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Association of Serum Phosphorus with Left Ventricular Mass in Men and Women With Stable Cardiovascular Disease: Data from the Heart and Soul Study

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Abstract

Background—Higher serum phosphorus levels are associated with cardiovascular disease (CVD) events in the general population, an association that may be stronger in men. Estradiol has phosphaturic properties. Whether higher serum phosphorus levels are associated with left ventricular (LV) mass in persons without end-stage renal disease (ESRD), and whether the association is modified by sex is unknown.

Study Design—Cross-sectional observational study

Setting and Participants—978 outpatients with stable CVD.

Predictor—The primary predictor variable was serum phosphorus levels. Sex was evaluated as an effect modifier.

Outcome & Measurements—LV mass by transthoracic echocardiography.

Results—The association of serum phosphorus with LV mass differed by sex (interaction $P=0.04$). In models adjusted for age, race, kidney function, smoking, diabetes, blood pressure, cholesterol, C-reactive protein, and ACE inhibitor/ARB use, each 1 mg/dL higher serum phosphorus level was associated with a 4.52 g/m² greater LV mass (95% confidence interval [CI]

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1.04 to 8.01; $p=0.01$) in men. Conversely, among women, no statistically significant association was found between serum phosphorus and left ventricular mass.

Limitations—Older adult population with stable CVD, and 19% were women.

Conclusions—Among outpatients with stable CVD, higher serum phosphorus levels are associated with greater LV mass in men, but not women. Whether differences in sex hormones may account for these differences requires future study.

Keywords

Sex Hormones; Phosphorus; Cardiovascular Disease; Kidney Dysfunction

Higher serum phosphorus levels are associated with cardiovascular disease (CVD) events and all-cause mortality in persons with end-stage renal disease (ESRD).^{1, 2} Recently, several studies have demonstrated similar associations in the general population among populations predominantly without kidney disease.^{3–5} The mechanism(s) responsible for these associations are unknown, but may be related to vascular stiffness and associated changes in left ventricular (LV) mass.

The past decade has provided novel insights into mechanisms through which higher serum phosphorus levels may contribute to vascular calcium deposition and arterial stiffness. *In vitro*, higher extra-cellular phosphorus concentrations induce human aortic vascular smooth muscle cells to transform into osteoblast-like cells, and to calcify the vascular extracellular matrix. A sodium phosphorus co-transporter (PIT-1; encoded by the *SLC20A1* gene) on the cell surface of vascular smooth muscle cells is both necessary and sufficient to induce these changes.⁶ Higher serum phosphorus levels are associated with coronary artery calcification and vascular stiffness in humans; findings that are consistent in cohorts with^{7, 8} or without CKD.^{9–11} In animal models and in human studies in persons with CKD, higher serum phosphorus levels have been associated with left ventricular hypertrophy (LVH) and myocardial fibrosis.^{12–14} Thus, it is possible that phosphorus leads to vascular calcification and associated increased vascular stiffness, and that chronic exposure to vascular stiffness may contribute to greater LV mass.

Recent evidence has suggested that the association of serum phosphorus and subclinical and clinical CVD in the general population may differ by sex.^{4, 15} In the ARIC (Atherosclerosis Risk in Communities) study; a large community-based observational study of middle aged adults predominantly without CKD, high serum phosphorus levels were associated with carotid intima-media thickness¹⁵ and CVD events⁴ in men, but not in women. Biological mechanisms responsible for these sex differences, or their reproducibility in other studies are uncertain. However, phosphorus homeostasis is different in men and women. It is consistently observed that women of post-menopausal age have serum phosphorus levels that are 0.15 to 0.30 mg/dL higher than similar aged men.^{3, 5, 11, 16} This relationship may be related to declines in endogenous estradiol that occurs through the menopausal transition in women. Rodent studies demonstrate that exogenous estradiol suppresses mRNA and protein levels of the main phosphorus reclamation channel (sodium phosphorus cotransporter IIa [encoded by the *SLC34A1* gene]) in the proximal tubule, thereby leading to increased in urinary phosphorus excretion.¹⁷ In a large cohort of community-living Italians, Cirillo and colleagues demonstrated that at age 45–50, there was a marked increase in serum phosphorus and a commensurate decrease in urinary phosphorus in women, but not men.¹⁸ And, in a large cohort of older men, serum estradiol levels and phosphorus levels were inversely correlated, independent of kidney function, vitamin D, parathyroid hormone concentrations, and bone density.¹⁹

