University Library

MINERVA ACCESS

A gateway to Melbourne's research publications

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:
Toussaint, ND;Damasiewicz, MJ;Holt, SG;Lu, ZX;Magliano, DJ;Atkins, RC;Chadban, SJ;Shaw, JE;Polkinghorne, KR

Title:
Relationship Between Urinary Phosphate and All-Cause and Cardiovascular Mortality in a National Population-Based Longitudinal Cohort Study

Date:
2022-09-01

Citation:
Toussaint, N. D., Damasiewicz, M. J., Holt, S. G., Lu, Z. X., Magliano, D. J., Atkins, R. C., Chadban, S. J., Shaw, J. E. & Polkinghorne, K. R. (2022). Relationship Between Urinary Phosphate and All-Cause and Cardiovascular Mortality in a National Population-Based Longitudinal Cohort Study. Journal of Renal Nutrition, 32 (5), pp.510-519. https://doi.org/10.1053/j.jrn.2021.10.009.

Persistent Link:
https://hdl.handle.net/11343/336008

Relationship Between Urinary Phosphate and All-Cause and Cardiovascular Mortality in a National Population-Based Longitudinal Cohort Study

Check for updates

Nigel D. Toussaint, MBBS, FRACP, PhD,[*,†] *Matthew J. Damasiewicz, MBBS, FRACP, PhD,*[‡,§] *Stephen G. Holt, MBBS, FRACP, PhD,*[*,†] *Zhong X. Lu, MBBS, MAACB, PhD, FRCPA,*[§,¶] *Dianna J. Magliano, PhD,*[**,††] *Robert C. Atkins, MBBS, MSc, DSc, FRACP,*[**] *Steven J. Chadban, FRACP, PhD,*[‡‡,§§] *Jonathan E. Shaw, MD, MRCP(UK), FRACP,*[**] *and Kevan R. Polkinghorne, MBChB, FRACP, PhD*[‡,§,††]

Objectives: High dietary phosphate intake may lead to adverse outcomes including cardiovascular disease (CVD). Urinary phosphate excretion, a marker of intestinal phosphate absorption, may be a more reliable marker of phosphate homeostasis in steady state than serum phosphate. Studies report good agreement between urine phosphate-to-creatinine ratio (uPiCr) and 24-hour urinary phosphate; however, whether uPiCr is associated with increased risk of CVD or mortality remains uncertain. This study aimed to assess the relationship between uPiCr and all-cause and CVD mortality.

Design and Methods: This is an observational longitudinal cohort study using data from the population-based national Australian Diabetes, Obesity and Lifestyle study (n = 10,014 participants). Non-linear association between uPiCr and all-cause and CVD mortality was assessed using fractional polynomial transformations. Cox proportional hazards regression models were used to estimate adjusted hazard ratios for all-cause and CVD mortality.

Results: Median age [interquartile range] was 50 [41-62] years, and 46% were male. Median uPiCr was 1.38 [1.02-1.79] mmol/mmol. Median follow-up time was 16.9 years with 1,735 deaths. uPiCr was associated with all-cause and CVD mortality in univariate models and when adjusted for age and gender. However, associations were not significant in multivariate models. Sensitivity analyses excluding participants with chronic kidney disease (CKD) revealed a significant J-shaped association between uPiCr and all-cause mortality. Urine phosphate alone showed an association with increased all-cause mortality in a similar J-shape relationship.

Conclusion: Although no association between uPiCr and all-cause and CVD mortality was observed in multivariate analyses in the whole cohort, a significant relationship between uPiCr and mortality in those without CKD suggests that uPiCr may have predictive validity for future adverse outcomes in people with no CKD.

Keywords: cardiovascular disease; chronic kidney disease; dietary phosphate; mineral metabolism; mortality; phosphate; urinary phosphate excretion

© 2021 by the National Kidney Foundation, Inc. All rights reserved.

Introduction

PHOSPHATE HOMEOSTASIS IS essential for normal cellular function in many living organisms. In humans, the majority of phosphate is stored in bone as hydroxyapatite, and less than 1% is extracellular.[1] In good health, the kidneys are largely responsible for maintaining normal extra-cellular phosphate concentrations,[2] with intestinal absorption and flux from bone being the main determinants of the phosphate load filtered by the kidneys.[3] The exact regulatory mechanisms of phosphate homeostasis however remain poorly understood. Complex and interconnected kidney and bone endocrine and paracrine

[*]*Department of Nephrology, The Royal Melbourne Hospital, Parkville, Victoria, Australia.*
[†]*Department of Medicine, University of Melbourne, Parkville, Victoria, Australia.*
[‡]*Department of Nephrology, Monash Health, Clayton, Victoria, Australia.*
[§]*Department of Medicine, Monash University, Clayton, Victoria, Australia.*
[¶]*Monash Pathology, Monash Health, Melbourne, Victoria, Australia.*
[**]*Baker Heart and Diabetes Institute, Melbourne, Victoria, Australia.*
[††]*School of Public Health and Preventive Medicine, Monash University, Melbourne, Victoria, Australia.*
[‡‡]*Department of Nephrology and Transplantation, Royal Prince Alfred Hospital, Sydney, New South Wales, Australia.*
[§§]*University of Sydney, Sydney, New South Wales, Australia.*

Conflict of Interest: The authors have no conflict of interest.

Address correspondence to Nigel D. Toussaint, MBBS, FRACP, PhD, Department of Nephrology, The Royal Melbourne Hospital, Grattan Street, Parkville, Victoria 3052, Australia. E-mail: Nigel.Toussaint@mh.org.au

© 2021 by the National Kidney Foundation, Inc. All rights reserved.

1051-2276/$36.00
https://doi.org/10.1053/j.jrn.2021.10.009

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

pathways are involved which are, in part, regulated by parathyroid hormone, 1,25-dihydroxyvitamin D (calcitriol), and fibroblast growth factor-23 (FGF-23).[4,5]

Phosphate deficiency is associated with muscle weakness, impaired leukocyte function, and abnormal bone mineralization.[3] Conversely, phosphate excess has been associated with secondary hyperparathyroidism, vascular calcification, endothelial dysfunction, cardiovascular disease (CVD), and increased cell senescence.[6-11] Elevated serum phosphate levels are independent risk factors for CVD and all-cause mortality in advanced chronic kidney disease (CKD).[12,13] More recently, observational studies in healthy individuals or those with CVD but normal kidney function have reported an independent and positive association between serum phosphate levels and increased risk of incident CVD, all-cause mortality, and progression of kidney impairment.[14-20]

In steady state, urinary phosphate excretion (UPE), as measured by 24-hour urine collection, is a reliable marker of intestinal phosphate absorption and has been used to examine effects of phosphate lowering interventions in patients with CKD.[21] Fractional excretion of phosphate (FePi) is a measure of renal phosphate excretion relative to serum phosphate levels, and both UPE and FePi may be helpful surrogate markers for disorders of phosphate homeostasis in clinical practice.[22] Timed urine collections are inconvenient and prone to error, particularly from inadequate collection. Some, but not all, previous studies report reasonable agreement between spot urine phosphate-to-creatinine ratio (uPiCr) and 24-hour UPE, and a spot uPiCr ratio may permit reliable and rapid estimation of daily UPE.[23-25] In a population study in which participants should generally be in a steady state of phosphate turnover, this would more than likely be true.

