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Association between CKD-MBD and mortality in older patients with advanced CKD—results from the EQUAL study

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ABSTRACT

Background. Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a common complication of CKD; it is associated with higher mortality in dialysis patients, while its impact in non-dialysis patients remains mostly unknown. We investigated the associations between parathyroid hormone (PTH), phosphate and calcium (and their interactions), and all-cause, cardiovascular (CV) and non-CV mortality in older non-dialysis patients with advanced CKD.

Methods. We used data from the European Quality study, which includes patients aged ≥65 years with estimated glomerular filtration rate ≤20 mL/min/1.73 m^2 from six European countries. Sequentially adjusted Cox models were used to assess the association between baseline and time-dependent CKD-MBD biomarkers and all-cause, CV and non-CV mortality. Effect modification between biomarkers was also assessed.

Results. In 1294 patients, the prevalence of CKD-MBD at baseline was 94%. Both PTH [adjusted hazard ratio (aHR) 1.12, 95% confidence interval (CI) 1.03–1.23, $P = .01$] and phosphate (aHR 1.35, 95% CI 1.00–1.84, $P = .05$), but not calcium (aHR 1.11, 95% CI 0.57–2.17, $P = .76$), were associated with all-cause mortality. Calcium was not independently associated with mortality, but modified the effect of phosphate, with the highest mortality risk found in patients with both hypercalcemia and hyperphosphatemia. PTH level was associated with CV mortality, but not with non-CV mortality, whereas phosphate was associated with both CV and non-CV mortality in most models.

Conclusions. CKD-MBD is very common in older non-dialysis patients with advanced CKD. PTH and phosphate are independently associated with all-cause mortality in this population. While PTH level is only associated with CV mortality, phosphate seems to be associated with both CV and non-CV mortality.

Keywords: cardiovascular, CKD-MBD, mineral, mortality, PTH

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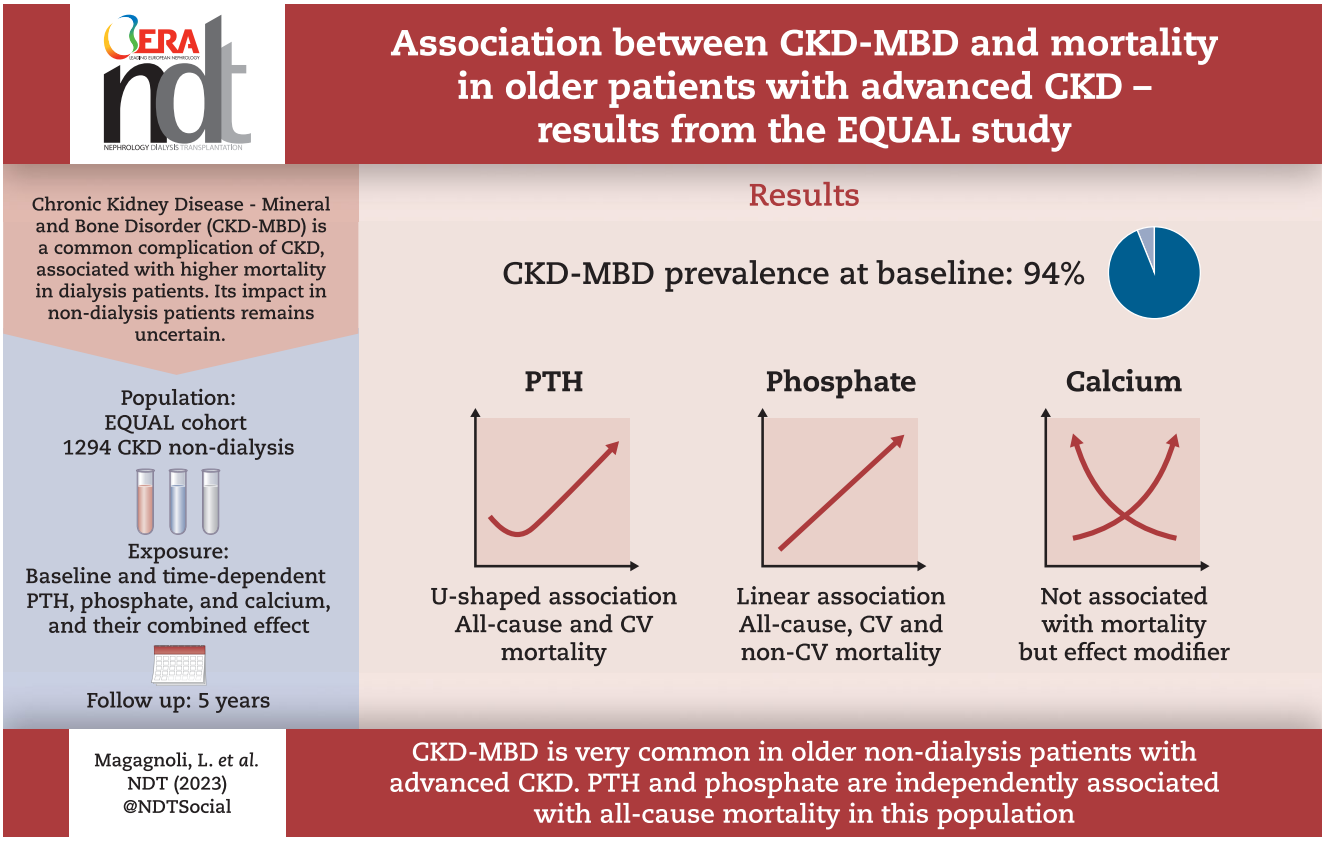
GRAPHICAL ABSTRACT



KEY LEARNING POINTS

What was known:

- Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a common complication of CKD.
- Based on studies showing an association between deranged markers of CKD-MBD and mortality risk in dialysis patients, international guidelines have defined optimal ranges for calcium, phosphate and parathyroid hormone (PTH) for these patients.
- The impact of CKD-MBD on mortality in the larger population of patients with CKD not on dialysis remains unknown.

This study adds:

- In our large cohort of 1294 non-dialysis patients, with repeated measurements, from six different European countries, baseline and longitudinal PTH and phosphate, but not calcium levels, were associated with mortality risk.
- Moreover, we found that PTH was associated with increased cardiovascular (CV) mortality risk, but not with the risk of non-CV mortality. On the other hand, phosphate levels were associated with both CV and non-CV mortality.
- Our study also disentangles individual and combined effects among CKD-MBD biomarkers, evaluating both effect modification and effect mediation

Potential impact:

- Although the observational nature of the study precludes the establishment of target values, we believe that, in the absence of randomized controlled trials addressing this issue, our results lead to a better understanding of mortality risk associated with CKD-MBD in non-dialysis patients, in which the optimal values of mineral biomarkers are not fully known.
- Our findings underline the complex interplay between CKD-MBD biomarkers, highlighting the importance of considering their combined effect in future research (e.g. by exploring effect modification and mediation among biomarkers) and in clinical practice (e.g. maintaining a reasonable balance of all biomarkers could be better than focusing on optimally controlling phosphate levels at the expense of the other biomarkers)

INTRODUCTION

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a common complication of CKD, manifested by abnormalities in calcium, phosphate, parathyroid hormone (PTH) or vitamin D metabolism, which lead to bone and cardiovascular (CV) disease [1, 2]. Several studies have shown an association between

deranged markers of CKD-MBD and mortality in dialysis patients [3–10]. Consequently, international guidelines have defined optimal ranges for calcium, phosphate and PTH for patients on dialysis [11, 12]. However, the impact of CKD-MBD on mortality in the larger population of patients with CKD not on dialysis remains largely unknown.

