Relations of serum phosphorus levels to echocardiographic left ventricular mass and incidence of heart failure in the community

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Aims	To evaluate the association of serum phosphorus with cardiac structure/function and incident heart failure.
Methods and results	We related serum phosphorus to echocardiographic left ventricular (LV) measurements cross-sectionally, and to incident heart failure prospectively in 3300 participants (mean age 44 years, 51% women) free of heart failure, myocardial infarction, and chronic kidney disease (estimated glomerular filtration rate [eGFR]<60 mL/min/1.73 m^2). Cross-sectionally, serum phosphorus was related positively to LV mass, internal dimensions, and systolic dysfunction. On follow-up (mean 17.4 years), 157 individuals developed heart failure. In models adjusting for established risk factors as time-varying covariates, each mg/dL increment in serum phosphorus was associated with a 1.74-fold risk of heart failure [95% confidence intervals (CI) 1.17–2.59]. Individuals in the highest serum phosphorus quartile experienced a two-fold (95% CI 1.28–3.40) risk of heart failure compared with participants in the lowest quartile. These relations were maintained upon additional adjustment for LV mass/dimensions and systolic dysfunction. In analyses restricted to individuals with eGFR >90 mL/min/1.73 m^2, no proteinuria and serum phosphorus <4.5 mg/dL, the association of serum phosphorus with heart failure remained robust.
Conclusion	In our community-based sample, higher serum phosphorus was associated with greater LV mass cross-sectionally, and with an increased risk of heart failure prospectively.
Keywords	Phosphorus • Congestive heart failure • Ventricle • Epidemiology • Risk factors

Introduction

Serum phosphorus concentration is tightly regulated, being determined by intestinal absorption, utilization, and renal excretion.[1] The intestinal absorption of phosphorus correlates positively with dietary intake.[2] Dietary phosphorus intake also regulates levels of the fibroblast growth factor-23 (FGF-23), which modulates renal excretion of phosphorus.[3] In chronic kidney disease (CKD) patients, phosphorus excretion is impaired, which results in the elevation of serum phosphorus concentrations. High serum phosphorus levels in CKD patients are associated with increased cardiovascular disease (CVD) mortality.[4] These clinical observations are consistent with experimental evidence that a greater dietary intake of phosphorus and higher resultant serum phosphorus levels are associated with cardiac fibrosis in uraemic rodents.[5]

Recent data suggest that higher serum phosphorus concentrations within the 'normal range' are associated with greater risk of developing CVD in individuals without CKD,[6] and in the general population.[7] One mechanism by which phosphorus may

pose greater cardiovascular hazard is the association of higher serum concentrations with left ventricular (LV) hypertrophy[8] and systolic dysfunction, a relationship well described in CKD.[9] Investigators have also linked higher serum phosphorus to a greater prevalence[10] and a higher incidence of heart failure in patients with prior myocardial infarction (MI).[6]

It is unclear, however, if serum phosphorus concentrations within the 'normal' range are associated with LV remodelling and heart failure in individuals without prior MI or CKD. We examined this hypothesis by relating serum phosphorus concentrations to LV mass, dimensions, and systolic function cross-sectionally, and to the incidence of heart failure longitudinally in a community-based sample.

Methods

Study sample

In 1972, the children of the original Framingham Study participants were enrolled along with their spouses into the Framingham Offspring Study ($n = 5124$).[11] Attendees of the second examination of the Offspring cohort (1979–82) with available laboratory data for serum phosphorus ($n = 3666$) were eligible for the present investigation. We excluded 366 individuals for the following reasons: a previous MI, congestive heart failure, atrial fibrillation, or an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m^2. After exclusions, 3300 participants (1684 women) remained eligible. For cross-sectional analyses, echocardiographic data were available on 3088 of the 3300 participants (93.6%). The present study complies with the Declaration of Helsinki. All participants provided written informed consent, and the study protocol was approved by Institutional Review Board of the Boston University Medical Center.