On the basis of these observations, we hypothesize that the endogenous declines in serum estrogen that occur through the menopausal transition in women may lead to urinary phosphorus retention, and commensurate increases in serum phosphorus levels. Further, on the basis of sex differences of phosphorus with subclinical and clinical CVD in the ARIC study, we hypothesized that higher phosphorus levels would be associated with greater LV mass, and that the association of phosphorus with LV mass would be stronger in men than in women, despite the later group having higher phosphorus levels. Last, to inform potential mechanisms mediated through estradiol, we preliminarily explore whether relationships differed among women who were vs. were not users of hormone replacement therapy

METHODS

Participants

The Heart and Soul Study is an observational study designed to evaluate the association of psychological factors and CVD. Methods have been described previously.²⁰ Briefly, subjects with prevalent CVD, defined as: history of myocardial infarction, angiographic evidence of >50% stenosis in ≥ 1 coronary vessels, evidence of exercise-induced ischemia by treadmill or nuclear testing, or history of coronary revascularization, were recruited from outpatient clinics in the San Francisco bay area. Exclusion criteria included an inability to walk one block, myocardial infarction within the previous six months, or plans to leave the local area within three years. The study protocol was approved by the Institutional Review boards at participating centers, and all participants provided written informed consent.

Between September 2000 and December 2002, 1024 subjects were enrolled. For the present analysis, we excluded 34 (4%) subjects with missing serum phosphorus measurements and 12 (1%) subjects with missing LV mass measurements by echocardiography, resulting in a final sample size of 978 participants.

Measurements

Serum phosphorus—Fasting morning blood specimens were collected at the study visit. Phosphorus levels were measured using a Vitros 950IRC with measurement ranges of 0.3 mg/dL to 13 mg/dL and coefficient of variation of 3.5% as previously described.²¹

Left ventricular mass—Participants underwent transthoracic echocardiography at rest on the same day as their serum phosphorus measurements. An Acuson Sequoia ultrasound system (www.medical.siemens.com) using a 3.5-MHz transducer was used to perform a complete 2-dimensional echocardiogram, including Doppler imaging in all standard views and subcostal imaging of the inferior vena cava. We obtained standard 2-dimensional parasternal short axis and apical 2- and 4-chamber views during suspended inspiration. An expert cardiologist (N.B.S.) who was blinded to all other clinical information interpreted the echocardiograms.

LV mass was derived from wall thickness measurements using a truncated ellipsoid technique and indexed to body surface area.²² LV mass served as the primary outcome for this manuscript. In companion analysis, we evaluate LV hypertrophy (LVH) as a dichotomous outcome, which was defined as LV mass > 95 g/m² in females and > 110 g/m² in males.²³ Because we were interested in sex-specific associations of phosphorus with LVH, we also explored the association of phosphorus with a unifying definition of left ventricular hypertrophy (LVH) (i.e. LV mass > 110 g/m² in both men and women) in sensitivity analyses. Results were similar in all cases so data are presented using the standard sex-specific cut-points for LVH.