Previous studies have investigated the associations between PTH, phosphate or calcium, and mortality risk [13–19] and CV outcomes [19–21] in CKD patients, each with their own limitations. First, some focused only on a single biomarker, whereas we believe that, given the complexity of CKD-MBD syndrome and the tangled interplay among mineral biomarkers, researchers should also consider their combined effect (e.g. by testing for both effect modification and effect mediation among all three biomarkers). Second, most studies only assessed the effect of a single baseline measurement, but since these biomarkers are constantly changing, we believe a time-dependent analysis could add some important insights. Third, some studies focused on the presence of secondary hyperthyroidism (SHPT), using varying definitions, which may have led to some degree of misclassification bias. Last, some studies may be biased by the enrolment of prevalent patients with various stages of CKD, instead of incident patients. In the present study we aim to investigate the associations between baseline and repeated measurements of longitudinal PTH, phosphate and calcium (as well as their reciprocal interactions) on all-cause, CV and non-CV mortality in an international cohort of older, incident, non-dialysis patients in CKD stages 4–5.

MATERIALS AND METHODS

Study design and population

The European Quality (EQUAL) study is an ongoing prospective cohort study on 1728 patients with CKD stages 4–5 from Germany, Italy, the Netherlands, Poland, Sweden and the UK, which started in March 2012, and is fully described elsewhere [22]. Patients aged ≥65 years were included after an incident drop in estimated glomerular filtration rate (eGFR) to ≤20 mL/min/1.73 m^2 and excluded if their eGFR drop was due to an acute event, or if they previously had kidney replacement therapy (Supplementary data, Table S1). For the current study, we selected EQUAL participants with an available baseline measurement of CKD-MBD biomarkers. Patients were followed for 5 years or until kidney transplantation, death, refusal for further participation or loss to follow-up. The study received approval by the Medical Ethics Committee or Institutional Review Boards of all participating countries. Written informed consent was obtained from all patients.

Data collection

Data on demographics, CV risk factors, pre-existing comorbid conditions and primary kidney disease (classified by the ERA coding system [23]) were collected at baseline. Data on laboratory measurements, medication and physical examination were collected at baseline and updated at each study visit, scheduled at 6-month intervals. eGFR was calculated from serum creatinine level standardized to isotope dilution mass spectrometry using the CKD Epidemiology Collaboration (CKD-EPI) 2009 equation.

Exposures and outcomes

The measurement of PTH, phosphate and calcium was performed according to local practice and not standardized across centres. Therefore, specific reference ranges were unknown and for prevalence estimation we used average ranges based on clinical experience: 1–7 pmol/L for PTH, 0.8–1.5 mmol/L for phosphate and 2.1–2.6 mmol/L for calcium. Albumin-corrected calcium (Ca_{ALB}) was calculated by Payne's formula [24]. Data on mortality were collected as part of the study protocol and causes of death were classified by the ERA coding system [25]. Myocardial ischaemia, heart failure, cardiac arrest, other cardiac causes and cerebrovascular events were considered CV causes of death.

Statistical analysis

Data were reported as frequencies, means and standard deviation (SD) or medians and interquartile range (IQR), as appropriate. Kaplan–Meier survival curves by baseline tertiles of each CKD-MBD biomarker were compared by log-rank test. PTH was log-transformed to improve normality. The association between baseline and time-dependent CKD-MBD biomarkers and the risk of death (for all-cause, CV and non-CV causes) was assessed through Cox proportional hazards models, sequentially adjusted for potential confounders. The proportional hazard assumption was checked by Schoenfeld test. For variables violating the assumption, a step function was used to split the follow-up time into 1-year periods. The same methods were used to investigate the association between phosphate level and the mortality risk due to the most frequent non-CV causes of death (malignancies and infections). Non-linearity was examined using restricted cubic splines and by repeating the analysis using biomarkers categories. Effect modification between pairs of continuous biomarkers (PTH and phosphate, PTH and calcium, phosphate and calcium) were tested by including interaction terms in the fully adjusted models. Subgroup analyses were conducted for sex, age group, diabetes mellitus and dialysis status (as a binary time-varying variable, for those patients who started dialysis during follow-up) by the inclusion of interaction terms in the fully adjusted models. All analyses were performed with R version 4.0.3.

Sensitivity analyses

First, the same methods as described above were used to investigate the association between Ca_{ALB} and all outcomes. Second, to address any selection bias due to missing values, baseline characteristics and survival probabilities were compared between the included and excluded EQUAL participants. In addition, the association between baseline biomarkers and mortality risk was also tested in the whole EQUAL cohort after multiple imputation of missing data. Third, to reduce the risk of overadjustment bias [26] (Supplementary data, Fig. S1B), the analyses were repeated without adjusting for other mineral biomarkers. Last, to reduce the risk of bias due to treatment-confounder feedback [27, 28] (Supplementary data, Fig. S1C), the time-dependent analyses were repeated adjusting for only baseline values instead of time-varying values for those covariates that could lie in the causal pathway.

RESULTS

Patient characteristics

Baseline characteristics of the 1294 patients included in the study are reported in Table 1. The mean age was 76 years, 66% were male, with a high prevalence of hypertension, diabetes mellitus and CV diseases. The median eGFR was 16.8 mL/min/1.73 m^2. Median PTH was high (15.4 pmol/L, IQR 9.3–23.8), whereas mean levels of phosphate and calcium were in the normal range (1.3 ± 0.3 mmol/L and 2.3 ± 0.2 mmol/L, respectively).

Table 1: Baseline characteristics of study participants.

	Overall (N = 1294)	Missing (%)
Demographics		
Age, years	76.2 ± 6.7	0
Sex, male	850 (66)	0
Primary cause of kidney disease		0.4
Glomerular disease	111 (9)	
Tubulo-insterstitial disease	105 (8)	
Diabetes mellitus	278 (22)	
Hypertension	473 (37)	
Other/unknown	322 (25)	
Physical exam		
BMI (kg/m²)	28.2 ± 5.3	7
SBP (mmHg)	142 ± 22	2
DBP (mmHg)	74 ± 11	2
Comorbidities		
Hypertension	1110 (89)	4
Diabetes mellitus	543 (43)	2
Coronary artery disease	332 (27)	3
Myocardial infarction	223 (18)	1
Congestive heart failure	224 (18)	3
Left ventricular hypertrophy	299 (26)	10
Atrial fibrillation	231 (18)	3
Peripheral vascular disease	218 (17)	3
Cerebrovascular disease	194 (15)	2
Psychiatric disorders	85 (7)	1
Malignancies	257 (20)	3
Renal function		
CKD-EPI eGFR, mL/min/1.73 m²	16.8 (13.8, 20.0)	0
Creatinine, µmol/L	279.7 (229.2, 331.4)	0
Urea, mmol/L	19.3 (15.5, 24.3)	1
Blood chemistry		
Sodium, mmol/L	140.1 ± 3.4	0.8
Potassium, mmol/L	4.6 ± 0.6	0.2
PTH, pmol/L	15.4 (9.3, 23.8)	0
Phosphate, mmol/L	1.3 ± 0.3	0
Calcium, mmol/L	2.3 ± 0.2	0
Albumin, g/L	37.7 ± 5.8	5
Corrected calcium (mmol/L)	2.3 ± 0.2	5
Bicarbonate, mmol/L	23.1 ± 3.9	24
Hemoglobin, mmol/L	11.6 ± 1.5	0.4
Medications		
Vitamin D		
Inactive and prodrugs	210 (16)	0.9
Active	58 (5)	0.9
Phosphate binders		
Calcium-based	83 (7)	0.9
Calcium-free	114 (9)	0.9
Calcimimetics	13 (1)	0.9

Data are presented as mean ± SD, median (IQR) or number (%).
BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure.