Measurement of serum phosphorus and risk factors

At Heart Study visits, attendees underwent medical history, physical examination, and laboratory assessment of vascular risk factors. Hypertension was defined as a systolic blood pressure ≥ 140 mmHg or a diastolic blood pressure ≥ 90 mmHg or the use of antihypertensive medications. Alcohol intake was assessed by averaging the self-reported weekly consumption of alcoholic drinks. Valvular disease was defined as the presence of any diastolic murmur, or of a systolic murmur $\geq 3/6$ on physical examination by a Heart Study physician. Diabetes was defined as a fasting blood sugar level of ≥ 126 mg/dL or the use of any hypoglycaemic agent. Fasting concentrations of serum total cholesterol, high-density lipoprotein cholesterol, serum albumin, blood sugar, and haemoglobin were measured using standardized assays. Serum creatinine was measured using the modified Jaffe method, and values were calibrated to the Cleveland Clinic Laboratory standard using a correction factor of 0.23 mg/dL. The modification of diet in renal disease (MDRD) equation was used to calculate eGFR thus: $186.3 \times$ (serum creatinine)$^{-1.154} \times$ age$^{-0.203} \times$ (0.742 for women). Proteinuria was measured by the urine dipstick test (Ames labstix, Elkhardt, IN, USA) and coded as none, trace, 1+, 2+, or more. For analytical purposes, we dichotomized proteinuria as 'none' vs. $\geq$'trace.' Serum phosphorus concentrations were measured on fasting blood samples using the standard colorimetric method (Roche Diagnostics, Alameda, CA, USA) with an intra-assay coefficient of variation of 5.6%.[7]

Echocardiographic measurements

All attendees at the second Offspring examination underwent routine transthoracic two-dimensionally guided M-mode echocardiography using a Hoffrel 201 ultrasound machine with an Aerotech 2.25-MHz transducer. The end-diastolic measurements of the left ventricle internal diameter (LVID) and the thicknesses of the posterior wall (PW) and interventricular septum (IVS) were obtained by averaging M-mode measurements in three cardiac cycles using a 'leading edge' technique, in accordance with the American Society of Echocardiography guidelines. Left ventricular wall thickness (LVWT) was derived by summing the diastolic thicknesses of the IVS and the PW. Left ventricular mass was calculated by using the formula:

$$\text{LV mass} = 0.8[1.04 \ (\text{LVID} + \text{LVWT})^3 - (\text{LVID})^3] + 0.6.$$

Left ventricular endocardial fractional shortening (FS) was calculated as (LVID − LV end-systolic diameter)/LVID.

Assessment of heart failure on follow-up

The follow-up period for the current investigation was from the second examination (1979–82) through December 2007. All Heart Study participants were under continuous surveillance for the occurrence of CVD. A team of three investigators reviewed all medical records for adjudicating possible CVD events. A diagnosis of heart failure was based on the presence of two major, or of one major and two minor criteria (Appendix 1).[12]

Statistical analyses

For cross-sectional analyses, we standardized the LV variables within each sex (mean = 0, SD = 1). We used sex-pooled multivariable linear regression to relate serum phosphorus (independent variable) to the following sex-standardized measurements (dependent variables): LV mass, LVWT, LVID, and FS. We used multivariable logistic regression models to assess the cross-sectional association of serum phosphorus with LV systolic dysfunction (FS < 0.29, corresponding to an ejection fraction of 0.50).[13] All multivariable models adjusted for age, sex, height, weight, diabetes mellitus, systolic blood pressure, treatment for hypertension, smoking, total cholesterol/HDL cholesterol ratio, valve disease, albumin, haemoglobin, eGFR, and proteinuria. We also assessed for interactions of serum phosphorus with age, sex, pulse pressure, and hypertension in multivariable models.

Our prospective analyses pooled sexes to maximize statistical power. We used Cox regression to relate serum phosphorus to the heart failure incidence, modelling serum phosphorus as a continuous variable, and as sex-specific quartiles. In primary analyses, models adjusted for baseline age, haemoglobin, and serum albumin, and for the following variables modelled as time-dependent covariates (updated every 4 years): body mass index, systolic and diastolic blood pressure, use of antihypertensive drugs, diabetes, smoking, total/high-density cholesterol ratio, presence of valve disease, eGFR, proteinuria, and occurrence of an MI on follow-up. We also performed several secondary analyses (Appendix 2). A two-sided P-value < 0.05 was considered statistically significant.