Other laboratory measurements and patient characteristics—Age, sex, and race were defined by self-report. Diabetes was defined as a self reported history of diabetes, or use of diabetic medications including insulin. Blood pressure was determined by trained study personnel using a calibrated sphygmomanometer. Hypertension was defined as self reported history of hypertension, systolic blood pressure (SBP) > 140 mmHg or diastolic blood pressure (DBP) > 90 mmHg. Medication use was not considered part of the definition as in the prevalent CVD setting, participants may have been taking these medications for secondary prevention rather than for hypertension control. Participants were weighed and height was measured without shoes, and body mass index (BMI) was calculated (kg/m^2). High-sensitivity C-reactive protein (CRP) was measured with the Roche Integra Assay and Beckman Extended Range Assay as previously described.²⁴ Fasting serum samples were used to measure total cholesterol, high-density lipoprotein cholesterol, and triglyceride levels. Cystatin C was measured using a BNII nephelometer (Dade Behring Inc., www.dadebehring.com) that used a particle-enhanced immunonephelometric assay (N Latex Cystatin-C) as previously described.²⁵ Glomerular filtration rate (eGFR) was estimated using a cystatin-C based equation [$\text{eGFR} = 76.6 * (\text{serum cystatin-C})^{-1.19}$].²⁶ Cystatin C was chosen as the measure of GFR in the regression models rather than creatinine or associated estimating equations because prior studies demonstrate that cystatin C is a more accurate measure of GFR among subjects with normal or near-normal kidney function.²⁷ As a comparator, GFR was also estimated using the Modification of Diet in Renal Disease (MDRD) Study equation.²⁸ Hemoglobin values were obtained with the Beckman Coulter LH 750 (www.beckmancoulter.com); interassay coefficient of variation was 0.4%. Urine studies were available for 787 of the participants. Urine albumin and creatinine were measured using nephelometry and the rate Jaffe method, respectively, and an (milligram per gram).²¹ urine albumin-creatinine ratio (UACR) was calculated. Participants brought all (prescription and non-prescription) medications to their study appointment. Trained study personnel recorded all medications, including use of ACE/ARBs and hormone replacement therapy.

Statistical Analysis

Univariate associations of clinical and demographic variables were compared individually in each sex by tertiles of serum phosphorus using ANOVA, Kruskal-Wallis, Chi Square, or Fisher's Exact tests, as appropriate. Subsequently, multivariate linear regression was used to evaluate the association of serum phosphorus and LV mass. We elected to model serum phosphorus as a continuous predictor variable to maximize statistical power. However, we explored the assumptions of a linear relationship, and evaluated for possible threshold effects by evaluating serum phosphorus tertiles.

LV mass was indexed to body surface area, calculated by the DuBois and DuBois formula.²⁹ We conducted several additional sensitivity analyses. First, we explored whether results were similar with or without inclusion of BMI as an adjustment variable. Second, we evaluated whether results were similar when LV mass was indexed to height squared instead of BSA. Last, we explored associations of LV mass without any indexing. In all cases, results were similar, so data are presented for LV mass indexed to body surface area only. For linear regression, the initial model was unadjusted. A second model was adjusted for age, and race. The final model was adjusted for age, race, smoking status, diabetes, systolic and diastolic blood pressure, angiotensin converting enzyme inhibitor or angiotensin receptor blocker use (ACE/ARB), CRP, total cholesterol, triglycerides, hemoglobin, and cystatin-based eGFR ($\text{eGFR}_{\text{CysC}}$). These variables were chosen *a priori* on the basis of prior literature demonstrating their associations with LV mass.^{30–33} We evaluated whether sex modified the association of phosphorus with LV mass, a variable that was selected *a priori* on the basis of prior literature. We also evaluated whether CKD ($\text{eGFR}_{\text{CysC}} < 60 \text{ ml}/\text{min}/$

1.73m² vs. greater) modified the association. In both cases, multiplicative interaction terms were included in the final multivariable model, and subsequent models were evaluated within strata of sex and CKD, respectively. In companion analysis, we evaluated the association of serum phosphorus with LVH as a dichotomous outcome, using logistic regression. The model was adjusted for identical covariates as in linear regression analysis, described above. A figure depicting the mean LV mass by tertiles of phosphorus in men and women was created by calculating the adjusted mean LV mass by setting each variable contained in the final linear regression model to their mean. Corresponding 95% confidence intervals around the adjusted means were calculated, and a P-value for trend is provided. Finally, to preliminarily investigate whether the association of serum phosphorus with LV mass might be mediated through differences in estradiol, we limited the analysis to women, and explored whether the association differed among those who used hormone replacement therapy (HRT) compared to non-HRT using women. We hypothesized that estradiol provided through HRT might result in lower serum phosphorus levels, and that among users, the relationship of serum phosphorus with LV mass would be more similar to men than to non-HRT using women. All statistical analysis was performed using STATA version 9.2 SE (StataCorp LP, www.stata.com).