Prevalence of CKD-MBD

Considering CKD-MBD as defined by having abnormal levels of either PTH, phosphate or total calcium, a combination of these disorders, or taking CKD-MBD medications, its prevalence in our cohort was 94% at baseline. Only 15% of patients had normal PTH, whereas the majority had hyperparathyroidism (Fig. 1A), defined as PTH >7 pmol/L. Phosphate levels were normal in 74% of patients, whereas almost a quarter had hyperphosphatemia (Fig. 1B), defined as phosphate levels >1.5 mmol/L. Total calcium was normal in most patients, 10% had hypocalcemia, defined as calcium levels <2.1 mmol/L, and 3% had hypercalcemia, defined as calcium levels >2.6 mmol/L (Fig. 1C). We did not find any relevant differences in the distribution of these biomarkers by age group, sex and country (Supplementary data, Figs S2 and S3).

All-cause mortality

During 5 years of follow-up, a total of 460 deaths occurred, with an overall patient survival of 53% (95% CI 49%–56%) and a median time at risk of 3 years (IQR 1.5–4.2). Survival probability by tertiles of baseline biomarkers are presented in Supplementary data, Fig. S4. In the Cox regression models using repeated measurements of biomarkers (Table 2), both a doubling in PTH level and 1 mmol/L increase in phosphate level were associated with a higher mortality risk after full adjustment [respectively, adjusted hazard ratio (aHR) 1.12, 95% confidence interval (CI) 1.03–1.23, $P = .01$, and aHR 1.35, 95% CI 1.00–1.84, $P = .05$]. A 1 mmol/L increase in calcium was inversely associated with mortality risk, but this association was lost after adjusting for serum albumin (HR 0.24, 95% CI 0.15–0.40, $P < .001$ and aHR 1.11, 95% CI 0.57–2.17, $P = .76$). Results for baseline values of biomarkers provided similar results. The standardized effect sizes of these associations are shown in Fig. 2A for comparison purposes. When analysing linearity, we identified a U-shaped association between PTH and mortality risk (P for non-linearity .002, Fig. 3), with the lowest risk found at a PTH value of 11.6 pmol/L. Mortality risk for categories of mineral biomarkers are shown in Supplementary data, Table S2. No significant effect modification was detected between either PTH and phosphate, or PTH and calcium. Phosphate and calcium, however, acted as reciprocal effect modifiers, with the highest mortality risk found in patients with both hyperphosphatemia and hypercalcemia (P for interaction .02 at baseline, .07 in the time-dependent analysis), as shown in Fig. 4.

Subgroup analysis

Sex and age did not modify the associations between CKD-MBD biomarkers and mortality (Supplementary data, Fig. S5). The association between PTH and phosphate and mortality risk tended to be stronger in non-diabetic patients, especially for baseline phosphate (P for interaction .02). When considering dialysis status as a time-dependent variable (339 patients started dialysis during follow-up), increased phosphate seemed to be associated with a higher mortality risk only in non-dialysis patients, although this did not reach statistical significance.

CV and non-CV mortality

Of all deaths, 28% were CV in nature, while 40% had non-CV causes (Supplementary data, Fig. S6). As shown in Table 3, PTH was associated with a higher CV mortality risk, but not with non-CV mortality. Phosphate was associated with both a higher CV and non-CV mortality risk in most models. In particular, 1 mmol/L increase in phosphate level was not significantly associated with the risk of dying due to malignancies (HR 1.57, 95% CI 0.79–3.10, $P = .19$), but it was associated with increased risk of dying due to infections (HR 2.63, 95% CI 1.42–4.85, $P = .002$), although the association was lost after adjustment for eGFR (aHR 1.67, 95% CI 0.78–3.54, $P = .19$, Supplementary data, Fig. S7). Longitudinal calcium showed an inverse association with both CV and non-CV mortality risk, but these associations were lost after adjusting for serum albumin. All associations were linear. Regarding secondary outcome, no significant effect modification was detected between PTH, phosphate and calcium in the fully adjusted models. The standardized effect sizes of these associations are shown in Fig. 2B and C for comparison purposes.

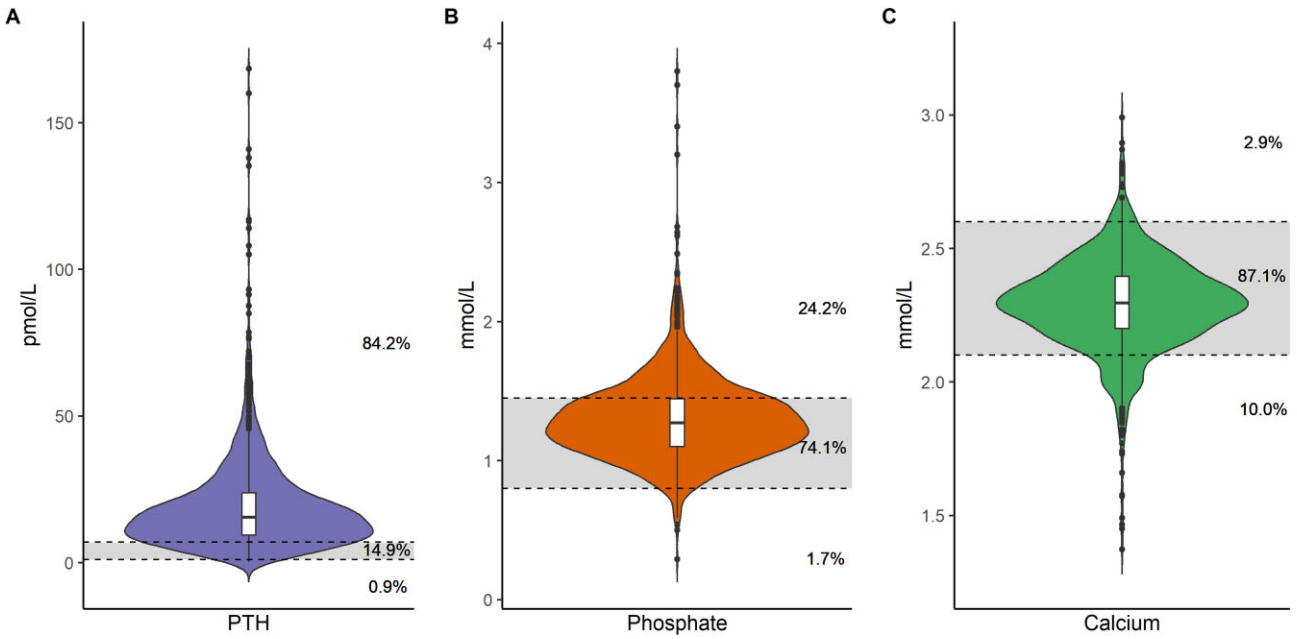


Figure 1: Prevalence of deranged biomarkers of CKD-MBD at baseline. Violin plots for the distribution of PTH (**A**), phosphate (**B**) and calcium (**C**) in our cohort at baseline. The boxplot inside each violin represents the 25, 50th and 75th percentiles of the distribution. The dashed lines indicate the lower and upper limit for normal values and grey bands the normal ranges. Percentages indicate the proportion of patients with low, normal or high biomarker.

