03$). Additional adjustment for dipstick proteinuria and serum calcium resulted in minimal attenuation of CKD risk [OR 2.06 (95% CI 1.01–4.20, $P = 0.047$)] and 2.06 (95% CI, 1.01–4.18, $P = 0.046$).

No significant association with incident CKD was observed when serum phosphorus was analyzed as a continuous variable in either age-, sex- or eGFR-adjusted (OR per 1 mg/dL increase in serum phosphorus 1.0, 95% CI 0.97–1.04; $P = 0.9$) or multivariable-adjusted analyses (OR 1.0; 95% CI, 0.97–1.04; $P = 0.64$).

Secondary analyses in FHS

The association of serum phosphorus levels with increased risk of CKD was similar when analyses were repeated excluding participants with prevalent CVD (multivariable-adjusted OR 2.03; 95% CI, 0.98–4.21, $P = 0.058$).

Cross-sectional correlates of serum phosphorus level in NHANES III

The baseline characteristics of the participants in NHANES III are presented by serum phosphorus in Table 3. Participants in NHANES III with serum phosphorus levels ≥4mg/dL were more likely to be female, Mexican-American, have baseline CKD, use cholesterol-lowering medication, have a lower serum hemoglobin and a higher serum calcium and HDL cholesterol compared to participants with serum phosphorus levels <4mg/dL.

Associations between serum phosphorus level and incident ESRD in NHANES III

During a median of 9.1 years (interquartile range 7.6–10.7), 65 NHANES III participants developed ESRD. Similar to the observations with incident CKD in Framingham, participants with baseline phosphorus ≥ 4 mg/dL had an increased risk of ESRD in both age, sex and race/ethnicity adjusted (RR 2.41; 95% CI 1.29–4.50; $P = 0.007$) and multivariable-adjusted analyses (RR 1.90; 95% CI 1.03–3.53; $P = 0.04$; Table 4) compared to those with baseline phosphorus < 4mg/dL. When serum phosphorus was analyzed as a continuous variable, an increased risk for ESRD was observed (multivariable-adjusted models RR 2.01; 95% CI 1.32–3.07; $P = 0.002$).

Table 1. Baseline characteristics in FHS by phosphorus category[a]

	Phosphorus category				
Characteristic	Category 1	Category 2	Category 3	Category 4	P-value[b]
Serum phosphorus, mg/dL	<2.5	2.5–3.49	3.5–3.99	≥4.0	<0.0001
Participants, *n*	119	1650	426	74	-
Age, years	42 (8)	42 (9)	41 (10)	43 (9)	0.4
Female sex, %	32.8 (39)	50.1 (826)	69.0 (294)	63.5 (47)	<0.0001
BMI, kg/m^2	25.6 (3.5)	25.4 (4.2)	24.2 (3.9)	24.1 (3.9)	0.04
Systolic BP, mmHg	125 (14)	120 (15)	116 (14)	121 (15)	0.05
Hypertension, %	23.5 (28)	16.0 (265)	9.9 (42)	21.6 (16)	0.4
Hypertension treatment, %	9.2 (11)	6.0 (99)	4.9 (21)	12.2 (9)	0.9
Smoking, %	24.4 (29)	33.4 (551)	39.7 (169)	55.4 (41)	<0.0001
Diabetes mellitus, %	0.8 (1)	0.9 (14)	0.7 (3)	0.0 (0)	0.97
HDL cholesterol, mg/dL	48 (12)	49 (13)	52 (13)	48 (15)	0.05
eGFR, mL/min/1.73 m^2	108 (36)	105 (35)	107 (35)	134 (43)	<0.0001
Serum calcium, mg/dL	9.5 (0.4)	9.6 (0.4)	9.7 (0.4)	9.6 (0.5)	0.003
Dipstick proteinuria (trace or above, %)	1.7 (2)	1.1 (18)	0.5 (2)	0.0 (0)	0.95

[a]Data presented mean with standard deviation in parenthesis for continuous variables or percent with number in parenthesis for categorical data.

[b]P values are for significance of trend across quartiles, adjusted for age and sex (except age, which is sex adjusted and sex, which is age adjusted).

Table 2. ORs for CKD associated with level of serum phosphorus in FHS

	Phosphorus, <2.5 mg/dL	Phosphorus, 2.5–3.49 mg/dL	Phosphorus, 3.5–3.99 mg/dL	Phosphorus, ≥4 mg/dL
N events/total *n* (%)	14/119 (11.8)	186/1650 (11.3)	53/426 (12.4)	14/74 (18.9)
Age, sex and GFR adjusted[a]	1.20 (0.65–2.20)	1.0 (Referent)	1.11 (0.77–1.58)	2.15 (1.10–4.22)
Multivariate model[a,b]	1.15 (0.62–2.14)	1.0 (Referent)	1.18 (0.82–1.71)	2.14 (1.07–4.28)

[a]Data presented as OR for CKD with 95% CI in parentheses.
[b]All multivariable models are adjusted for age, sex, body mass index, diabetes mellitus, systolic BP, treatment for hypertension, smoking, HDL cholesterol and eGFR.