Dietary phosphate intake is only weakly linked to serum phosphate levels and the relationship between phosphate intake and adverse outcomes remains unclear.[26-29] Several studies have reported associations between phosphate intake and adverse outcomes in both CKD and general population cohorts.[26-29] The small number of studies that have examined phosphate excretion, either 24-hour UPE or uPiCr, have reported conflicting associations with all-cause and CVD mortality.[29-31] We examined the relationship between UPE, determined by uPiCr, and all-cause and CVD mortality in a large, population-based cohort from the Australian Diabetes, Obesity and Lifestyle study (AusDiab). We hypothesized that in a general population cohort, elevated UPE would be associated with increased adverse outcomes.

Methods

Study Design and Population

The AusDiab study is a national population-based longitudinal study with baseline examinations conducted between May 1999 and December 2000. Its primary aim is to evaluate the prevalence of diabetes, obesity, and CVD risk factors in Australian adults aged ≥25 years. Survey methods and sample collection have been previously described in detail.[32] In brief, a population-based sample was obtained using a stratified sampling cluster method. A total of 20,237 adults completed the household interview, and 11,247 (55.3%) presented for the on-site examination. Participants provided informed consent, and the Human Research Ethics Committees of the International Diabetes Institute, Alfred Hospital, and the Australian Institute of Health and Welfare approved the study. For this analysis, participants were excluded from the current analysis if they were pregnant, had missing or implausibly high uPiCr values (uPiCr >8 mmol/mmol), had a missing date of death, or had missing values for any of the covariates included in the final models.

Study Measurements

Details of the biomedical tests in the AusDiab study have been previously reported.[33-35] Participants who attended a testing site at baseline underwent a physical examination and had a fasting blood sample and random morning spot urine collected. Demographic data and information were collected using standardized interviewer-administered questionnaires. Hypertension was defined as a systolic blood pressure ≥140 mm Hg or a diastolic blood pressure ≥90 mm Hg. Height, weight, and waist circumference were calculated using standard procedures. Body mass index was calculated from weight and height measurements, with obesity defined as a body mass index ≥30 kg/m^2. Standard World Health Organization criteria for the diagnosis of abnormal glucose metabolism were used. Diabetes was diagnosed on the basis of fasting plasma glucose level ≥7.0 mmol/L (126.1 mg/dL), 2-hour plasma glucose level ≥11.1 mmol/L (200 mg/dL), or current treatment with insulin or oral hypoglycemic medication. Smoking status was self-reported. Cholesterol and triglyceride levels were measured on fasting serum samples and assessed as continuous variables. CVD at baseline was assessed by a questionnaire using standard questions which were repeated and then adjudicated. Dietary phosphate intake was assessed through a validated self-administered questionnaire, the Anti-Cancer Council of Victoria Dietary Questionnaire.[36] Leisure time physical activity was reported for the previous week as none, insufficient (1-149 minutes), and sufficient (≥150 minutes), using the Active Australia Questionnaire.[37]

Laboratory Measures

Blood and urine specimens were centrifuged on-site, transported to a central laboratory, and stored at −80°C until analysis. Urine albumin was measured by rate nephelometry using a Beckman Array (Beckman Coulter, Inc., Brea, CA) in fresh urine samples at the time of original collection before freezing for storage. Urine creatinine (uCr) was measured by the modified kinetic Jaffe reaction using the

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

Olympus AU600 auto-analyzer, with a coefficient of variation (CV) of 9.9% at 7.5 mmol/L. Albuminuria was defined as urine albumin-to-creatinine ratio (ACR) ≥2.5 mg/mmol in males and ≥3.5 mg/mmol in females. Urine phosphate (uPi) was measured in thawed stored samples using molybdate by a photometric ultraviolet method on an AU5812 Chemistry Analyzer (Beckman Coulter, Inc.); the CVs for uPi were 4.8% at 4.35 mmol/L, 3.8% at 12.6 mmol/L, and 3.4% at 24.3 mmol/L. Serum creatinine (Cr) was measured using an isotope dilution mass spectrometry aligned enzymatic method (Roche Modular; Roche Diagnostics, North Ryde, NSW, Australia). Estimated glomerular filtration rate (eGFR) was calculated using the CKD Epidemiology Collaboration equation,[38] with impaired eGFR defined as an eGFR <60 mL/min/1.72 m^2, consistent with CKD stage 3a or higher. Serum 25-hydroxyvitamin D was measured using a direct competitive chemiluminescent immunoassay on a LIAISON analyzer (DiaSorin Inc., Stillwater, MN) with an interassay CV of 7.0% at 45 nmol/L and 6.3% at 93 nmol/L.

Mortality and Cardiovascular Outcomes

Mortality status and cause(s) of death were obtained from the National Death Index using methods previously described.[39] Follow-up for all-cause and CVD mortality was to the date of death or April 17, 2017, whichever occurred first. CVD mortality was defined by an underlying cause of death coded I10-I25, I46.1, I48, I50-I99, or R96 according to the 2006 International Classification of Diseases 10th revision. In cases where the underlying cause of death was uncomplicated diabetes (E109, E119, or E149) or unspecified hyperlipidemia (E785), CVD was considered to be the cause of death if any of the CVD codes (I10-I25, I46.1, I48, I50-I99, or R96) were recorded in the first position on the death certificate.

Statistical Analysis

Differences in baseline characteristics of the study population were compared across increasing quartiles of uPiCr. Continuous and categorical variables were assessed using one-way analysis of variance and chi-squared tests, respectively. Based on previously published literature[27-29] we hypothesized that a non-linear association, potentially U-shaped relationship, exists between uPiCr and mortality. This was formally tested with fractional polynomial transformations, which are a special case of the conventional polynomial.[40] First-degree fractional polynomial functions are monotonic and second-degree fractional polynomial functions can represent a variety of curve shapes with at most one maximum or minimum. Here, a predefined set of unique and repeated powers of the continuous predictor are chosen (where the powers [p] are −2, −1, −0.5, 0, 0.5, 1, 2, 3), and then are formally compared to the linear model with a closed test procedure (the *fp* command in Stata). Comparison of the final selected fractional polynomial of uPiCr to the linear form was assessed using a likelihood ratio test.

After initial testing, the best fitting function form for the relationship between uPiCr and mortality was the second-degree fractional polynomial transformation 0.5, 0.5 ($P < .001$ compared to the linear model), formally represented by $x^{0.5}$, $x^{0.5} \log x$, where x represents the continuous covariate, in this case uPiCr. The second-degree fractional polynomial transformed uPiCr variables were used for all subsequent analyses. As the hazard ratios for the transformed uPiCr variables are themselves not directly interpretable, model results are presented in 2 ways. First, the non-linear relationship between uPiCr and the outcomes of interest was plotted graphically using the model-based coefficients and second, representative hazard ratios were calculated across the range of uPiCr values in the study population, with the 25th centile acting as the reference value. Cox proportional hazards regression models were constructed to estimate all-cause and CVD mortality hazard ratios. Proportional hazards assumptions were satisfied for all variables except participant age and therefore all models were additionally stratified by participant age group (25-34, 35-44, 45-54, 55-64, 65-74, ≥75 years). We constructed 3 models: model 1 (age stratified, unadjusted), model 2 (age stratified, adjusted for age and gender), and model 3 (age stratified, adjusted for gender, age, dietary phosphate intake, eGFR, urine ACR, diabetes status, systolic and diastolic blood pressure, CVD, waist-to-hip ratio, smoking status and serum cholesterol, triglyceride, 25(OH) D levels). Urine ACR and triglyceride levels were log-transformed to ensure a normal distribution prior to analysis.