Sensitivity analyses

First, Ca_{ALB} was not associated with any of the outcomes (bottom panels of Tables 2 and 3). Moreover, HRs for total calcium and Ca_{ALB} were the same after adjusting for serum albumin. Second, we did not find any meaningful differences in either baseline characteristics (Supplementary data, Table S3) or survival probability (Supplementary data, Fig. S8A) in patients included in the study compared with those excluded due to missing values. Furthermore, after imputation of missing data, the associations between baseline CKD-MBD biomarkers and the primary outcome were similar to the complete case analysis (Supplementary data, Fig. S8B). Third, when repeating the analyses without the adjustment for the other mineral biomarkers to avoid potential overadjustment bias (Supplementary data, Table S4, fully adjusted model vs model I), the associations of PTH and phosphate with the outcomes remained similar, except for a stronger association between phosphate and CV mortality. In addition, the HRs for calcium were markedly stronger, although none reached statistical significance. Last, when accounting for possible treatment-confounder feedback bias (Supplementary data, Table S4, fully adjusted model vs model II), the results on PTH remained similar, phosphate showed a stronger association with all outcomes and calcium tended to be inversely associated with all outcomes, although this reached statistical significance only in the association with CV mortality.

DISCUSSION

In the current study, we describe how abnormal CKD-MBD biomarkers are individually and jointly associated with all-cause, CV and non-CV mortality. PTH levels were associated with all-cause and CV mortality, but not with non-CV causes of death. Phosphate levels were associated with all-cause mortality, and both CV and non-CV mortality. Calcium seemed to play a less important role as an independent marker of mortality risk, but its interaction with phosphate enhanced mortality risk in patients with both hypercalcemia and hyperphosphatemia. Finally, we attempt to disentangle the pathways between the minerals and mortality risk, showing that the associations between phosphate and calcium on mortality risk may be partially mediated by their counterparts.

SHPT has previously been linked to a higher mortality risk in dialysis patients [3–7, 9] and KDIGO guidelines suggest maintaining their PTH levels in the range of approximately two to nine times the upper normal limit for the assay [12]. Only a few studies have been conducted in non-dialysis patients, and consensus regarding the optimal PTH level has not yet been reached [29]. First, Kovesdy *et al.* [16] showed a linear association between baseline PTH levels and mortality in a cohort of 515 men with CKD3–5. Later, in a Thai cohort of 466 patients with CKD2–4, Chartsrisak *et al.* [17] found that a baseline PTH in the range of 65–105 pg/mL (equal to 6.9–11.1 pmol/L) or >105 pg/mL was associated with a 3.5-fold and 6-fold greater risk, respectively, for the combined outcome of progression to end-stage kidney disease or death, independent of other mineral parameters. In a cohort of 5108 patients with a GFR ≤60 mL/min, Geng *et al.* [18] found a 19% higher risk of death associated with a baseline PTH >58 pg/mL (6.2 pmol/L), although without adjustment for phosphate and calcium levels. Recently, Xu *et al.* [19] described a 40% increase in mortality risk for patients with any stage CKD and incident SHPT compared with those without SHPT. Our results confirm these findings, and further strengthen them through longitudinal analysis. However, our time-updated PTH showed a U-shaped relationship with mortality risk, with the lowest risk found at a PTH value of 11.6 pmol/L. Although limited by the observational nature of our study, this finding suggests that, similar to dialysis patients [9], the optimal values for PTH might not correspond to the normal range. Indeed, increasing PTH is an adaptive clinical response and having moderate hyperparathyroidism might be beneficial because of its phosphaturic properties or in the presence of bone

Table 2: Cox regression models for baseline and time-dependent exposures and all-cause mortality.

	Outcome: all-cause mortality							
	Baseline				Time-dependent			
	No. obs	No. events	HR (95% CI)	*P*-value	No. obs	No. events	HR (95% CI)	*P*-value
Exposure: PTH (×2)								
Models								
Unadjusted	1294	460	1.16 (1.07–1.26)	<.001	5840	460	1.08 (1.00–1.17)	.04
Adjusted for phosphate° and calcium°	1294	460	1.13 (1.04–1.23)	.003	5840	460	1.02 (0.95–1.11)	.54
Previous + age + sex + country	1294	460	1.14 (1.05–1.24)	.002	5840	460	1.03 (0.95–1.11)	.44
Previous + eGFR°	1294	460	1.15 (1.05–1.25)	.001	5827	460	1.01 (0.94–1.09)	.77
Previous + albumin°	1228	434	1.19 (1.09–1.29)	<.001	5472	431	1.07 (0.99–1.16)	.10
Previous + BMI°	1145	406	1.17 (1.07–1.28)	<.001	5194	403	1.07 (0.99–1.16)	.11
Previous + pre-existing comorbities[a]	1050	374	1.16 (1.05–1.28)	.003	4902	375	1.08 (0.99–1.18)	.07
Previous + medications[b]	1042	373	1.15 (1.05–1.27)	.004	4736	357	1.12 (1.03–1.23)	.01
Exposure: phosphate (+1 mmol/L)								
Models								
Unadjusted	1294	460	1.79 (1.32–2.42)	<.001	5840	460	1.79 (1.43–2.24)	<.001
Adjusted for PTH (log2)° and calcium°	1294	460	1.65 (1.21–2.25)	.002	5840	460	1.56 (1.24–1.97)	<.001
Previous + age + sex + country	1294	460	2.18 (1.60–2.98)	<.001	5840	460	1.80 (1.43–2.26)	<.001
Previous + eGFR	1294	460	2.28 (1.63–3.19)	<.001	5827	460	1.55 (1.19–2.02)	.001
Previous + albumin°	1228	434	2.21 (1.51–3.23)	<.001	5472	431	1.52 (1.16–2.00)	.003
Previous + BMI°	1145	406	2.35 (1.58–3.49)	<.001	5194	403	1.54 (1.17–2.03)	.002
Previous + pre-existing comorbities[a]	1050	374	2.04 (1.33–3.11)	<.001	4902	375	1.52 (1.14–2.04)	.005
Previous + medications[b]	1042	373	1.98 (1.28–3.06)	.002	4736	357	1.35 (1.00–1.84)	.05
Exposure: calcium (+1 mmol/L)								
Models								
Unadjusted	1294	460	0.47 (0.27–0.80)	.006	5840	460	0.24 (0.15–0.40)	<.001
Adjusted for PTH (log2)° and phosphate°	1294	460	0.68 (0.39–1.20)	.19	5840	460	0.31 (0.19–0.53)	<.001
Previous + age + sex + country	1294	460	0.76 (0.42–1.37)	.36	5840	460	0.31 (0.18–0.53)	<.001
Previous + eGFR°	1294	460	0.75 (0.41–1.36)	.34	5827	460	0.33 (0.19–0.56)	<.001
Previous + albumin°	1228	434	0.94 (0.50–1.77)	.85	5472	431	0.88 (0.49–1.57)	.66
Previous + BMI°	1145	406	0.96 (0.50–1.86)	.91	5194	403	0.81 (0.44–1.48)	.49
Previous + pre-existing comorbities[a]	1050	374	0.90 (0.45–1.80)	.76	4902	375	0.90 (0.47–1.71)	.75
Previous + medications[b]	1042	373	0.90 (0.44–1.83)	.78	4736	357	1.11 (0.57–2.17)	.76
Exposure: Ca_{ALB} (+1 mmol/L)								
Models								
Unadjusted	1228	434	0.97 (0.56–1.66)	.90	5485	431	1.46 (0.83–2.58)	.19
Adjusted for PTH (log2)° and phosphate°	1228	434	1.48 (0.85–2.60)	.17	5485	431	1.90 (1.08–3.36)	.03
Previous + age + sex + country	1228	434	1.52 (0.86–2.71)	.15	5485	431	1.90 (1.06–3.40)	.03
Previous + eGFR°	1228	434	1.53 (0.86–2.72)	.15	5476	431	1.88 (1.05–3.37)	.03
Previous + albumin°	1228	434	0.94 (0.50–1.77)	.85	5472	431	0.88 (0.49–1.57)	.66
Previous + BMI°	1145	406	0.96 (0.50–1.86)	.91	5194	403	0.81 (0.44–1.48)	.49
Previous + pre-existing comorbities[a]	1050	374	0.90 (0.45–1.80)	.76	4902	375	0.90 (0.47–1.71)	.75
Previous + medications[b]	1042	373	0.90 (0.44–1.83)	.78	4736	357	1.11 (0.57–2.17)	.76