RESULTS

The mean age of the 978 study participants was 67 years. The study recruited heavily from a Veterans Affairs medical center, therefore 19% (n=181) were female. Thirty percent had moderate CKD (eGFR_{CysC} < 60 ml/min/1.73m²). The mean serum phosphorus level was 3.7 ± 0.6 mg/dL overall, however this differed by sex (3.6 ± 0.5 mg/dL in men, and 4.0 ± 0.7 mg/dL in women; P< 0.001). Baseline characteristics by phosphorus tertiles are shown separately in men and women (Tables 1 and 2, respectively). Among men, those in the highest phosphorus tertile were younger, had higher serum triglyceride levels, and more frequently had diabetes, were current smokers, and had evidence of reduced renal clearance and albuminuria (Table 1). Among women, those in the highest phosphorus tertile showed similar trends in age, smoking, and reduced kidney function but these results did not reach statistical significance. Unlike men, the prevalence of diabetes was similar across tertiles and lower triglyceride levels were seen in the highest tertile among women (Table 2).

Adjusted mean LV mass increased across phosphorus tertiles among men (Figure 1). When examined as a continuous predictor variable each 1 mg/dL higher serum phosphorus level was associated with a 6.06 g/m² greater LV mass in unadjusted analysis in men; an association that was moderately attenuated but remained statistically significant and in the same direction in the final multivariable model (Table 3). In contrast, we observed no association of serum phosphorus levels with LV mass in unadjusted analysis in women. In the final multivariable model, however, an association was revealed that was in the opposite direction to that observed in men (p for gender interaction=.04), such that each 1mg/dL higher serum phosphorus level was associated with a 4.78 g/m² lower LV mass. This finding did not reach statistical significance (p=.08, Table 2). The covariates responsible for the negative confounding that allowed the relationship to emerge were eGFR and smoking status. These associations were consistent in direction in individuals with or without moderate CKD in either sex (Table 4). Results were also similar when BMI was included as an additional adjustment covariate, when LV mass was indexed to height squared rather than to BSA, or when LV mass was evaluated without indexing (data not shown). While we lacked data on menopausal status, previous studies have demonstrated that 99% of women undergo natural menopause by age 57.³⁴ In sensitivity analyses limited to women > 57 years, results were similar (data not shown).

When evaluating LVH as a dichotomous outcome, results were similar (Table 5). The association of serum phosphorus with LVH was also modified by sex (interaction $P = 0.01$). In men, each 1mg/dL higher serum phosphorus level was associated with a 39% higher odds of LVH in the multivariable model ($p = .04$). In contrast, higher phosphorus levels were associated with a 51% lower odds of LVH in women ($P = 0.03$).

Of the 181 women, 45 (25%) were HRT users. These women had mean serum phosphorus levels of 3.8 ± 0.6 mg/dL compared to 4.1 ± 0.7 mg/dL in non-users (P value = 0.005). The association of serum phosphorus with LV mass differed qualitatively by HRT use. Among HRT users, there was no association of serum phosphorus with LV mass, while among non-users we observed an inverse association of serum phosphorus with LV mass (Table 6). However, the number of women taking HRT was relatively small, and formal testing for interaction by HRT status was not statistically significant (interaction $p = 0.2$).

DISCUSSION

In this study among outpatients with stable CVD, higher serum phosphorus levels were associated with greater LV mass in men, but not in women. Two prior studies conducted in the ARIC cohort demonstrated that the association of phosphorus levels with carotid intima media thickness and CVD events was limited to men.^{4, 15} The sex difference in the association of phosphorus with LV mass demonstrated here provides additional evidence in support of unique relationships of phosphorus with CVD in men and women in an independent study sample. The responsible mechanisms are uncertain, but preliminary data provided here suggests that they may, in part, be explained by differences in sex hormones.