Finally, 2 sensitivity analyses were performed. First, we assessed the relationship of uPi concentrations alone (not corrected for uCr concentration) on mortality. Second, we reassessed the uPiCr mortality relationship in a subgroup which was free of CKD at baseline (CKD defined as an eGFR <60 mL/min/1.72 m^2 with or without albuminuria or an eGFR ≥60 mL/min/1.72 m^2 with albuminuria). This sensitivity analysis was performed to exclude people with CKD where phosphate homeostasis may be impaired and instead analyze a subgroup with normal kidney function ideally expected to be in steady state. Also, uPiCr measurement may not be an accurate determination of phosphate balance and correlates well with 24-hour UPE in those with CKD.[25] All analyses were conducted using Stata version 15.1 (Stat Corp, College Station, TX).

Results

A total of 11,247 participants attended the baseline AusDiab survey. Of these, 131 had missing and 3 had extreme (>8 mmol/mmol) uPiCr values; 58 were pregnant at the time of the survey; 9 were identified as deceased at subsequent follow-up but did not have a date of death recorded; and a further 1,032 participants had missing values for one

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

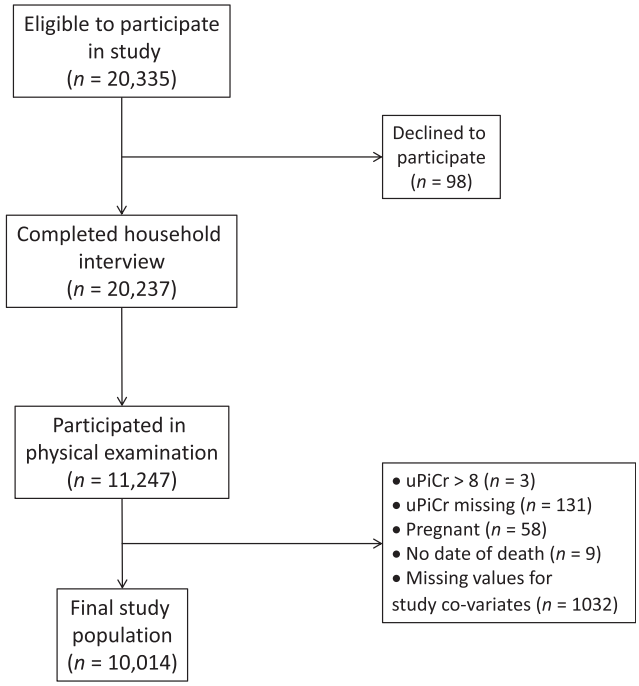

Figure 1. Population flow during the study period and determination of final cohort. uPiCr, urine phosphate-to-creatinine ratio.

or more of the covariates included in the final models. After excluding these, 10,014 participants were left for analysis (Fig. 1).

Baseline characteristics of the overall cohort, as well as stratified by quartiles of uPiCr, are presented in Table 1. The distribution of uPiCr of the study cohort is shown in Figure S1, with a median value (interquartile range) of 1.38 [1.02-1.79] mmol/mmol. The majority of the study cohort had a uPiCr between 0.5 and 2.5 mmol/mmol.

Overall, the median age [interquartile range] of participants was 50 [41-62] years, 46% were male, 33.1% had a diagnosis of hypertension, 8.5% had diabetes mellitus, and 8.4% had CVD. Participants with a higher uPiCr quartile were older, more likely to be female, and had a higher prevalence of diabetes, CVD, and hypertension. Kidney function differed significantly across the quartiles and decreased as uPiCr quartile increased, although the absolute difference was not large. The proportion of participants with albuminuria increased 60% between those in the lowest quartile compared to the highest (5.9 vs. 9.9%). Dietary phosphate intake was inversely related to uPiCr, with lower dietary intake in participants with higher uPiCr.

People with CKD (n = 991) had higher uPiCr compared to those without CKD (1.56 ± 0.67 vs. 1.43 ± 0.61 mmol/mmol, $P < .001$) but lower uPi (17.16 ± 9.7 vs. 19.36 ± 10.4 mmol, $P < .001$) and lower dietary phosphate intake (19.4 ± 38.5 vs. 31.7 ± 48.0 mg/day, $P < .001$).

All-Cause Mortality

During a median follow-up of 16.9 years, there were 1747 deaths, representing a crude mortality rate of 190.4 per 1,000 person-years of follow-up. A J-shaped relationship was demonstrated between uPiCr and all-cause mortality in the unadjusted and age- and gender-adjusted models (Tables 2 and 3) with increasing risk of death at low and high uPiCr values with a nadir of uPiCr at 1.0 mmol/mmol. Representative hazards ratios, referenced to a uPiCr at 1.0 mmol/mmol, are presented in Table 2. After full adjustment in the multivariable model, the association between uPiCr and all-cause mortality was attenuated and no longer significant (Tables 2 and 3, Fig. 2A).

Cardiovascular Disease Mortality

During a median follow-up of 13.6 years, there were 518 deaths due to CVD, representing a crude mortality rate of 39.6 per 1,000 person-years of follow-up. Similarly, for CVD mortality both low and high uPiCr was significantly associated with CVD mortality in the unadjusted and age- and gender-adjusted model (Tables 2 and 3). Similarly, after full adjustment in the multivariable model the relationship between uPiCr and CVD mortality was no longer significant (Tables 2 and 3, Fig. 2B).

Sensitivity Analyses

In the first sensitivity analysis, we explored the relationship between uPi concentrations alone and all-cause and CVD mortality. The distribution of uPi of the study cohort is shown in Figure S2. Again, a non-linear J-shape relationship was demonstrated ($P = .019$ vs. the linear model) between uPi and all-cause mortality in the unadjusted and age- and gender-adjusted models (Table S1). In the multivariable model, the association with uPiCr was attenuated but remained significant at increasing uPi values (Table S1, Figure S3A). Representative hazards ratios, referenced

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

Table 1. Baseline Cohort Characteristics: Overall AusDiab Cohort and Stratified by Quartiles of Urine Phosphate/Creatinine Ratio