°indicates time-dependent covariates in the longitudinal models; [a]include diabetes mellitus, hypertension, coronary artery disease, myocardial infarction, heart failure, atrial fibrillation, cerebrovascular disease, peripheral vascular disease, malignancies, psychiatric disorders; [b]include vitamin D supplements, active vitamin D, phosphate binders, calcimimetics, renin–angiotensin–aldosterone system inhibitors, beta-blockers.
BMI, body mass index.

hyporesponsiveness to PTH secondary to CKD [30, 31]. Moreover, we show that the association between PTH and mortality remains similar independent of other mineral parameters or time-varying confounders, suggesting that this relationship is not modified, or mediated, by phosphate or calcium levels, and that PTH has a direct link with mortality.

Our results demonstrate that PTH may be specifically associated with CV mortality, but not with mortality risk from other causes. The association between PTH levels and CV mortality has previously been established and thought to be mediated by left ventricular hypertrophy, atherosclerosis, and vascular, valvular and myocardial calcifications [32–36]. In the non-dialysis CKD population, SHPT is associated with prevalent CV disease [37, 38] and incident CV events [19–21]. Our results are in line with the existing knowledge linking PTH to CV burden in CKD, and they reinforce it through the additional use of longitudinal data, the exclusion of any mediating effects by calcium or phosphate as discussed above, and by demonstrating an apparent null association between of PTH and non-CV mortality.

Previous studies have associated phosphate levels with mortality in CKD non-dialysis patients. Kestenbaum *et al.* found that each 1 mg/dL (equal to 0.32 mmol/L) unit increase in baseline phosphate level was associated with a 33% higher risk of death in a cohort of US veterans affected by CKD at various stages [13], while this risk increased to 62% in a cohort of patients with eGFR <20 mL/min/1.73 m^2 [14]. Bellasi *et al.* [15] confirmed that CKD patients with a baseline phosphate >4.3 mg/dL (1.39 mmol/L) had a 49% greater mortality risk compared with those with phosphate of 3.3–3.8 mg/dL (1.07–1.23 mmol/L). Our results further strengthen these previous reports through longitudinal analyses,

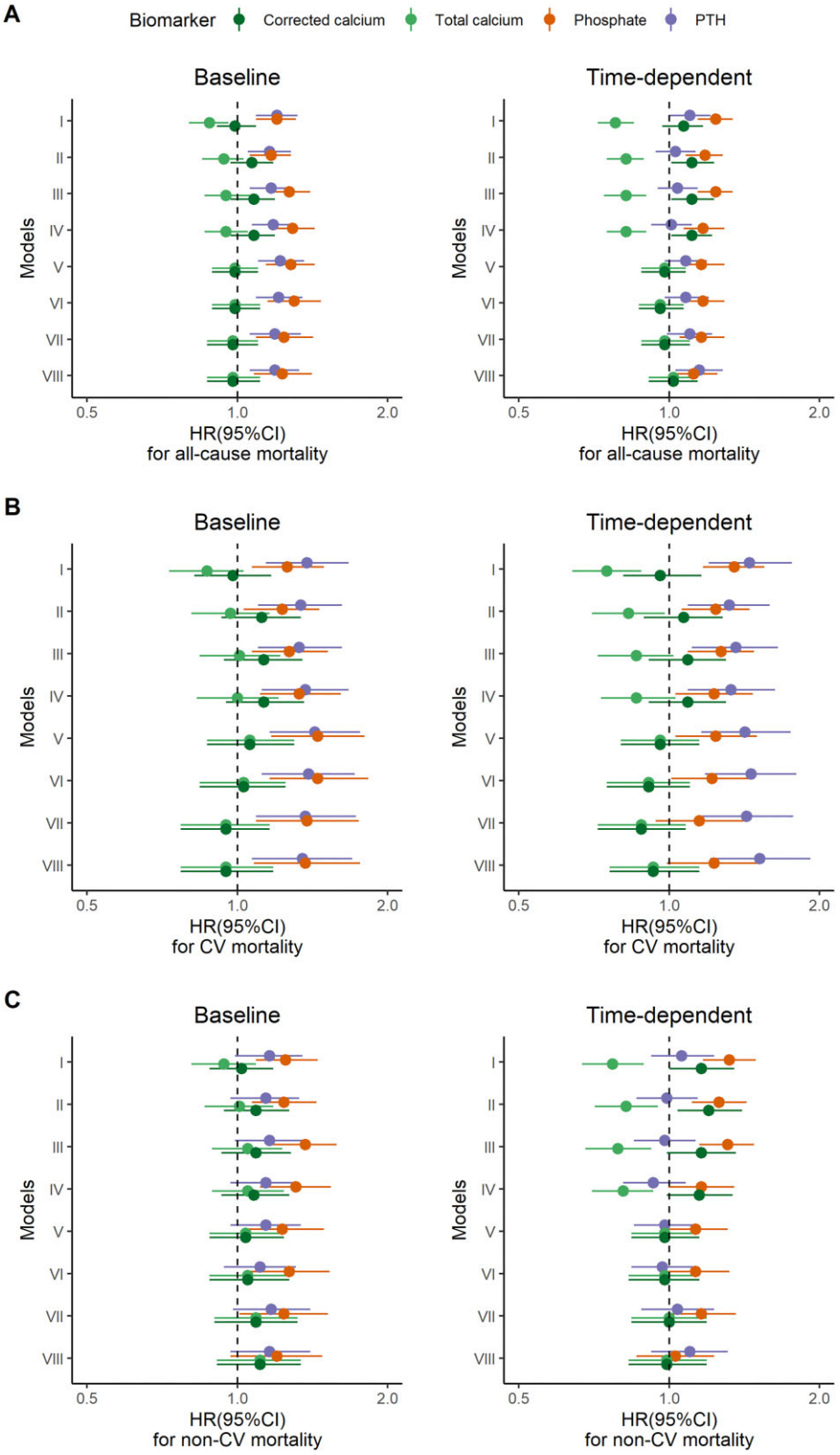


Figure 2: Effect sizes of CKD-MBD biomarkers on all outcomes. HRs for all-cause (**A**), CV (**B**) and non-CV (**C**) mortality associated with 1 SD increase in baseline and time-dependent biomarkers in unadjusted and sequentially adjusted models (I, unadjusted; II, adjusted for other mineral biomarkers; III, previous further adjusted for age sex and country; IV, previous further adjusted for eGFR; V, previous further adjusted for albumin; VI, previous further adjusted for BMI; VII, previous further adjusted for pre-existing comorbidities; VIII, previous further adjusted for medications), as in Tables 2 and 3. BMI, body mass index.