Table 3. Baseline characteristics by phosphorus category in NHANES III ($n = 13372$)[a]

Characteristic	Phosphorus category		P-value
Phosphorus category, mg/dL	<4.0	≥4.0	-
Participants, *n*	11 308	2064	-
Age, years	44.4 (0.5)	43.6 (0.7)	0.2
Female sex, %	50.4 (0.6)	61.7 (1.5)	<0.001
Race, %			
Non-Hispanic white	78.1 (1.3)	75.6 (1.8)	0.1
Non-Hispanic black	9.9 (0.5)	11.1 (0.9)	0.07
Mexican-American	4.6 (0.4)	5.7 (0.6)	0.004
Other race	7.4 (0.9)	7.6 (1.2)	0.9
Body mass index, kg/m^2	26.6 (0.1)	26.3 (0.3)	0.3
Hypertension, %	23.9 (0.9)	22.9 (1.5)	0.5
Current smoking, %	28.1 (0.8)	29.5 (1.8)	0.4
Prior cardiovascular disease, %	7.5 (0.5)	8.0 (0.8)	0.5
Use of cholesterol-lowering medications, %	2.6 (0.2)	4.6 (0.8)	0.002
Low socio-economic status, %	32.2 (1.2)	36.7 (2.5)	0.07
Diabetes mellitus, %	6.5 (0.4)	6.8 (0.8)	0.8
HDL cholesterol, mg/dL	50.6 (0.39)	52.1 (0.44)	0.008
Estimated GFR <60 mL/min/1.73m^2, %	3.7 (0.2)	6.0 (0.6)	<0.001
Calcium, mg/dL	9.24 (0.02)	9.36 (0.03)	<0.001
Urine albumin/creatinine >30 mg/g, %	8.1 (0.4)	9.0 (1.0)	0.3
Hemoglobin, g/dL ($N = 13\ 214$)	14.2 (0.03)	13.8 (0.05)	<0.001
Albumin, g/dL	4.18 (0.02)	4.20 (0.03)	0.3
C-reactive protein >0.21 mg/L, %	27.9 (1.3)	29.2 (2.1)	0.5
Total cholesterol, mg/dL	203.3 (0.7)	206.0 (1.8)	0.06
Serum phosphorus, mg/dL	3.31 (0.01)	4.22 (0.01)	<0.001

[a]Data presented mean with standard error in parenthesis for continuous variables or percent with standard error in parenthesis for categorical data; GFR, glomerular filtration rate.

Table 4. Unadjusted and adjusted RRs for ESRD associated with serum phosphorus in NHANES III ($n = 13\ 372$)[a]

	Serum phosphorus level		
Serum phosphorus level, mg/dL	<4.0	≥4.0	P-value
N events/total *n*	43/11 308	22/2064	-
Unadjusted	1.0 (Referent)	2.29 (1.24–4.23)	0.009
Age, sex, race adjusted	1.0 (Referent)	2.41 (1.29–4.50)	0.007
Multivariable adjusted[b]	1.0 (Referent)	1.90 (1.03–3.53)	0.04

[a]Data presented as RR for ESRD with 95% CI in parentheses.
[b]Multivariable adjusted for age, sex, race, diabetes mellitus, hypertension, prior CVD, low SES, use of cholesterol-lowering medications, BMI, serum albumin, log C-reactive protein, log urinary albumin/creatinine ratio, HDL cholesterol and eGFR <60 mL/min/1.73m^2.

Sensitivity analyses in NHANES III

The multivariable-adjusted RR of ESRD was 5.41 (95% CI 1.60–18.4; P = 0.008) in NHANES III participants with serum phosphorus ≥4.5 mg/dL compared with those <4.5 mg/dL. Additionally, the multivariable-adjusted RR of ESRD associated with serum phosphorus ≥3.5 mg/dL was 3.27 (95% CI 1.43–7.50; P = 0.006) compared with participants with serum phosphorus of <3.5 mg/dL.

When participants with prevalent CVD were excluded from multivariable analysis, the RR for incident ESRD was attenuated in NHANES III participants with serum phosphorus ≥4.0 mg/dL compared with those <4.0 mg/dL (RR 1.52; 95% CI 0.55–4.22; P = 0.41). The multivariable-adjusted RR was 2.01 per 1 mg/dL increase in serum phosphorus (95% CI, 1.32–3.07; P = 0.002) after excluding NHANES III participants with prevalent CVD.