Characteristic	Overall	Quartile 1 (<1.02)	Quartile 2 (1.02 to <1.38)	Quartile 3 (1.38 to <1.79)	Quartile 4 (≥1.79)	*P* Value
uPiCr (mmol/mmol)	1.38 [1.02-1.79]	0.79 [0.60-0.92]	1.21 [1.12-1.30]	1.57 [1.47-1.67]	2.12 [1.93-2.42]	<.001
Age (y)	50 [41-62]	45 [37-55]	50 [40-61]	52 [42-63]	54 [45-67]	<.001
Male sex (%)	4,610 (46.0)	1,456 (57.9)	1,279 (51.2)	1,120 (44.4)	755 (30.5)	<.001
Smoker (%)	1,591 (15.9)	435 (17.3)	377 (15.1)	388 (15.4)	392 (15.8)	.16
BMI (%)	26.4 [23.6-29.6]	26.4 [23.7-29.1]	26.5 [23.8-29.3]	26.4 [23.5-29.6]	26.2 [23.3-29.7]	.21
SBP (%)	129.7 (18.9)	128.2 (17.1)	129.9 (18.6)	130.1 (19.0)	130.8 (20.5)	<.001
DBP (%)	70.4 (11.8)	71.2 (11.5)	71.2 (11.6)	70.1 (12.0)	68.9 (11.9)	<.001
Hypertension (%)	3,330 (33.1)	725 (26.9)	822 (32.8)	889 (35.1)	940 (37.8)	<.001
DM (%)	847 (8.5)	115 (4.6)	180 (7.2)	241 (9.5)	311 (12.6)	<.001
CVD (%)	841 (8.4)	168 (6.7)	201 (8.0)	201 (8.0)	222 (10.1)	<.001
IHD (%)	685 (6.8)	146 (5.8)	161 (6.5)	176 (7.0)	202 (8.2)	.009
eGFR (mL/min/1.73 m^2)	95.6 ± 17.1	97.9 ± 16.0	95.0 ± 17.1	94.5 ± 17.5	94.8 ± 17.6	<.001
CKD* (%)	991 (9.9)	184 (7.3)	230 (9.2)	273 (10.8)	304 (12.3)	<.001
uACR (mg/mmol)	0.57 [0.40-1.01]	0.52 [0.37-0.89]	0.54 [0.39-0.95]	0.57 [0.41-1.00]	0.68 [0.46-1.28]	<.001
Cholesterol (mmol/L)	5.66 ± 1.07	5.58 ± 1.09	5.67 ± 1.08	5.66 ± 1.03	5.73 ± 1.07	<.001
Triglycerides (mmol/L)	1.29 [0.90-1.90]	1.30 [0.92-1.95]	1.30 [0.91-1.93]	1.27 [0.87-1.89]	1.20 [0.83-1.88]	<.001
Serum 25(OH)D (nmol/L)	64.0 ± 24.7	65.6 ± 25.2	64.7 ± 24.6	63.6 ± 24.6	62.0 ± 24.1	<.001
Sufficient exercise† (%)	5,219 (52.1)	1,433 (57.0)	1,313 (52.6)	1,277 (50.6)	1,196 (48.3)	<.001
Dietary phosphate intake (mg/d)	9.4 [0.9-41.3]	11.4 [0.9-45.9]	10.7 [1.0-43.6]	8.3 [0.6-40.5]	7.1 [0.6-35.5]	<.001
All-cause mortality (%)	1,735 (17.3)	314 (12.5)	398 (15.9)	451 (17.9)	572 (23.1)	<.001
Cardiovascular mortality (%)	518 (5.2)	100 (4.0)	102 (4.1)	136 (5.4)	180 (7.3)	<.001

Continuous variables are presented as median [interquartile range], mean ± standard deviation, or categorical n (%).

25(OH)D, 25-hydroxyvitamin D; AusDiab, Australian Diabetes, Obesity and Lifestyle study; BMI, body mass index; CKD, chronic kidney disease; CVD, cardiovascular disease; DBP, diastolic blood pressure; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; IHD, ischemic heart disease; SBP, systolic blood pressure; uACR, urinary albumin-to-creatinine ratio; uPiCr, urinary phosphate-to-creatinine ratio.

*CKD defined as eGFR <60 mL/min/1.73 m^2 or uACR ≥3 if eGFR ≥60 mL/min/1.73 m^2.

†Exercise was classified as sufficient physical activity >150 min/wk.

to a uPi at 1.4 mmol (25th centile) are presented in Table S2. As for all-cause mortality, uPi concentration was significantly associated with CVD mortality in the unadjusted model and age- and gender-adjusted model but not in the multivariable model (Tables S1 and S2, Figure S3B).

In the second sensitivity analysis, we repeated the main analysis after excluding 991 participants with baseline CKD to exclude participants who may have impaired phosphate homeostasis (due to reduction in kidney function). In contrast to the main analysis, in all models the relationship

Table 2. All-Cause and Cardiovascular Disease Mortality as a Function of Urine Phosphate-to-Creatinine Ratio

	All-Cause Mortality			CVD Mortality		
uPiCr (mmol/mmol)	Model 1*	Model 2†	Model 3‡	Model 1*	Model 2†	Model 3‡
0.5	1.17 (1.05-1.30)	1.10 (0.98-1.22)	1.03 (0.92-1.15)	1.36 (1.13-1.63)	1.21 (1.00-1.46)	1.08 (0.90-1.31)
0.7	1.07 (1.02-1.13)	1.04 (0.98-1.09)	1.00 (0.96-1.06)	1.14 (1.05-1.25)	1.08 (0.99-1.18)	1.03 (0.94-1.13)
1.0	Reference	Reference	Reference	Reference	Reference	Reference
1.4	0.98 (0.94-1.02)	1.00 (0.96-1.04)	1.01 (0.97-1.05)	0.94 (0.88-1.01)	0.98 (0.91-1.05)	1.01 (0.94-1.08)
1.8	0.99 (0.93-1.13)	1.03 (0.97-1.10)	1.04 (0.98-1.11)	0.96 (0.86-1.08)	1.01 (0.90-1.14)	1.05 (0.93-1.18)
2.2	1.04 (0.95-1.13)	1.08 (0.99-1.19)	1.08 (0.98-1.18)	1.02 (0.88-1.19)	1.07 (0.92-1.27)	1.11 (0.94-1.30)
3.0	1.18 (1.01-1.37)	1.23 (1.06-1.42)	1.17 (1.01-1.37)	1.25 (0.97-1.60)	1.28 (1.00-1.64)	1.27 (0.98-1.65)
4.0	1.44 (1.12-1.86)	1.48 (1.16-1.88)	1.32 (1.03-1.70)	1.74 (1.16-2.59)	1.70 (1.15-2.47)	1.54 (1.02-2.33)
5.0	1.82 (1.25-2.63)	1.81 (1.28-2.57)	1.50 (1.03-2.16)	2.54 (1.43-4.50)	2.30 (1.33-3.95)	1.91 (1.06-3.44)
6.0	2.31 (1.41-3.80)	2.24 (1.41-3.60)	1.70 (1.04-2.78)	3.80 (1.77-8.19)	3.18 (1.55-6.50)	2.39 (1.09-5.21)

25(OH)D, 25-hydroxyvitamin D; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; uPiCr, urinary phosphate-to-creatinine ratio.

Data are presented as hazard ratios (95% confidence intervals). Hazard ratios are calculated from the model $ln(HR) = (\beta_1 \times [\text{uPiCr}]^{0.5}) + (\beta_2 \times [\text{uPiCr}]^{0.5} \times \ln[\text{uPiCr}]) + (\beta_k X_K)$, where $\beta_k X_K$ represents the k other covariates in models 2 and 3. The referent for the model is 1.0 mmol/mmol.

*Age stratified, unadjusted model.

†Age stratified, model adjusted for age and gender.

‡Age stratified, model adjusted for age, gender, eGFR, albuminuria, diabetes status, systolic and diastolic blood pressure, CVD, cholesterol, triglycerides, waist-to-hip ratio, smoking status, and serum 25(OH)D level.

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

Table 3. β Coefficients for 2-Term Fractional Polynomials for All-Cause and Cardiovascular Disease Mortality According to Urine Phosphate-to-Creatinine Ratio

Two-Term Fractional Polynomial	Model 1*		Model 2†		Model 3‡	
	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value	β Coefficient (95% CI)	*P* Value
All-cause mortality						
uPiCr [0.5]§	−1.92 (−3.02 to −0.82)	.001	−1.37 (−2.44 to −0.34)	.01	−0.66 (−1.74 to 0.42)	.23
uPiCr [0.5]§	0.82 (0.37-1.28)	<.001	0.64 (0.21-1.07)	.003	0.34 (−0.10 to 0.78)	.13
CVD mortality						
uPiCr [0.5]§	−3.46 (−5.21 to −1.71)	<.001	−2.44 (−4.15 to −0.73)	.005	−1.37 (−3.13 to 0.44)	.14
uPiCr [0.5]§	1.45 (0.74-2.15)	<.001	1.07 (0.39-1.75)	.002	0.64 (−0.08 to 1.36)	.08

25(OH)D, 25-hydroxyvitamin D; CI, confidence interval; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; uPiCr, urinary phosphate-to-creatinine ratio.