Women had significantly higher serum phosphorus levels than men in this study; a finding consistent with many other studies in older community-living populations.^{3, 4, 11, 15, 16} We hypothesize that this may reflect differences in estradiol levels between older men and women. Serum phosphorus levels increase abruptly, with a commensurate decrease in urine phosphorus levels at the menopausal transition in women, but not in men.¹⁸ In rodents, estrogen directly down-regulates the major phosphorus reclamation transporter in the proximal convoluted tubule (sodium phosphorus co-transporter IIa).¹⁷ In community-living older men, higher estradiol levels were associated with lower serum phosphorus levels, independent of kidney function, parathyroid hormone levels, or 25-hydroxyvitamin D levels.¹⁹ And, in several small randomized clinical trials and prospective cross-over studies of HRT therapy, women randomized to HRT consistently develop lower serum phosphorus levels and greater urinary phosphorus levels than women randomized to placebo.^{35, 36} While our cohort does not include data on serum estradiol levels, preliminary data evaluating HRT use are consistent with this hypothesis. HRT therapy should lead to higher serum estradiol levels, which may have increased urinary phosphorus loss and lowered serum phosphorus levels. Through this mechanism, the association of serum phosphorus with LV mass may also have been altered, as the inverse association of phosphorus and LV mass observed in women not taking HRT was absent in those taking HRT. However, we had relatively few women in this study, and even fewer who were taking HRT. Despite qualitative differences in HRT users and non-users, formal testing for effect modification was not statistically significant. These data should be considered hypothesis generating, and require confirmation in future studies with larger numbers of women, and users and non-users of HRT.

Why would higher phosphorus be associated with LV mass in men only, despite women having higher serum levels? This important question remains unanswered. It is possible that relative estradiol deficiency after menopause results in changes in LV mass through mechanisms independent of serum phosphorus. For example, in addition to its pro-thrombotic properties, estradiol may also influence expression of the vitamin D receptor³⁷

and FGF-23 (fibroblast growth factor 23),³⁸ while simultaneously inducing phosphaturia. It is possible that these pathways may blunt the association of phosphorus with LV mass in women. Studies investigating these and other potential mechanisms should be a high priority as they may ultimately provide new insights to mechanisms contributing to LV remodeling.

Strengths of this study include the relatively large sample size, availability of echocardiography to determine LV mass in all subjects, and measurement of multiple potential confounding variables, including HRT use. The study also has important limitations. First, as stated above, the number of women enrolled in this study was small, and among them, the number taking HRT was even smaller, and HRT use was not given in a blinded randomized fashion. While evaluation of LV mass as a continuous outcome measure improved statistical power, results should be interpreted within the confines of the 95% confidence intervals. The cross-sectional study design precludes the determination of temporality. We lacked data on menopausal status, yet results were similar in sensitivity analysis limited to older women among whom > 99% would be expected to have reached menopause. Finally, all participants in this study had prevalent CVD and most were older. Results may differ in other populations.

In conclusion, in outpatients with stable CVD, higher serum phosphorus levels are associated with greater LV mass in men but not women. These data add to a growing body of literature demonstrating that phosphorus regulation and its associations with subclinical and clinical CVD differ by sex. Preliminary data support the hypothesis that these differences may be mediated through the effects of sex hormones on renal phosphorus excretion. Future studies should evaluate whether differences in serum estradiol levels may account for the sex-specific associations of serum phosphorus with LV mass and CVD events.

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Figure 1.

Adjusted mean LV mass by serum phosphorus tertiles, stratified by sex. Error bars reflect 95% confidence intervals. Models are adjusted for age, race, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, ACEi/ARB use, C-reactive protein, total cholesterol, triglycerides, hemoglobin, and cystatin based eGFR. Phosphorus tertiles were (I) < 3.4, (II) 3.5–3.8, and (III) > 3.8 mg/dL in men, and (I) < 3.8, (II) 3.9–4.2, and (III) > 4.2 mg/dL in women.