Results

The baseline characteristics of the study sample according to sex are displayed in Table 1. Mean serum phosphorus levels were approximately 0.20 mg/dL lower in men compared with women in each corresponding quartile including in subgroups, as reported by others.[14]

Table 1 Baseline characteristics of study participants

Characteristic	Men (N = 1616)	Women (N = 1684)
Age (years)	44.7 (10.3)	44.0 (9.9)
Body mass index (kg/m^2)	26.9 (3.7)	24.8 (4.8)
Systolic blood pressure (mmHg)	126 (16)	118 (16)
Diastolic blood pressure (mmHg)	81 (9)	75 (9)
Pulse pressure (mmHg)	45 (11)	43 (11)
Hypertension (%)	28.0	17.2
Treatment for hypertension (%)	9.9	8.3
Diabetes (%)	6.5	3.0
Smoking (%)	35.7	37.0
Alcohol (drinks/week)	5.3 (6.5)	2.3 (3.1)
Laboratory parameters		
Total/HDL cholesterol	5.1 (1.6)	4.0 (1.3)
Triglycerides (mg/dL)	125 (88)	87 (70)
eGFR (mL/min/1.73 m^2)[a]	106 (43)	114 (76)
Serum creatinine (mg/dL)	1.2 (0.2)	1.0 (0.2)
Albumin (gm/dL)	4.5 (0.3)	4.4 (0.3)
Haemoglobin (gm/dL)	15.5 (1.0)	13.7 (1.0)
Proteinuria (%)	2.4	1.4
Electrolytes		
Calcium (mg/dL)	9.64 (0.39)	9.58 (0.38)
Corrected calcium (mg/dL)[b]		
Quartile 1, mean (range)	9.2 (6.1–9.4)	9.1 (8.5–9.3)
Quartile 1, mean (range)	9.6 (9.4–9.6)	9.5 (9.3–9.6)
Quartile 1, mean (range)	9.8 (9.7–9.9)	9.7 (9.6–9.8)
Quartile 1, mean (range)	10.1 (9.9–11.1)	10.1 (9.8–11.2)
Phosphate (mg/dL)[c]		
Quartile 1, mean (range)	2.5 (1.6–2.7)	2.7 (1.8–2.9)
Quartile 2, mean (range)	2.9 (2.8–3.0)	3.1 (3.0–3.2)
Quartile 3, mean (range)	3.2 (3.1–3.3)	3.4 (3.3–3.5)
Quartile 4, mean (range)	3.6 (3.4–5.0)	3.8 (3.6–6.2)
Echocardiographic variables[d]		
LV mass (g)	186.3 (41.5)	127.1 (28.8)
LV mass indexed to BSA	94.2 (18.7)	76.0 (14.0)
LV diastolic dimension (cm)	5.12 (0.38)	4.62 (0.34)
LV wall thickness (cm)	1.93 (0.26)	1.64 (0.22)
Fractional shortening	0.36 (0.03)	0.38 (0.04)

All values are mean (standard deviation) unless otherwise indicated.

LV, left ventricle; BSA, body surface area.

[a]Corrected serum calcium = observed serum calcium + [0.8 × (4 − serum albumin)], if the serum albumin level is less than 4 g/dL.

[b]To convert serum phosphorus levels from mg/dL to mmol/L multiply by 0.3229.

[c]eGFR denotes estimated glomerular filtration rate calculated by using the MDRD equation (see text).

[d]All echocardiographic variables are standardized for each sex and represent the subgroup of individuals with available data (men = 1589, women = 1657).

Cross-sectional relations of serum phosphorus and echocardiographic variables

Higher serum phosphorus was positively associated with LV mass (*P* = 0.04) and LVID (*P* = 0.008) in multivariable-adjusted models (*Table 2*). The association of serum phosphorus with LV mass was maintained when LV mass was indexed to body surface area (*P* = 0.04) and when individuals with angina or coronary insufficiency (*n* = 38) were excluded from the analyses (*P* = 0.03). Left ventricular wall thickness was not related to serum phosphorus cross-sectionally. In logistic regression models, higher serum phosphorus was associated with a 2.2-fold higher odds of reduced FS (*P* = 0.052). We did not observe effect modification by age, sex, or hypertension status (*P*-value for interactions >0.05). The magnitude of the association with LV mass was quite modest (footnote, *Table 2*).