All-cause mortality n = 10,014 and CVD mortality n = 10,002.

*Age stratified, unadjusted model.

†Age stratified, model adjusted for age and gender.

‡Age stratified, model adjusted for age, gender, dietary phosphate intake, eGFR, albuminuria, diabetes status, systolic and diastolic blood pressure, CVD, cholesterol, triglycerides, waist-to-hip ratio, smoking status, and serum 25(OH)D level.

§Values in brackets represent the powers used in the second-degree factional polynomials where uPiCr [0.5, 0.5] represents: $ln(HR) = (\beta_1 \times [\text{uPiCr}]^{0.5}) + (\beta_2 \times [\text{uPiCr}]^{0.5} \times \ln[\text{uPiCr}]) + (\beta_k X_K)$, where $\beta_k X_K$ represents the k other covariates in models 2 and 3.

between uPiCr and all-cause mortality remained significant (Table S3). Representative hazards ratios, referenced to a uPiCr at 1.0 mmol/mmol, are presented in Table S4 with the plot of the model-based hazard ratios presented in Figure 3A. For CVD mortality, the results in the non-CKD-only population were unchanged compared to the whole cohort main analysis (Tables S3 and S4, Figure S3B).

Discussion

In a large, population-based cohort study of Australian adults, we did not demonstrate a relationship between urinary phosphate, as measured by uPiCr, and all-cause and CVD mortality on multivariate adjustment. In a sensitivity analysis excluding participants with CKD, however, there was a significant relationship between uPiCr and all-cause mortality. Analysis of uPi alone also showed a similar significant association with all-cause mortality. The findings of our study suggest that measurement of uPiCr could be a potential marker for predicting adverse outcomes in the general population with no evidence of CKD.

Serum phosphate levels reflect a highly dynamic balance among dietary absorption, renal excretion, and exchanges within bone, soft tissue, and intracellular phosphate stores. Serum phosphate alone, however, provides a limited assessment of risk associated with disturbances in phosphate metabolism. Thus, other indices of mineral flux may provide important prognostic information with respect to CVD and mortality risk. As a surrogate for daily UPE, uPiCr may be a marker for dietary phosphate intake in steady state, which itself has been reported in studies to be associated with markers of CVD.[26-29] When participants with CKD were excluded from our general population cohort, therefore eliminating a sub-group who may have impaired UPE through reduction in kidney function and subsequently abnormal phosphate homeostasis, extremes of uPiCr, both high and low, were associated with increased mortality. Although the nature of this relationship is similar to that seen in the general population, the magnitude of effect and statistical significance suggest that uPiCr may potentially serve as a useful marker for interventions aimed at targeting phosphate balance in people with normal kidney function and no albuminuria.

The results of our study are similar to previous analyses of the Osteoporotic Fracture in Men study, where neither fasting morning FePi measurement nor uPiCr were found to predict all-cause or CVD mortality in 1,325 community-dwelling older men (>65 years) followed up for a median of 9.3 years.[30] In contrast, a subgroup analysis of the Heart and Soul Study cohort, involving 880 patients with stable CVD and normal kidney function, reported that higher 24-hour UPE was significantly associated with *lower* risk of cardiovascular events and a non-significant association with reduced mortality.[31] Our larger and younger cohort differs from these 2 published studies in gender distribution, age, and existing co-morbidities. The Osteoporotic Fracture in Men cohort was exclusively men, and the Heart and Soul Study involved over 80% men. Lack of female representation in these studies may potentially reduce generalizability of results to the wider community. In our population cohort, there was equal representation of both genders, although we found no difference in association with uPiCr and outcomes between genders. Higher uPiCr in females in our general population cohort was not unexpected as estrogens possess phosphaturic properties.[41]

Prevalent CVD was also a prerequisite for inclusion in the Heart and Soul Study, and notably there was no reported association between serum phosphate and CVD events. This may explain the inverse relationship between UPE and CVD events in this study cohort, suggesting that other factors may contribute to UPE in differing settings.[31] Only a minority of our study participants had

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

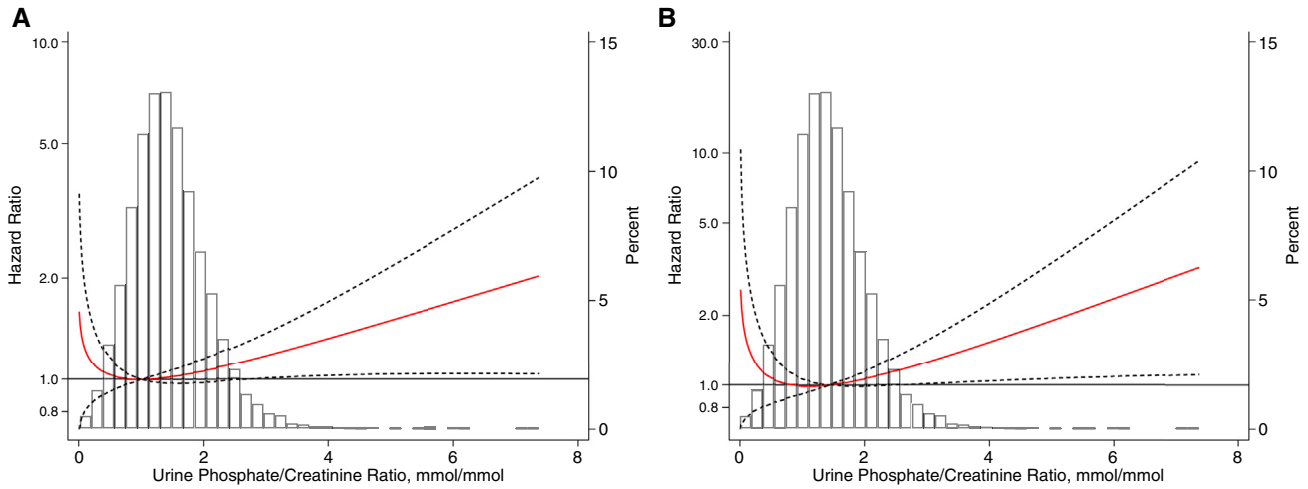

Figure 2. (A) Multivariable adjusted hazard ratios for all-cause mortality associated with uPiCr with superimposed histogram of uPiCr included in the analysis cohort. Values calculated in age-stratified Cox models using fractional polynomials for uPiCr adjusted for gender, age, dietary phosphate intake, eGFR, albuminuria, diabetic status, systolic and diastolic blood pressure, CVD, cholesterol, triglycerides, waist-to-hip ratio, smoking status, and serum 25(OH)D level. Powers of fractional polynomials for uPiCr 0.5, 0.5. (B) Multivariable adjusted hazard ratios for CVD mortality associated with uPiCr with superimposed histogram of uPiCr included in the analysis cohort. Values calculated in age-stratified Cox models using fractional polynomials for uPiCr adjusted for gender, age, dietary phosphate intake, eGFR, albuminuria, diabetic status, systolic and diastolic blood pressure, CVD, cholesterol, triglycerides, waist-to-hip ratio, smoking status, and serum 25(OH)D level. Powers of fractional polynomials for uPiCr 0.5, 0.5. 25(OH)D, 25-hydroxyvitamin D; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; uPiCr, urine phosphate-to-creatinine ratio.