Discussion

Our data suggest an association between serum phosphorus levels in the 'high-normal' range and an increased risk for incident CKD. We were able to extend our findings and additionally document an association between serum phosphorus and ESRD in the nationally representative NHANES III study.

Hyperphosphatemia is a common complication of established CKD and the relationship between phosphorus and progression of kidney disease has been characterized in this context [23]. Several studies report elevated serum phosphorus levels as predictive of the rapid progression of kidney disease [8–10] and the development of ESRD [10]. The present study extends the current literature by demonstrating an independent association between phosphorus level and both incident CKD and ESRD.

There are several potential mechanisms that may explain our observations. First, baseline eGFR was substantially increased in the highest phosphorus group in FHS, replicating a relationship observed in an earlier analysis of the Cholesterol and Recurrent Events study [21]. A confounder likely mediates this association, as neither phosphorus administration nor serum phosphorus concentration has a direct effect on GFR [24, 25]. Diet is one such potential confounder, as serum phosphorus concentration correlates directly with dietary phosphate intake in humans [26]. A high-protein diet induces renal hyperfiltration in animal models, [27] patients with CKD [28] and in healthy volunteers [28], and may accelerate renal functional decline in

individuals with mild renal insufficiency via this mechanism [29]. Conversely, dietary protein restriction attenuates hyperfiltration in animal models of kidney disease [30–36] and delays the progression of established kidney disease in humans [37–39]. Processed foods high in phosphorus-based food additives [40] are associated with elevated phosphate intake and serum concentrations in CKD patients [41], and increasing poverty is also independently associated with increased serum phosphate, possibly mediated by a diet rich in such processed foods [42].

Secondly, the association between serum phosphorus and risk of CKD may be explained by renal calcific arterial disease. Serum phosphorus is associated with CVD risk in the general population [20] and in those with known CVD [21]. Evidence suggests that this risk is mediated by phosphorus-induced arteriosclerosis and vascular calcification [43], and hyperphosphatemia may directly stimulate arterial calcification via upregulation of core binding factor a-1 in vascular smooth muscle cells [44].

Finally, it is possible that a higher prevalence of subclinical renal disease existed in the highest phosphate group than is indicated by the MDRD eGFR equation. It has been suggested that as MDRD was originally developed in disease-based cohorts, it may perform poorly in healthy populations [45]. Misclassification of mild CKD could potentially explain both high phosphorus concentration and the higher risk of CKD/ESRD. However, as the MDRD equation generally overestimates the prevalence of CKD in a general population sample [46], any effect due to misclassification is likely to be small.

Notably, when analyzed as a continuous variable, serum phosphorus was associated with an increased risk of ESRD but not incident CKD. This may be due to differences in the composition of the two study samples, such as the inclusion of participants with baseline CKD in the NHANES III analysis or differences in the ethnic composition of the samples, which is known to influence phosphorus level [47].

The finding that serum phosphorus in the upper range of normal is associated with incident kidney disease may have important public health implications. As serum phosphorus levels $\geq$4.0 mg/dL, but within the normal range, are associated with both incident CKD and CVD [20, 21], the currently accepted upper limit of the 'normal range' of 4.5 mg/dL may require revision downwards.

There are several strengths to this study, including the well-characterized participants from FHS and NHANES III, the well-defined CVD risk factors and the long duration of follow-up. By making use of data from two distinct studies, we were able to extend our observations from incident CKD to ESRD. Also, there are some important limitations. Dietary information was not available for participants in this FHS exam cycle, and we cannot exclude its importance as a confounder. A time-to-event analysis would have been preferable in FHS, as was performed in NHANES III, but was not possible due to the cyclical nature of follow-up in that study and consequent inability to time CKD onset. The FHS sample was predominantly of European ancestry, which may limit the generalizability of these findings. However, we note that NHANES III is a multi-ethnic nationally representative sample that produced comparable results. We used slightly different analytic strategies in FHS as compared to NHANES because of low numbers of ESRD cases in NHANES and the lack of laboratory follow-up. We did not adjust for other unmeasured potential confounders of the associations seen including FGF-23, parathyroid hormone levels and urinary biomarkers. Also, laboratory follow-up for identifying incident cases of CKD was not available in NHANES III. As both studies have an observational design, causality cannot be inferred. Finally, a survival bias may have existed in our analysis, as participants were required to attend both the initial and follow-up examinations, and those with the greatest risk factor burden may have died during the long follow-up.

In conclusion, serum phosphorus levels in the high-normal range are associated with a 2-fold higher risk of developing new-onset CKD and ESRD in the general population. Further research is required to investigate the causes of this association between phosphorus homeostasis and an increased risk of developing renal disease.

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