Table 2 Cross-sectional relations of echocardiographic variables and serum phosphorus

Echocardiographic variables		
Linear regression	β^a (standard error)	P-value
LV mass	0.08 (0.04)	0.04
LV diastolic internal dimensions	0.11 (0.04)	0.008
LV wall thickness	0.03 (0.04)	0.43
Logistic regression	Odds ratio (95% CI)[b]	P-value
LV systolic dysfunction (fractional shortening <0.29)	2.20 (0.99–4.85)	0.052

[a]Beta coefficient is the increment in LV measure (dependent variable) in sex-specific standardized units for each 1 mg/dL increase in serum phosphorus (independent variable). Thus, a 1 mg/dL increment in serum phosphorus is associated with an increment in LV mass of: (0.08 × 41.5), or 3.32 gm in men; (0.08 × 28.8), or 2.30 gm in women.
[b]Per 1 mg/dL increment in serum phosphorus levels. There were 38 individuals with LV systolic dysfunction (total sample = 3088).

Relations of serum phosphorus to incidence of heart failure

On follow-up (mean 17.4 years), 157 participants (63 women) developed new-onset heart failure, 246 had an MI and 54 of them had both an MI and heart failure. Age- and sex-adjusted incidence rates of heart failure rose across quartiles of serum phosphorus in the entire sample and in the subsample with eGFR ≥90 mL/min/1.73 m^2, those without proteinuria or with serum phosphorus <4.5 mg/dL (Table 3).

In multivariable models, a 1 mg/dL increase in baseline levels of serum phosphorus was associated with a 74% higher [95% confidence intervals (CI) 17–159%; P = 0.007] risk of new-onset heart failure (Table 4) even with adjustment for interim MI on follow-up. We also substituted pulse pressure in place of systolic blood pressure in multivariable models and found no significant difference in the results [hazard ratio (HR) per 1 mg/dL increase of serum phosphorus 1.90, 95% CI 1.27, 2.85; P = 0.002].

In quartile-based analyses, the highest quartile of serum phosphorus was associated with a two-fold risk (95% CI 1.28–3.40; P = 0.003) of heart failure relative to the lowest quartile (Table 4); the use of sex-specific quartiles complemented the analyses of serum phosphorus as a continuous variable, in which values for men and women were pooled and models adjusted for sex. There was a statistically significant trend of rising heart failure risk across quartiles of serum phosphorus (P = 0.02). In sensitivity analyses using pooled sex quartiles (instead of sex-specific quartiles), we obtained results consistent with the primary analysis [HR per quartile increment 1.29, 95% CI 1.10–1.52, P = 0.002; HR for the top quartile (relative to the lowest) 2.14, 95% CI 1.31–3.50, P = 0.003]. These results were corroborated with regression splines that demonstrated a linear trend for higher heart failure risk across serum phosphorus values (Figure 1). We did not observe any effect modification by age, sex, hypertension, pulse pressure, or eGFR (all P-values exceeded 0.05).

Table 3 Age and sex-adjusted cumulative incidence of heart failure per 1000 person-years according to sex-specific quartiles of serum phosphorus

Quartiles of serum phosphorus[a]	No. events/no. at risk (%)	Age- and sex-adjusted incidence of heart failure per 1000 person-years (95% CI)
All individuals (n = 3300)		
Quartile 1	32/764 (4.19)	2.36 (1.61–3.33)
Quartile 2	43/885 (4.86)	2.70 (1.96–3.64)
Quartile 3	39/899 (4.34)	2.58 (1.84–3.53)
Quartile 4	43/752 (5.72)	3.45 (2.50–4.65)
Subgroup[b] (n = 1850)		
Quartile 1	11/405 (2.72)	1.59 (0.79–2.84)
Quartile 2	20/483 (4.14)	2.30 (1.40–3.55)
Quartile 3	16/497 (3.22)	1.99 (1.14–3.24)
Quartile 4	24/465 (5.16)	3.17 (2.03–4.71)

[a]All quartile data are calculated by pooling sex-specific quartiles. Sex-specific quartile cut-points for serum phosphorus (in mg/dL) are displayed in Table 1.
[b]Individuals with eGFR >90 mL/min/1.73 m^2, without proteinuria, and serum phosphorus <4.5 mg/dL.