CVD at baseline (8.9%) and our cohort was also younger, with a mean age of 51.7 years compared to 74 ± 6 years and 67 ± 11 years in previously described studies.[30,31] Higher uPiCr was present in older participants in our cohort, and may reflect a reduction in uCr, suggestive of renal compromise or lower muscle mass as a result of the aging process. Similarly, increased uPiCr seen with reduced eGFR and higher albuminuria was not unexpected. Both

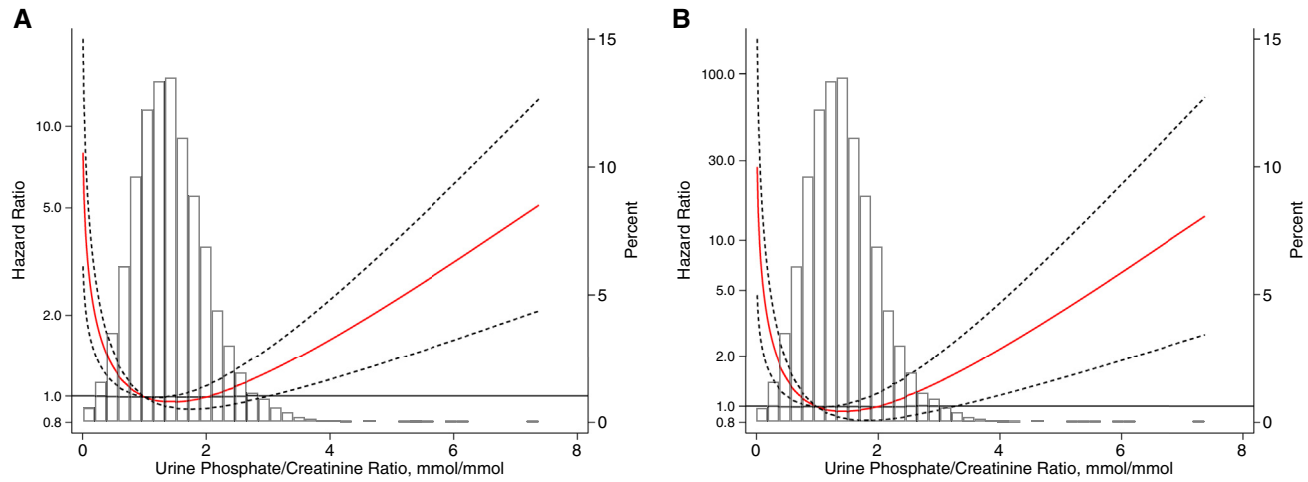

Figure 3. (A) Multivariable adjusted hazard ratios for all-cause mortality associated with urine phosphate/creatinine ratio (uPiCr) with superimposed histogram of uPiCr *excluding those with CKD* at baseline. Values calculated in age-stratified Cox models using fractional polynomials for uPiCr adjusted for gender, age, dietary phosphate intake, eGFR, albuminuria, diabetic status, systolic and diastolic blood pressure, CVD, cholesterol, triglycerides, waist-to-hip ratio, smoking status, and serum 25(OH)D level. Powers of fractional polynomials for uPiCr 0.5, 0.5. (B) Multivariable adjusted hazard ratios for CVD mortality associated with uPiCr with superimposed histogram of uPiCr *excluding those with CKD* at baseline. Values calculated in age-stratified Cox models using fractional polynomials for uPiCr adjusted for gender, age, dietary phosphate intake, eGFR, albuminuria, diabetic status, systolic and diastolic blood pressure, CVD, cholesterol, triglycerides, waist to hip ratio, smoking status, and serum 25(OH) D level. Powers of fractional polynomials for uPiCr 0.5, 0.5. 25(OH)D, 25-hydroxyvitamin D; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; uPiCr, urine phosphate-to-creatinine ratio.

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

parameters of impaired kidney function and albuminuria may indicate kidney injury and uCr is likely to decline as kidney function declines, and uPiCr would increase consequently. Although uCr is used with spot urine samples to correct values to reference parameters in order to reduce variations due to dilution (as levels are not influenced by diuresis), there can be marked intra- and inter-individual variation with uCr.[42] These variations may explain why our sensitivity analyses, either assessing uPi alone or evaluating uPiCr in participants without CKD, showed an association with all-cause mortality compared to no associations in the overall cohort.

Measurement of 24-hour UPE is considered to be a reasonable clinical estimate of phosphate intake in healthy individuals when in steady state, with a linear relationship to intestinal phosphate absorption across varying phosphate intakes.[43-45] Repeated collections of 24-hour UPE have also been reported as a useful determinant of dietary phosphate intake.[46,47] Data evaluating relationships of dietary phosphate intake with clinically significant meaningful outcomes however are lacking. Observational studies relating dietary phosphate content to clinical end-points often show U- or J-shaped curves, with elevated risks at both extremes of dietary phosphate.[26,28,48] However, all such studies have methodological issues relating to estimating dietary phosphate intake.

Interestingly, we found an inverse relationship between estimated dietary phosphate intake and uPiCr. Possible explanations for this finding are that potential differences in bioavailability of phosphate from various food sources may contribute to wide variability in uPiCr, and tools to predict dietary phosphate intake may underestimate or overestimate measured phosphate intake. It is also possible that uPiCr may reflect the dietary content of the last meal prior to the urine sample collected, rather than the habitual intake of phosphate in an individual. This theory, however, would not support the argument that reducing dietary phosphate intake might help reduce cardiovascular outcomes. In clinical practice, UPE has been used to estimate dietary phosphate load in individuals with preserved kidney function,[49] but on the contrary, phosphaturia may in fact reflect phosphate balance and not necessarily dietary intake. In one study of 8 patients with CKD, UPE was found to be more tightly correlated with measures of whole-body phosphate balance than intestinal phosphate absorption,[46] although this conclusion may not necessarily be applied to individuals in the general population. It is possible that uPiCr may not correlate as well with 24-hour UPE, and therefore not reflect habitual phosphate intake as well as 24-hour UPE (although this lack of correlation is predominantly reported in people with CKD). General population cohort studies are needed to assess associations between 24-hour UPE and adverse outcomes. Relationships among phosphate intake, digestibility, intestinal absorption, and urinary excretion are complex, and repeated measurements of UPE, not available in our study, may have been of value.

Our study investigated spot uPiCr as an estimate of dietary phosphate intake, or perhaps phosphate balance, assuming healthy participants are in steady state. High uPiCr (>3 mmol/mmol) may indicate higher dietary phosphate intake, despite the lack of association in our study with estimated dietary phosphate. Several small physiological studies have reported that higher dietary phosphate intake increased levels of the phosphatonin FGF-23, and conversely low dietary phosphate diets decreased FGF-23.[21,22] Epidemiological studies coupled with in vitro and animal data showing excess dietary phosphate promote arterial calcification, endothelial dysfunction, and myocardial hypertrophy, which suggest that elevated phosphate intake could be detrimental to cardiovascular health at all levels of kidney function.[6-8,12-18] A high uPiCr may also reflect a high dietary protein intake, as most phosphate-rich foods are also protein-rich. Several general population cohort studies have reported a positive association between dietary protein intake and mortality.[48,50] Any association between low uPiCr (<1 mmol/mmol) and mortality may potentially be confounded by poor nutritional intake and existing co-morbidities. Lower dietary protein intake has also been associated with poorer outcomes, and may accompany lower dietary phosphate intake with associated lower uPiCr.