Table 1

Baseline Characteristics of Men with CVD by Phosphorus Tertiles

	Phosphorus Tertiles			
	I	II	III	P-Value
Phosphorus Range (mg/dL)	< 3.4	3.5 – 3.8	> 3.9	
Demographics				
Age (years) ± SD	69 ± 11	68 ± 10	64 ± 11	< 0.001
Race				0.09
Caucasian (%)	213 (66%)	152 (64%)	136 (57%)	
African-American (%)	42 (13%)	27 (11%)	45 (19%)	
Other (%)	67 (21%)	57 (24%)	57 (24%)	
Co-morbidities				
Diabetes (%)	61 (19%)	60 (25%)	84 (35%)	< 0.001
Hypertension (%)	220 (69%)	154 (65%)	177 (74%)	0.1
Microalbuminuria ** (%)	35 (13%)	54 (18%)	45 (24%)	0.02
eGFR _{CysC} < 60 ml/min/1.73m ²	86 (27%)	66 (28%)	94 (39%)	0.003
eGFR _{MDRD} < 60 ml/min/1.73m ²	65 (20%)	49 (21%)	61 (26%)	0.3
CVD History				
Myocardial Infarction (%)	177 (55%)	125 (53%)	137 (57%)	0.7
Revascularization (%)	208 (65%)	136 (58%)	149 (62%)	0.2
Heart failure (%)	46 (14%)	51 (22%)	41 (17%)	0.08
Current Smoking (%)	48 (15%)	44 (19%)	64 (27%)	0.002
Medications				
ACEi/ARB (%) *	161 (50%)	124 (52%)	131 (55%)	0.5
Statins (%) *	223 (69%)	158 (67%)	150 (63%)	0.3
Beta blockers (%) *	179 (56%)	140 (59%)	149 (62%)	0.3
Diuretics (%)	86 (27%)	63 (27%)	72 (30%)	0.6
Physical Measurements				
Systolic BP (mmHg) [†]	130 (120,140)	130 (118,142)	130 (120,148)	0.8
Diastolic BP (mmHg) [†]	72 (66,80)	76 (68,80)	76 (65,84)	0.1
Body mass index (kg/m ²) [†]	27 (25,30)	28 (25,31)	27 (24,31)	0.7
Laboratory Measurements				
C-reactive protein (mg/L) [†]	1.9 (0.9,4.1)	2.0 (0.8,4.2)	2.4 (0.9,5.2)	0.5
Total Cholesterol (mg/dL) [†]	169 (146,191)	165 (144,188)	173 (150,204)	0.006
HDL Cholesterol (mg/dL) ± S.D.	45 ± 14	43 ± 12	44 ± 13	0.2
Triglycerides (md/dL) [†]	105 (73,156)	104 (70,151)	123 (77,193)	0.008
UACR (mg/g) ** [†]	9.4 (5.9,16.2)	8.7 (6.1,18.1)	9.8 (6.2,24.5)	0.2

	Phosphorus Tertiles			
	I	II	III	P-Value
eGFR _{CysC} (ml/min/1.73m ²) ^{*†}	70 (59,80)	70 (57,85)	66 (49,83)	0.09
eGFR _{MDRD} (ml/min/1.73m ²) ^{*†}	76 (62,88)	76 (63,91)	74 (59,94)	0.9
Hemoglobin (g/dL) [†]	14.2 (13.2,15.0)	14.1 (13.3,15.1)	13.9 (13.2,14.9)	0.4

Note: N= 797. Conversion factors for units: eGFR in mL/min/1.73 m² to mL/s/1.73 m², x0.01667; total and HDL cholesterol in mg/dL to mmol/L, x0.02586; triglycerides in mg/dL to mmol/L, x0.01129; hemoglobin in g/dL to g/L, x10.

* Abbreviations and definitions: “ACEi” angiotensin converting enzyme inhibitor; “ARB” angiotensin receptor blocker; BP, blood pressure; “Statin” HMG-Co-A reductase inhibitor; CVD, cardiovascular Disease; “HDL” high density lipoprotein; eGFR_{CysC} estimated glomerular filtration rate calculated using serum cystatin C levels; eGFR_{MDRD} estimated glomerular filtration rate calculated using serum creatinine and the MDRD Study equation; UACR, urine albumin-creatinine ratio

** Urinary studies available for only 787 of participants

[†] Median (interquartile range).