In adjusting for LV internal dimensions (or LV mass) and presence of LV systolic dysfunction, the results of primary analyses remained robust (Table 5). In analyses excluding the 38 individuals with prevalent LV systolic dysfunction, the association of serum phosphorus with heart failure was maintained (Table 5).

Subgroup analyses

Subgroup analyses were performed to exclude confounding by subclinical kidney disease. There were 71 incident heart failure events in the 1850 individuals with 'normal' renal function, (eGFR >90 mL/min/1.73 m^2, no proteinuria) and with a serum phosphorus <4.5 mg/dL (Table 3). In time-dependent covariate models, a 1 mg/dL increase in serum phosphorus was associated with a 2.40-fold incidence of heart failure (Table 4). Individuals in the fourth quartile of serum phosphorus carried a 3.11-fold risk of new-onset heart failure compared with those in the lowest quartile (Table 4). In this subgroup of individuals with potentially normal kidney functions, the increasing trend of higher incidence of heart failure with greater serum phosphorus remained significant (P = 0.02).

In additional analyses, the association remained strong in models adjusting for LV systolic dysfunction and LV internal dimensions (or LV mass; Table 5), and in analyses excluding 15 individuals with LV systolic dysfunction in this subsample (Table 5).

Discussion

Principal findings

First, cross-sectionally higher serum phosphorus was associated with greater LV mass and larger LV internal dimensions in individuals without CKD or prior MI, and this association was independent of hypertension, favouring the possibility that serum phosphorus is associated with eccentric hypertrophy (as

Table 4 Cox proportional hazard models examining the relations of serum phosphorus levels to incidence of heart failure

Model[a]	Entire sample		Subsample[b]	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Serum phosphorus, per mg/dL increment	1.74 (1.17–2.59)	0.007	2.40 (1.29–4.46)	0.006
Categorical model[c]				
Quartile 1	Referent		Referent	
Quartile 2	1.62 (0.99–2.64)	0.05	2.26 (1.00–5.11)	0.05
Quartile 3	1.18 (0.71–1.96)	0.53	1.40 (0.59–3.32)	0.45
Quartile 4	2.09 (1.28–3.40)	0.003	3.11 (1.40–6.94)	0.006
Trend across quartiles	1.20 (1.03–1.40)	0.02	1.33 (1.04–1.69)	0.02

[a]All multivariable models are adjusted for baseline age, sex, haemoglobin, serum albumin, and for the following time-dependent variables (updated every 4 years): BMI, diabetes mellitus, systolic blood pressure, treatment for hypertension, smoking, total/HDL cholesterol ratio, valve disease, eGFR, proteinuria, and interim MI on follow-up.
[b]Subsample included individuals with eGFR >90 mL/min/1.73 m^2, without proteinuria and with serum phosphorus <4.5 mg/dL. There were 71 heart failure cases in this subgroup.
[c]All quartiles for categorical models were analysed by pooling sex-specific quartiles (see *Table 1* for quartile cut-points for the whole sample. Subsample quartiles for men were 1.6–2.7, 2.8–3.0, 3.1–3.3, and 3.4–4.4 mg/dL; and for women were 1.9–2.9, 3.0–3.2, 3.3–3.5, and 3.6–4.4 mg/dL).
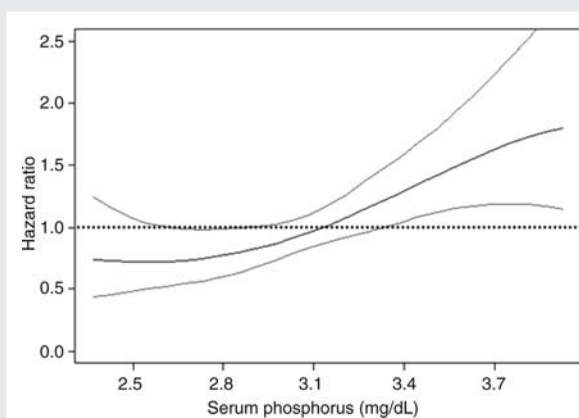