Twenty-four-hour UPE measurements can be difficult to accurately collect and spot uPiCr may provide similar estimates with reported good agreement between random uPiCr and 24-hour UPE.[23,24] Although there are limited epidemiological studies to definitively validate uPiCr as a surrogate marker of phosphate homeostasis, it remains an easy, rapid, and inexpensive parameter that could be used in clinical practice. One recent study however evaluated the relationship between uPiCr and 24-hour UPE in 143 participants with CKD who had been involved in a randomized controlled trial of phosphate binders, and concluded that in this population correlation between the 2 urinary measures was not significant.[51] Another study also questioned the relationship between spot uPiCr and 24-hour UPE in patients with CKD.[25] These studies may partly explain findings in our study cohort of a significant association between uPiCr and mortality when participants with CKD were excluded.

Strengths of our study include a well-characterized, large, national population-based cohort, with a long duration of follow-up. Limitations include lack of standardization on the timing of the morning spot urine samples (and therefore not taking into consideration possible circadian variation in phosphate and creatinine that may affect uPiCr), and lack of data on vitamin D supplementation use and concurrent serum phosphate or FGF-23 measurements. A concurrent serum phosphate measurement would have been useful to allow an estimate of FePi and

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

subsequent assessment of associations between this parameter and mortality.

Although the 24-hour urine collection is considered as the gold standard method for determining dietary phosphate intake, timed urine collections can be cumbersome and prone to errors. Spot urine measurement for uPiCr may be a surrogate marker for daily UPE and our study demonstrates an association with all-cause mortality in a large general population cohort when participants with CKD were excluded. Confirmation of these findings may allow uPiCr to be utilized as a simple tool alongside other initial assessments of CVD risk and mortality. Given the increasing evidence of an association between phosphate and CVD, it is important to prospectively investigate whether interventions aimed at reducing phosphate burden, such as restricting dietary phosphate intake and limiting food additives, reduce cardiovascular events and mortality. Better methods to measure phosphate intake may be important for monitoring dietary adherence to lower phosphate diet and uPiCr may serve as a useful marker for interventions aimed at understanding phosphate balance and the effects of these interventions, although this requires validation in future clinical studies.

CRediT authorship contribution statement

Nigel D. Toussaint: Conceptualization, Formal analysis, Methodology, Project administration, Supervision, Validation, Writing – original draft, Writing – review & editing. **Matthew J. Damasiewicz:** Formal analysis, Validation, Writing – review & editing. **Stephen G. Holt:** Supervision, Writing – review & editing. **Zhong X. Lu:** Methodology, Writing – review & editing. **Dianna J. Magliano:** Formal analysis, Funding acquisition, Supervision, Validation, Writing – review & editing. **Robert C. Atkins:** Funding acquisition, Writing – review & editing. **Steven J. Chadban:** Funding acquisition, Supervision, Validation, Writing – review & editing. **Jonathan E. Shaw:** Funding acquisition, Supervision, Validation, Writing – review & editing. **Kevan R. Polkinghorne:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Supervision, Validation, Writing – review & editing.

Acknowledgments

The AusDiab study, initiated and coordinated by the International Diabetes Institute, and subsequently coordinated by the Baker Heart and Diabetes Institute, gratefully acknowledges the support and assistance given by K. Anstey, B. Atkins, B. Balkau, E. Barr, A. Cameron, S. Chadban, M. de Courten, D. Dunstan, A. Kavanagh, S. Murray, N. Owen, K. Polkinghorne, T. Welborn, P. Zimmet, and all the study participants.

Also, for funding or logistical support, we are grateful to the National Health and Medical Research Council (NHMRC grants 233200 and 1007544), Australian Government Department of Health and Ageing, Abbott Australasia Pty Ltd, Alphapharm Pty Ltd, Amgen Australia, AstraZeneca, Bristol-Myers Squibb, City Health Centre-Diabetes Service-Canberra, Department of Health and Community Services - Northern Territory, Department of Health and Human Services – Tasmania, Department of Health – New South Wales, Department of Health – Western Australia, Department of Health – South Australia, Department of Human Services – Victoria, Diabetes Australia, Diabetes Australia Northern Territory, Eli Lilly Australia, Estate of the Late Edward Wilson, GlaxoSmithKline, Jack Brockhoff Foundation, Janssen-Cilag, Kidney Health Australia, Marian & FH Flack Trust, Menzies Research Institute, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk Pharmaceuticals, Pfizer Pty Ltd, Pratt Foundation, Queensland Health, Roche Diagnostics Australia, Royal Prince Alfred Hospital, Sydney, Sanofi Aventis, Sanofi-Synthelabo, and the Victorian Government's OIS Program.

The authors would like to thank Monash Pathology for providing the technical support for the analysis of urinary phosphate levels in the AusDiab cohort.

References

1. Komaba H, Fukagawa M. Phosphate-a poison for humans? *Kidney Int*. 2016;90:753-763.
2. Kuro-o M. A phosphate-centric paradigm for pathophysiology and therapy of chronic kidney disease. *Kidney Int Suppl (2011)*. 2013;3:420-426.
3. Lederer E. Regulation of serum phosphate. *J Physiol (Lond)*. 2014;592:3985-3995.
4. Komaba H, Fukagawa M. FGF23-parathyroid interaction: implications in chronic kidney disease. *Kidney Int*. 2010;77:292-298.
5. Berndt T, Kumar R. Phosphatonins and the regulation of phosphate homeostasis. *Annu Rev Physiol*. 2007;69:341-359.
6. Toussaint ND, Pedagogos E, Tan S-J, et al. Phosphate in early chronic kidney disease: associations with clinical outcomes and a target to reduce cardiovascular risk. *Nephrology (Carlton)*. 2012;17:433-444.
7. Giachelli CM. The emerging role of phosphate in vascular calcification. *Kidney Int*. 2009;75:890-897.
8. Chen NX, O'Neill KD, Duan D, Moe SM. Phosphorus and uremic serum up-regulate osteopontin expression in vascular smooth muscle cells. *Kidney Int*. 2002;62:1724-1731.
9. Di Marco GS, Hausberg M, Hillebrand U, et al. Increased inorganic phosphate induces human endothelial cell apoptosis in vitro. *Am J Physiol Ren Physiol*. 2008;294:F1381-F1387.
10. Shuto E, Taketani Y, Tanaka R, et al. Dietary phosphorus acutely impairs endothelial function. *J Am Soc Nephrol*. 2009;20:1504-1512.
11. Kuro-o, Klotho M. Phosphate and FGF-23 in ageing and disturbed mineral metabolism. *Nat Rev Nephrol*. 2013;9:650-660.
12. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31:607-617.
13. Block GA, Klassen, PS, Lazarus, JM, Ofsthun, N, Lowrie, EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15:2208-2218.
14. Dhingra R, Sullivan, LM, Fox CS, et al. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. *Arch Intern Med*. 2007;167:879-885.
15. Dhingra R, Gona, P, Benjamin, EJ, et al. Relations of serum phosphorus levels to echocardiographic left ventricular mass and incidence of heart failure in the community. *Eur J Heart Fail*. 2010;12:812-818.
16. O'Seaghdha CM, Hwang S-J, Muntner P, Melamed ML, Fox CS. Serum phosphorus predicts incident chronic kidney disease and end-stage renal disease. *Nephrol Dial Transpl*. 2011;26:2885-2890.
17. Cancela AL, Santos, RD, Titan, SM, et al. Phosphorus is associated with coronary artery disease in patients with preserved kidney function. *PLoS One*. 2012;7:e36883.
18. Foley RN, Collins AJ, Herzog CA, Ishani A, Kalra. PA. Serum phosphorus levels associate with coronary atherosclerosis in young adults. *J Am Soc Nephrol*. 2009;20:397-404.