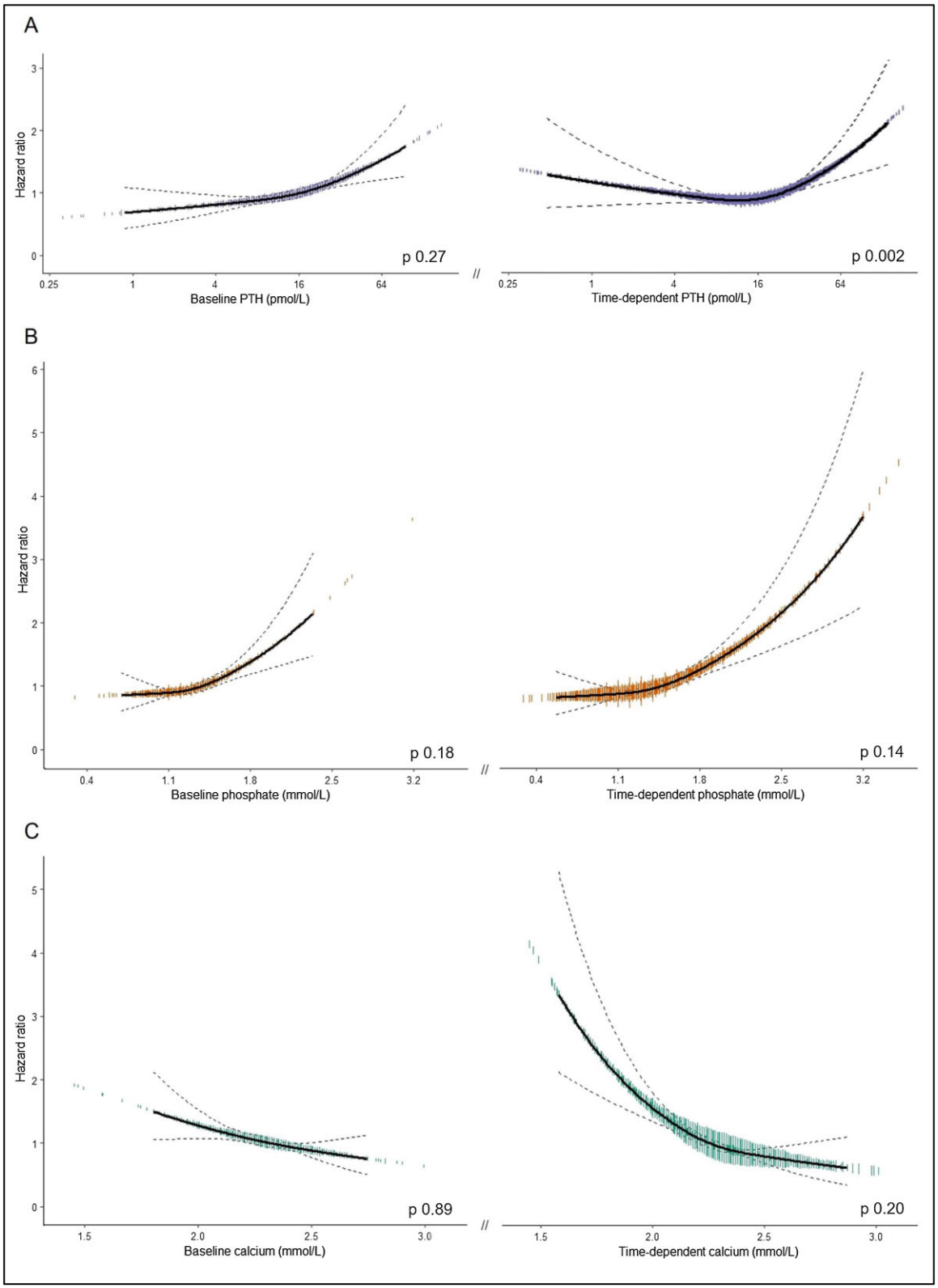


Figure 3: Mortality risk according to PTH (**A**), phosphate (**B**) and calcium (**C**) levels in the baseline and time-dependent analyses. The thick black line represents the unadjusted HR for all-cause mortality based on the continuous exposure, with the median value as reference. Dashed lines represent the limits for 95% CIs. Coloured segments represent the density of the observations. *P*-values for non-linearity are reported.

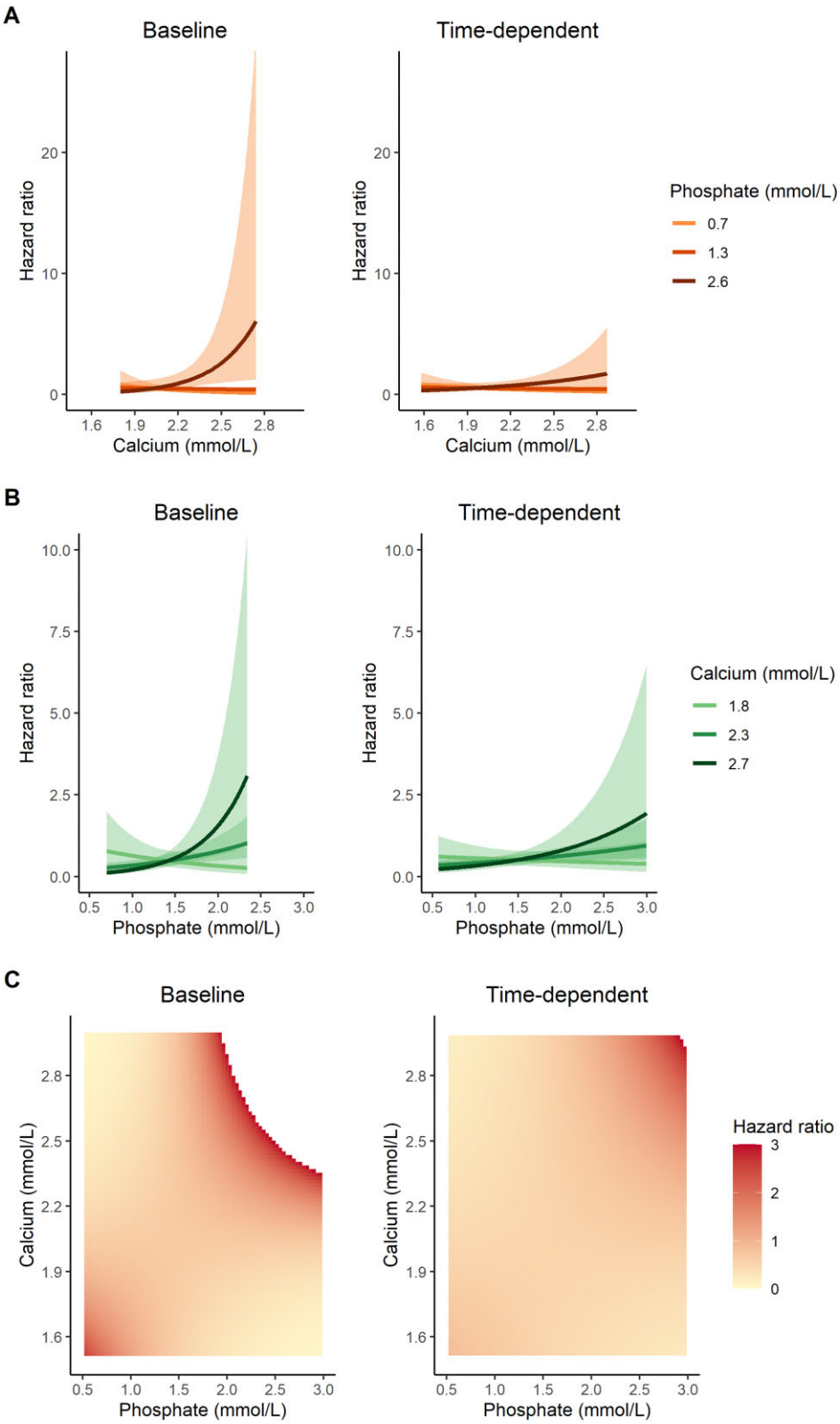


Figure 4: The interaction between phosphate and calcium in affecting all-cause mortality. The interaction between continuous phosphate and calcium, tested in the fully adjusted models (baseline analysis to the left and time-dependent analysis to the right), represented by line graphs and heatmaps. (**A**) Thick lines represent the HR for all-cause mortality based on calcium levels for different phosphate levels (1st, 50th and 99th percentile). Orange bands represent 95% CIs. (**B**) Thick lines represent the HR for all-cause mortality based on phosphate levels for different calcium levels (1st, 50th and 99th percentile). Green bands represent 95% CIs. (**C**) Heatmap of the risk of dying (the darker the colour, the higher the risk) based on calcium and phosphate levels.