Figure 1 Regression spline based on curve with multivariable models (adjusted for all baseline covariates—see text) examining relations of serum phosphorus to the incidence of heart failure on follow-up. Figure shows estimated multivariable hazard ratios for heart failure (*Y* axis) in relation to serum phosphate (*X* axis) as a function of penalized regression splines.

opposed to concentric hypertrophy). The magnitudes of these associations were modest, rendering their clinical significance unclear. Second, serum phosphorus within a 'normal' range was positively associated with the risk of heart failure. Individuals in the highest quartile of serum phosphorus experienced a more than two-fold risk of heart failure compared with the lowest quartile, a finding that remained robust in the subgroup of individuals with 'normal' kidney function (as defined by eGFR calculated with the MDRD equation). Third, the association of serum phosphorus with heart failure risk persisted in analyses adjusting for LV dimensions/mass, and in subsamples excluding individuals with LV systolic dysfunction, suggesting that the cross-sectional relations to subclinical LV remodelling could not entirely account for the observed association. This is not surprising, given the modest

strength of the cross-sectional association. The strength of the association, its consistency across multiple analyses, the biological plausibility, and the temporal sequence are consistent with the possibility that the observed association may be causal. Of note, serum phosphorus levels may be modifiable with alterations of dietary intake[2,15,16] and affirmed by the Institute of Medicine.[17] However, this issue is controversial because some investigators disagree.[18] Additionally, serum phosphorus may differ in individuals secondary to genetic polymorphisms influencing FGF-23 production,[19] or to *Klotho* gene variants.[20] Therefore, if confirmed, our observations raise the possibility that serum phosphorus may be a modifiable risk factor for heart failure.

Mechanisms

Several mechanisms may explain our observations. First, higher serum phosphorus may be a marker of low vitamin D levels.[15] Lower serum vitamin D is cross-sectionally associated with greater plasma renin activity,[21] higher blood pressure,[22] prevalent heart failure,[10] and with a greater risk of CVD in the community.[23] Additionally, vitamin D supplementation lowers serum phosphorus and is associated with an improvement in LV systolic function[24] and in the circulating cytokine profile in patients with overt heart failure.[25] On a parallel note, vitamin D receptor knockout animals demonstrate hypertrophy of cardiomyocytes, perhaps secondary to over-stimulation of the renin-angiotensin system[26] or as a result of the direct action of calcitriol.[27] Thus, alterations in vitamin D levels in those with higher serum phosphorus may contribute to the observed link between the mineral and LV mass and heart failure.

Second, higher serum phosphorus levels (>2 mg/dL) are associated with greater vascular smooth muscle calcification *in vitro*, which may be partly regulated through increased osteopontin expression.[28] Furthermore, higher serum phosphorus may indirectly stimulate smooth muscle cell to undergo phenotypic changes pre-disposing them to calcification through a sodium-dependent phosphate co-transporter identified as Pit-1.[29] Such vascular calcification may increase vascular stiffness[30] that can

Table 5 Cox proportional hazard models examining the relations of serum phosphorus levels to incidence of heart failure: additional adjustment for LV measurements

Multivariable models[a]	Entire sample with echocardiographic data		Subsample[b]	
	Hazard ratio per mg/dL serum phosphorus increment[a] (95% CI)	P-value	Hazard ratio per mg/dL serum phosphorus increment[a] (95% CI)	P-value
A. Samples including individuals with prevalent LV systolic dysfunction[c]				
1. Adjusting for LV mass and LV systolic dysfunction	1.79 (1.14–2.81)	0.01	3.06 (1.47–6.36)	0.003
2. Adjusting for LV diastolic dimensions and LV systolic dysfunction	1.71 (1.09–2.68)	0.02	2.73 (1.33–5.62)	0.007
B. Samples excluding individuals with prevalent LV systolic dysfunction[c]				
1. Adjusting for LV mass	1.86 (1.17–2.94)	0.008	3.26 (1.56–6.81)	0.002
2. Adjusting for LV diastolic dimensions	1.79 (1.13–2.82)	0.02	2.96 (1.43–6.15)	0.004