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

19. Tonelli M, Sacks, F, Pfeffer, M, et al. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation*. 2005;112:2627-2633.

20. Onufrak SJ, Bellasi, A, Shaw, LJ, et al. Phosphorus levels are associated with subclinical atherosclerosis in the general population. *Atherosclerosis*. 2008;199:424-431.

21. Isakova T, Gutiérrez OM, Smith K, et al. Pilot study of dietary phosphorus restriction and phosphorus binders to target fibroblast growth factor 23 in patients with chronic kidney disease. *Nephrol Dial Transplant*. 2011;26:584-591.

22. Oliveira RB, Cancela, ALE, Graciolli FG, et al. Early control of PTH and FGF23 in normophosphatemic CKD patients: a new target in CKD-MBD therapy? *Clin J Am Soc Nephrol*. 2010;5:286-291.

23. Matos V, van Melle G, Boulat O, Markert M, Bachmann C, Guignard JP. Urinary phosphate/creatinine, calcium/creatinine, and magnesium/creatinine ratios in a healthy pediatric population. *J Pediatr*. 1997;131:252-257.

24. Gökçe C, Gökçe O, Baydinç C, et al. Use of random urine samples to estimate total urinary calcium and phosphate excretion. *Arch Intern Med*. 1991;151:1587-1588.

25. Tan S-J, Smith ER, Cai, MM, Holt, SG, Hewitson, TD, Toussaint ND. Relationship between timed and spot urine collections for measuring phosphate excretion. *Int Urol Nephrol*. 2016;48:115-124.

26. Yamamoto KT, Robinson-Cohen C, de Oliveira, MC, et al. Dietary phosphorus is associated with greater left ventricular mass. *Kidney Int*. 2013;83:707-714.

27. Chang AR, Lazo M, Appel LJ, Gutiérrez OM, Grams ME. High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. *Am J Clin Nutr*. 2014;99:320-327.

28. Noori N, Kalantar-Zadeh K, Kovesdy CP, Bross, R, Benner D, Kopple. JD. Association of dietary phosphorus intake and phosphorus to protein ratio with mortality in hemodialysis patients. *Clin J Am Soc Nephrol*. 2010;5:683-692.

29. Selamet U, Tighiouart H, Sarnak MJ, et al. Relationship of dietary phosphate intake with risk of end-stage renal disease and mortality in chronic kidney disease stages 3-5: the Modification of Diet in Renal Disease Study. *Kidney Int*. 2016;89:176-184.

30. Dominguez JR, Kestenbaum, B, Chonchol M, et al. Relationships between serum and urine phosphorus with all-cause and cardiovascular mortality: the Osteoporotic Fractures in Men (MrOS) Study. *Am J Kidney Dis*. 2013;61:555-563.

31. Palomino HL, Rifkin DE, Anderson C, Criqui MH, Whooley MA, Ix. JH. 24-hour urine phosphorus excretion and mortality and cardiovascular events. *Clin J Am Soc Nephrol*. 2013;8:1202-1210.

32. Dunstan DW, Zimmet PZ, Welborn TA, et al. The Australian diabetes, obesity and Lifestyle study (AusDiab)–methods and response rates. *Diabetes Res Clin Pract*. 2002;57:119-129.

33. Damasiewicz MJ, Magliano DJ, Daly RM, et al. 25-Hydroxyvitamin D levels and chronic kidney disease in the AusDiab (Australian Diabetes, Obesity and Lifestyle) study. *BMC Nephrol*. 2012;13:55.

34. Polkinghorne KR, Su Q, Chadban SJ, Shaw JE, Zimmet, PZ, Atkins. RC. Population prevalence of albuminuria in the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study: immunonephelometry compared with high-performance liquid chromatography. *Am J Kidney Dis*. 2006;47:604-613.

35. Gagnon C, Lu ZX, Magliano DJ, et al. Serum 25-hydroxyvitamin D, calcium intake, and risk of type 2 diabetes after 5 Years: results from a national, population-based prospective study (the Australian diabetes, obesity and Lifestyle study). *Diabetes Care*. 2011;34:1133-1138.

36. Hodge A, Patterson AJ, Brown WJ, Ireland P, Giles. G. The Anti Cancer Council of Victoria FFQ: relative validity of nutrient intakes compared with weighed food records in young to middle-aged women in a study of iron supplementation. *Aust N Z J Public Health*. 2000;24:576-583.

37. Australian Institute of Health and Welfare. *The Active Australia Survey: a guide and manual for implementation, analysis and reporting*. Canberra, Australia: Australian Institute of Health and Welfare; 2003.

38. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.

39. Barr ELM, Zimmet, PZ, Welborn, TA, et al. Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). *Circulation*. 2007;116:151-157.

40. Royston P, Sauerbrei W. *Multivariable Model - Building*. Hoboken, New Jersey: John Wiley & Sons; 2008.

41. Faroqui S, Levi M, Soleimani M, Amlal H. Estrogen downregulates the proximal tubule type IIa sodium phosphate cotransporter causing phosphate wasting and hypophosphatemia. *Kidney Int*. 2008;73:1141-1150.

42. Alessio L, Berlin A, Dell'Orto A, Toffoletto F, Ghezzi I. Reliability of urinary creatinine as a parameter used to adjust values of urinary biological indicators. *Int Arch Occup Environ Health*. 1985;55:99-106.

43. Hill KM, Martin BR, Wastney ME, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. *Kidney Int*. 2013;83:959-966.

44. Moe SM, Zidehsarai MP, Chambers, MA, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. *Clin J Am Soc Nephrol*. 2011;6:257-264.

45. Block GA, Wheeler DC, Persky MS, et al. Effects of phosphate binders in moderate CKD. *J Am Soc Nephrol*. 2012;23:1407-1415.

46. Morimoto Y, Sakuma M, Ohta H, et al. Estimate of dietary phosphorus intake using 24-h urine collection. *J Clin Biochem Nutr*. 2014;55:62-66.

47. Sun Q, Bertrand KA, Franke AA, Rosner B, Curhan GC, Willett WC. Reproducibility of urinary biomarkers in multiple 24-h urine samples. *Am J Clin Nutr*. 2017;105:159-168.

48. Lagiou P, Sandin S, Weiderpass E, et al. Low carbohydrate-high protein diet and mortality in a cohort of Swedish women. *J Intern Med*. 2007;261:366-374.

49. Stremke ER, McCabe LD, McCabe GP, et al. Twenty-four-hour urine phosphorus as a biomarker of dietary phosphorus intake and absorption in CKD. *Clin J Am Soc Nephrol*. 2018;13:1002-1012.

50. Trichopoulou A, Psaltopoulou T, Orfanos P, Hsieh CC, Trichopoulos D. Low-carbohydrate-high-protein diet and long-term survival in a general population cohort. *Eur J Clin Nutr*. 2007;61:575-581.

51. Robinson-Cohen C, Ix H, Smits G, et al. Estimation of 24-hour urine phosphate excretion from spot urine collection: development of a predictive equation. *J Ren Nutr*. 2014;24:194-199.

Downloaded for Anonymous User (n/a) at The Royal Melbourne Hospital from ClinicalKey.com.au by Elsevier on July 07, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.