Table 3: Cox regression models for baseline and time-dependent exposures and CV and non-CV mortality.

	Outcome: CV mortality						Outcome: non-CV mortality			
	Baseline			Time-dependent			Baseline		Time-dependent	
	No. obs	No. events	HR (95% CI)	No. obs	No. events	HR (95% CI)	No. events	HR (95% CI)	No. events	HR (95% CI)
Exposure: PTH (×2)										
Models										
Unadjusted	1294	129	1.31 (1.12–1.54)***	5840	129	1.36 (1.16–1.60)***	182	1.13 (0.99–1.28)	182	1.05 (0.93–1.19)
Adjusted for phosphate° and calcium°	1294	129	1.28 (1.09–1.50)**	5840	129	1.26 (1.07–1.47)**	182	1.11 (0.98–1.27)	182	0.99 (0.88–1.11)
Previous + age + sex + country	1294	129	1.27 (1.08–1.50)**	5840	129	1.29 (1.09–1.52)**	182	1.13 (0.99–1.29)	182	0.98 (0.87–1.11)
Previous + eGFR°	1294	129	1.30 (1.10–1.54)**	5827	129	1.27 (1.08–1.50)**	182	1.11 (0.98–1.27)	182	0.95 (0.84–1.07)
Previous + albumin°	1228	121	1.35 (1.13–1.61)***	5472	120	1.34 (1.13–1.59)***	176	1.12 (0.98–1.28)	172	0.99 (0.88–1.12)
Previous + BMI°	1145	116	1.32 (1.10–1.58)**	5194	111	1.36 (1.14–1.62)***	165	1.09 (0.95–1.25)	166	0.99 (0.87–1.12)
Previous + pre-existing comorbities[a]	1050	108	1.30 (1.07–1.57)**	4902	106	1.33 (1.12–1.59)**	152	1.14 (0.98–1.33)	153	1.05 (0.91–1.20)
Previous + medications[b]	1042	108	1.28 (1.05–1.55)*	4736	99	1.40 (1.16–1.69)***	151	1.14 (0.98–1.32)	146	1.10 (0.95–1.27)
Exposure: phosphate (+1 mmol/L)										
Models										
Unadjusted	1294	129	2.13 (1.25–3.63)**	5840	129	2.26 (1.53–3.34)***	182	2.09 (1.31–3.33)**	182	2.13 (1.53–2.98)***
Adjusted for PTH (log2)° and calcium°	1294	129	1.94 (1.11–3.40)*	5840	129	1.81 (1.18–2.77)**	182	2.04 (1.26–3.29)**	182	1.89 (1.33–2.67)***
Previous + age + sex + country	1294	129	2.21 (1.24–3.93)**	5840	129	1.93 (1.26–2.96)**	182	2.76 (1.70–4.47)***	182	2.09 (1.48–2.95)***
Previous + eGFR°	1294	129	2.55 (1.39–4.69)**	5827	129	1.77 (1.08–2.91)*	182	2.39 (1.40–4.09)**	182	1.51 (1.00–2.29)
Previous + albumin°	1228	121	3.36 (1.67–6.77)***	5472	120	1.82 (1.09–3.05)*	176	1.98 (1.08–3.63)*	172	1.37 (0.89–2.09)
Previous + BMI°	1145	116	3.39 (1.60–7.15)**	5194	111	1.73 (1.02–2.96)*	165	2.15 (1.16–4.02)*	166	1.38 (0.91–2.10)
Previous + pre-existing comorbities[a]	1050	108	2.81 (1.28–6.17)*	4902	106	1.48 (0.84–2.61)	152	2.00 (1.03–3.91)*	153	1.44 (0.93–2.22)
Previous + medications[b]	1042	108	2.76 (1.23–6.18)*	4736	99	1.83 (1.01–3.30)*	151	1.81 (0.91–3.61)	146	1.04 (0.65–1.68)
Exposure: calcium (+1 mmol/L)										
Models										
Unadjusted	1294	129	0.44 (0.16–1.21)	5840	129	0.19 (0.07–0.47)***	182	0.69 (0.29–1.65)	182	0.23 (0.10–0.50)***
Adjusted for PTH (log2)° and phosphate°	1294	129	0.85 (0.29–2.43)	5840	129	0.34 (0.13–0.90)*	182	1.05 (0.42–2.59)	182	0.32 (0.14–0.73)**
Previous + age + sex + country	1294	129	1.06 (0.35–3.22)	5840	129	0.41 (0.15–1.10)	182	1.30 (0.49–3.40)	182	0.26 (0.11–0.61)**
Previous + eGFR°	1294	129	1.02 (0.34–3.11)	5827	129	0.42 (0.16–1.14)	182	1.33 (0.58–3.47)	182	0.29 (0.12–0.67)**
Previous + albumin°	1228	121	1.44 (0.44–4.65)	5472	120	0.78 (0.27–2.25)	176	1.26 (0.46–3.44)	172	0.81 (0.33–1.98)
Previous + BMI°	1145	116	1.16 (0.36–3.75)	5194	111	0.57 (0.19–1.68)	165	1.37 (0.47–3.96)	166	0.79 (0.32–1.98)
Previous + pre-existing comorbities[a]	1050	108	0.72 (0.21–2.48)	4902	106	0.49 (0.16–1.54)	152	1.64 (0.53–5.06)	153	0.92 (0.35–2.47)
Previous + medications[b]	1042	108	0.73 (0.21–2.56)	4736	99	0.74 (0.22–2.47)	151	1.82 (0.58–5.68)	146	0.84 (0.31–2.32)
Exposure: Ca_{ALB} (+1 mmol/L)										
Models										
Unadjusted	1228	121	0.90 (0.32–2.50)	5485	120	0.81 (0.27–2.36)	176	1.12 (0.48–2.60)	172	2.45 (0.99–6.01)
Adjusted for PTH (log2)° and phosphate°	1228	121	1.89 (0.66–5.41)	5485	120	1.49 (0.51–4.30)	176	1.64 (0.68–3.94)	172	3.02 (1.24–7.34)*
Previous + age + sex + country	1228	121	2.00 (0.70–5.68)	5485	120	1.64 (0.57–4.72)	176	1.68 (0.67–4.20)	172	2.43 (0.96–6.16)
Previous + eGFR°	1228	121	2.07 (0.72–5.95)	5476	120	1.65 (0.58–4.75)	176	1.58 (0.64–3.94)	172	2.31 (0.92–5.81)
Previous + albumin°	1228	121	1.44 (0.44–4.65)	5472	120	0.78 (0.27–2.25)	176	1.26 (0.46–3.44)	172	0.81 (0.33–1.98)
Previous + BMI°	1145	116	1.16 (0.36–3.75)	5194	111	0.57 (0.19–1.68)	165	1.37 (0.47–3.96)	166	0.79 (0.32–1.98)
Previous + pre-existing comorbities[a]	1050	108	0.72 (0.21–2.48)	4902	106	0.49 (0.16–1.54)	152	1.64 (0.53–5.06)	153	0.92 (0.35–2.47)
Previous + medications[b]	1042	108	0.73 (0.21–2.56)	4736	99	0.74 (0.22–2.47)	151	1.82 (0.58–5.68)	146	0.84 (0.31–2.32)