Table 2

Baseline Characteristics of Women with CVD by Phosphorus Tertiles

	Phosphorus Tertiles			
	I	II	III	P-Value
Phosphorus Range (mg/dL)	< 3.8	3.9 – 4.2	> 4.3	
Demographics				
Age (years) ± SD	65 ± 11	65 ± 12	62 ± 10	0.3
Race				0.7
Caucasian (%)	37 (53%)	22 (40%)	29 (51%)	
African-American (%)	17 (24%)	16 (30%)	13 (23%)	
Other (%)	16 (23%)	16 (30%)	15 (26%)	
Co-morbidities				
Diabetes (%)	15 (21%)	17 (31%)	19 (33%)	0.3
Hypertension (%)	45 (64%)	43 (80%)	46 (81%)	0.06
Microalbuminuria (%) **	7 (13%)	12 (27%)	8 (18%)	0.2
eGFR _{CysC} < 60 ml/min/1.73m ²	16 (23%)	12 (22%)	20 (35%)	0.2
eGFR _{MDRD} < 60 ml/min/1.73m ²	15 (21%)	10 (19%)	21 (35%)	0.05
CVD History				
Myocardial Infarction (%)	19 (41%)	24 (45%)	20 (53%)	0.4
Revascularization (%)	36 (51%)	21 (39%)	22 (39%)	0.2
Heart failure (%)	16 (23%)	6 (11%)	10 (18%)	0.3
Current Smoking (%)	12 (17%)	9 (17%)	18 (32%)	0.08
Medications				
ACEi/ARB (%) *	31 (44%)	23 (43%)	30 (53%)	0.5
Statins (%) *	38 (54%)	23 (43%)	35 (61%)	0.1
Beta blockers (%) *	34 (49%)	29 (54%)	29 (51%)	0.9
Diuretics (%)	26 (37%)	20 (37%)	19 (33%)	0.9
Physical Measurements				
Systolic BP (mmHg) †	140 (120,150)	138 (122,150)	140 (120,150)	0.8
Diastolic BP (mmHg) †	77 (70,85)	79 (70,84)	72 (68,80)	0.3
Body mass index (kg/m ²)	28 (26,33)	29 (26,35)	29 (24,32)	0.4
Laboratory Measurements				
C-reactive protein (mg/L) †	3.4 (1.4,6.8)	3.2 (1.0,7.7)	2.9 (1.4,6.5)	0.9
Total Cholesterol (mg/dL) †	187 (159,219)	193 (161,232)	180 (157,207)	0.3
HDL Cholesterol (mg/dL) ± S.D.	55 ± 16	50 ± 16	52 ± 17	0.3
Triglycerides (md/dL) †	117 (80,162)	125 (76,219)	97 (68,134)	0.09
UACR (mg/g) **†	10.5 (6.8,18)	14.3 (8.8, 39.1)	13.9 (8.6,22.4)	0.2

	Phosphorus Tertiles			
	I	II	III	P-Value
eGFR _{CysC} (ml/min/1.73m ²) ^{*†}	79 (61,89)	79 (67,94)	69 (51,88)	0.09
eGFR _{MDRD} (ml/min/1.73m ²) ^{*†}	74 (63,89)	80 (72,95)	75 (55,81)	0.04
Hemoglobin (g/dL) [†]	13 (12.2,13.7)	13.4 (12.8,14.1)	13 (11.9,14.2)	0.1

Note: N= 181. Conversion factors for units: phosphorus in mg/dL to mmol/L, x0.3229; eGFR in mL/min/1.73 m² to mL/s/1.73 m², x0.01667; total and HDL cholesterol in mg/dL to mmol/L, x0.02586; triglycerides in mg/dL to mmol/L, x0.01129; hemoglobin in g/dL to g/L, x10.