[a]All multivariable models are adjusted for baseline age, sex, haemoglobin, serum albumin, and for the following time-dependent variables (updated every 4 years): BMI, diabetes mellitus, systolic blood pressure, treatment for hypertension, smoking, total/HDL cholesterol ratio, valve disease, eGFR, proteinuria, and interim MI on follow-up.
[b]Subsample included individuals with eGFR >90 mL/min/1.73 m^2, without proteinuria and with serum phosphorus <4.5 mg/dL, and with available echocardiographic measurements (n = 1739).
[c]A. There were 120 heart failure events in the entire sample with available echocardiographic data, and 56 heart failure events in the subsample (defined above). B. There were 115 heart failure events in the entire sample with available echocardiographic data, and 54 events in the subsample (defined above). Thirty-eight individuals with LV systolic dysfunction in the larger sample, and 15 individuals with LV systolic dysfunction in the smaller sample were excluded (compared with samples in A).

pre-dispose individuals to heart failure. Of note, in our analyses the association of serum phosphorus with heart failure risk was maintained in analyses adjusting for the occurrence of an MI during follow-up, suggesting that non-ischaemic mechanisms may contribute to the observed association.

Third, in animal models,[26] in in vitro human parathyroid tissue cells[31] and in humans,[2] greater phosphorus levels have been linked to the development of secondary hyperparathyroidism. Higher parathyroid hormone (PTH) levels have been shown to induce cardiac hypertrophy[32] and are related to higher CVD mortality in community dwelling individuals.[33] Therefore, higher serum phosphorus may reflect subtle alterations in the PTH system, which may mediate the associations with LV mass and heart failure risk.

Strengths and limitations

The large community-based sample, the long follow-up time, the comprehensive adjustment for confounders as time-dependent covariates, and the consistency of findings in multiple analyses strengthen the present investigation. There are several limitations that must be acknowledged. We do not have data on serum PTH or vitamin D supplementation/levels or on dietary phosphorus intake at the baseline examination at which serum phosphorus was available to clarify mechanisms underlying the observed association. Also we did not have repeated phosphorus levels to assess intra-individual variability, however data from another cohort study suggests fairly good stability of serum phosphorus within individuals with a high (0.72) reliability coefficient.[34] Participants in our study were mostly middle-aged and of European descent, which limits the generalizability of our results.

Conclusions

In our large community-based sample of individuals without prior MI or CKD, serum phosphorus within the 'normal range' was associated with greater LV mass cross-sectionally, and with increased risk of heart failure prospectively.

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Conflict of interest: none declared.

Appendix 1: heart failure criteria

Briefly, major criteria include the presence of paroxysmal nocturnal dyspnoea, jugular venous distension, orthopnoea, hepato-jugular reflex, pulmonary rales, acute pulmonary oedema, third heart sound, cardiomegaly on a radiograph, central venous pressure of >16 cm of water, and weight loss of >4.5 kg during first 5 days of treatment for suspected heart failure. Minor criteria consist of bilateral ankle oedema, dyspnoea on exertion, nocturnal cough, hepatomegaly, pleural effusion, and heart rate >120 b.p.m.[22]

Appendix 2: secondary analyses

In order to assess potential non-linearity of association between serum phosphorus and the risk of heart failure, we examined multivariable generalized additive models using penalized splines, adjusting for all the covariates in our multivariable models (same as in our primary analyses). We also evaluated effect modification of the association of serum phosphorus with heart failure risk by age, sex, hypertension, and eGFR by incorporating interaction terms in the multivariable models. We also performed additional analyses adjusting for baseline LV measurements (n = 3088, with available measurements were eligible) in addition to all covariates noted above, to evaluate if any potential association of serum phosphorus with heart failure was mediated by the association of the mineral with subclinical LV remodelling (as reflected by LV measurements).

To evaluate the impact of serum phosphorus within the 'normal range' and to avoid potential confounding by renal dysfunction, we repeated our analyses in a subsample that excluded all individuals with eGFR <90 mL/min/1.73 m^2, those with proteinuria (trace or more) or with serum phosphorus ≥ 4.5 mg/dL ($n = 1850$). Paralleling the analyses of the larger sample, we performed additional analyses adjusting for LV measurements ($n = 1739$, with available measurements).

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