Time-dependent covariate in the longitudinal models; [a]include diabetes mellitus, hypertension, coronary artery disease, myocardial infarction, heart failure, atrial fibrillation, cerebrovascular disease, peripheral vascular disease, malignancies; for non-CV mortality also include psychiatric disease; [b]include vitamin D supplements, active vitamin D, phosphate binders, calcimimetics; for CV also include renin-angiotensin-aldosterone system inhibitors and beta-blockers.
*$P < .05$, **$P < .01$, ***$P < .001$.
BMI, body mass index.

but also reveal some new insights into the topic. First, the effect size for phosphate increased notably after removing time-varying covariates from the model, suggesting that an increase in phosphate level could be associated with increased mortality, not only through a direct pathway, but also through the resulting increase in PTH levels, decrease in calcium levels or even worsening kidney function over time. This finding highlights the importance for clinical practice of considering all these biomarkers together. Second, phosphate levels seemed to be associated with both CV and non-CV mortality. Conventionally, the association between phosphate and mortality is attributed to CV causes, as it seems to affect atherosclerosis [35, 36], vascular calcification [39], left ventricular hypertrophy [40, 41] and CV disease both in CKD and non-CKD populations [10, 21, 42–44]. In line with the previous literature, our analysis confirmed a significant positive association between phosphate and CV mortality risk. This is a well-established and consistent association with temporal and biological plausibility. Interestingly, we also found that higher phosphate levels were associated with a higher risk of death for non-CV causes in most models. Notably, in the longitudinal analysis, phosphate was strongly associated with non-CV mortality risk until adjustment for time-varying eGFR, suggesting that the worsening of kidney function either confounds or mediates the association between phosphate and non-CV mortality. The evidence regarding the association between phosphate levels and non-CV mortality is scant. In dialysis patients, hyperphosphatemia seemed to be associated with non-CV events [45], and in particular with fractures [46–48] and infections [49]. Moreover, hyperphosphatemia is thought to be involved in tumorigenesis [50], since phosphate is essential in cell proliferation and growth, and tumor cells can store more inorganic phosphate than normal cells probably due to a higher expression and activity of phosphate cotransporter [51]. A positive association was found between serum phosphate and the risk of pancreatic, lung, thyroid and bone cancer in men, and oesophageal, lung and non-melanoma skin cancer in women [52]. However, this hypothesis has not been yet tested in CKD patients. Our sample size was not large enough to reliably test the association between biomarkers and death due to malignancies or infections.

Previous studies have linked abnormal calcium levels (hypo- and hypercalcemia) to increased mortality risk in advanced CKD [4, 6, 53, 54]. Subsequently, current guidelines suggest avoiding hypercalcemia in patients with CKD3–5D, while recommending an individualized approach to the treatment of hypocalcemia, given the unproven benefits and the potential harm of the treatment [12]. We found a significant interaction between calcium and phosphate levels, implying that hypercalcemia is associated with a higher mortality risk in combination with hyperphosphatemia. However, we did not find an association between calcium levels and mortality in our adjusted analyses, as the effect of calcium (either total calcium or Ca_{ALB}) was lost after adjusting for serum albumin, an established predictor of mortality in the CKD population [55–57]. Moreover, the effect sizes for calcium changed markedly when removing the other mineral biomarkers from the model, suggesting that calcium may have an indirect association with mortality, mediated mainly by phosphate and PTH. Consequently, until the precise pathophysiological pathways of these associations are fully understood, we recommend that researchers be aware of the risk of overadjustment bias.

Major strengths of our study were the large sample size from six different European countries improving the generalizability of our results, the use of interaction terms among biomarkers to account for their reciprocal nature and the relatively long follow-up time with repeated measurements. The repeated assessment of CKD-MBD biomarkers allowed us to perform both baseline and longitudinal analysis, addressing both long- and short-term associations, respectively [58]. We also acknowledge some limitations. First, the variety of assays used for PTH assessment in different centres and countries may have limited the accuracy of our results. However, it is reasonable to assume that the assays used did not change over time in each laboratory. Moreover, we did not find any meaningful difference in PTH distribution between different countries. Regarding PTH determination, we also acknowledge that currently used assays are unable to distinguish between the vast majority of oxidized forms of PTH and its non-oxidized form. Therefore, we cannot exclude the possibility that high levels of PTH in our cohort might only reflect a higher level of oxidative stress, which is also harmful to CKD patients [59, 60]. Another important limitation was the absence of ionized calcium, which more precisely represents the amount of calcium exerting a biological effect. Nonetheless, in clinical practice ionized calcium may often be missing and clinicians must make do with total calcium, possibly corrected for albumin level, although Payne's formula for calcium correction might not be suitable for CKD patients [61–63]. The observational nature of our study prevented us from including unmeasured confounders, including serum levels of 25-OH vitamin D and fibroblast growth factor 23 (FGF-23). Another limitation to our study was that 32% of the deaths in our cohort had an unknown cause, limiting our analysis of secondary outcomes (CV and non-CV mortality). We also acknowledge that our results may not be generalizable to non-European CKD patients, and we were unable to account for clustering of patients by CKD clinic as these data were unavailable. Finally, although we attempt to analyse to what extent PTH, phosphate and calcium modify each other's effects, we acknowledge that they are also connected with other biomarkers and given the complexity of the CKD-MBD syndrome, it is unlikely that our analysis could fully disentangle the individual contribution of each biomarker to mortality risk.

In conclusion, our findings illustrate that CKD-MBD is extremely common in older European patients with advanced CKD, and we show how abnormal values of PTH and phosphate are independently associated with mortality risk in this population.

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SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

L.M.: conceptualization, formal analysis, investigation and writing the original draft. M.C.: conceptualization and review. N.C.C.:

conceptualization, project administration, supervision and review. K.J.J.: conceptualization, funding acquisition, supervision and review. All authors contributed to data curation, reviewed the manuscript draft and approved the final version of the article.

CONFLICT OF INTEREST STATEMENT

The authors have nothing to disclose with respect to the present research. However, outside this work: M.C. declares advisory/lecture fees from Amgen, Abbvie, Shire, Vifor-Pharma and Baxter; F.J.C. received honoraria from Baxter Healthcare; M.E. reports payment for advisory boards and lectures by Astellas pharma, Vifor Pharma and AstraZeneca, and institutional grants from AstraZeneca and Astellas pharma; C.W. received honoraria for consultancy and lecturing from Amicus, AstraZeneca, Bayer, Boehringer-Ingelheim, Eli-Lilly, GILEAD, GSK, MSD, Sanofi-Genzyme and Takeda.

The authors declare that the results presented in this paper have not been published previously.

DATA AVAILABILITY STATEMENT

The data underlying this article are sensitive health data and cannot be shared publicly due to privacy reasons. The data will be shared on reasonable request to the corresponding author.

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