* Abbreviations and definitions: “ACEi” angiotensin converting enzyme inhibitor; “ARB” angiotensin receptor blocker; BP, blood pressure; “Statin” HMG-Co-A reductase inhibitor; CVD, cardiovascular Disease; “HDL” high density lipoprotein; eGFR_{CysC} estimated glomerular filtration rate calculated using serum cystatin C levels; eGFR_{MDRD} estimated glomerular filtration rate calculated using serum creatinine and the MDRD Study equation; UACR, urine albumin-creatinine ratio

** Urinary studies available for only 787 of participants

[†] Median (interquartile range).

Table 3

Association of Serum Phosphorus Levels with LV Mass in Men and Women*

	Difference in LV Mass (g/m ²)	(95% CI)	P-value
Men (N=797)			
Unadjusted	6.06	2.70 to 9.41	<.001
Age and race adjusted	7.00	3.57 to 10.42	<.001
Multivariable adjusted [†]	4.52	1.04 to 8.01	0.01
Women (N=181)			
Unadjusted	1.54	−3.41 to 6.48	0.5
Age and race adjusted	1.10	−3.86 to 6.07	0.7
Multivariable adjusted [†]	−4.78	−10.09 to 0.53	0.08

* Per 1mg/dL increase in serum phosphorus levels.

[†] P for interaction by sex in the multivariable model = 0.04. Adjusted for age, race, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, ACEi or ARB use, C-reactive protein, total cholesterol, triglycerides, hemoglobin, and cystatin-based eGFR levels.

Abbreviations: LV, left ventricular; CI, confidence interval.

Table 4
Adjusted* Association of Phosphorus with LV Mass in Persons With or Without CKD

	Difference in LV Mass (g/m ²)	(95% CI)	P-value	Interaction P-value
Men				
No CKD (n = 551)	2.40	-1.73 to 6.53	0.3	0.07
CKD (n=246)	6.98	0.29 to 13.59	0.04	
Women				
No CKD (n = 133)	-4.60	-10.81 to 1.62	0.2	0.6
CKD (n=48)	-8.98	-21.40 to 3.44	0.2	

* Adjusted for age, race, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, ACE or ARB use, C-reactive protein, total cholesterol, triglycerides, hemoglobin, and cystatin-based eGFR levels.

Abbreviations: CKD, chronic kidney disease; LV, left ventricular; CI, confidence interval.

Table 5

Association of Serum Phosphorus Levels with LVH in Men and Women *

	OR	(95% CI)	P-value
Men (N=797)			
Unadjusted	1.57	1.19 to 2.08	<.01
Age and race adjusted	1.72	1.28 to 2.31	<.001
Multivariable adjusted [†]	1.39	1.01 to 1.91	0.04
Women (N=181)			
Unadjusted	0.97	0.60 to 1.57	0.9
Age and race adjusted	0.95	0.58 to 1.53	0.8
Multivariable adjusted [†]	0.49	0.26 to 0.93	0.03

* Per 1mg/dL increase in serum phosphorus levels. LVH defined as LV mass >110 g/m² in men, and > 95 g/m² in women.

[†] P for interaction by sex = 0.01. Adjusted for age, race, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, ACE or ARB use, C-reactive protein, total cholesterol, triglycerides, hemoglobin, and cystatin based eGFR.

Abbreviations: OR, odds ratio; LVH, left ventricular hypertrophy; CI, confidence interval.

Table 6

Association of Serum Phosphorus with LV Mass by HRT Use in Women^{†,*}

	N (%)	Difference in LV Mass (g/m ²)	95% CI	P-value	Interaction P-value
HRT Non-users	136 (75%)	-7.03	-14.05 to 0.00	0.05	0.22
HRT Users	45 (25%)	1.39	-7.50 to 10.27	0.9	

[†] Per 1 mg/dL increase in serum phosphorus.

* Adjusted for age, race, smoking status, diabetes, systolic blood pressure, diastolic blood pressure, ACE or ARB use, C-reactive protein, total cholesterol, triglycerides, hemoglobin, and cystatin-based eGFR levels.

Abbreviations: HRT, hormone replacement therapy; LV, left ventricular; CI, confidence interval.