Causal assessment of CKD-MBD biomarker alterations on CKD progression through a g-formula analysis in the EQUAL study

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Abstract

Introduction: Chronic Kidney Disease–Mineral and Bone Disorder (CKD-MBD) may be both a cause and a consequence of CKD progression. Here, we examine the individual and joint effect of longitudinal circulating phosphate, parathyroid hormone, and calcium levels on estimated glomerular filtration rate (eGFR) decline, the risk of starting dialysis and the composite risk of death or dialysis, in a cohort of elderly patients with advanced CKD not on dialysis. Secondly, we explore whether these effects differ between men and women.

Methods: We used data from 1709 participants in the European Quality study, which includes patients aged 65 and older with eGFR 20 ml/min per 1.73 m^2 or less from six European countries. To avoid bias due to informative censoring, competing risks and time-varying confounding, we used the g-formula for causal inference.

Results: Isolated hyperphosphatemia and hyperparathyroidism were associated with a higher risk of CKD progression, whereas isolated hypercalcemia was not. The combination of hyperphosphatemia with hyperparathyroidism, and of hypocalcemia with hyperparathyroidism were also associated with significantly higher risk. The most adverse phenotype was the combination of hyperphosphatemia, hypocalcemia and hyperparathyroidism, which led to a mean difference in eGFR after three years of -3.71 ml/min (95% confidence intervals: -5.44, -2.15) and a 75% higher risk of starting dialysis (hazard ratio 1.75, 95% confidence interval 1.35-2.10), compared to having all biomarkers in their reference ranges. Most of this risk was attributable to hyperphosphatemia. Although the effect of abnormal mineral biomarkers on eGFR decline was similar between sexes, the associated risk of starting dialysis seemed stronger in men than in women.

Conclusions: Among older men and women with advanced CKD not receiving dialysis, the presence of hyperphosphatemia, especially when combined with hypocalcemia and hyperparathyroidism, leads to an increased risk of CKD progression.

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KEYWORDS: calcium; CKD-MBD; CKD progression; dialysis; phosphate; PTH

Chronic kidney disease–mineral and bone disorder (CKD-MBD) is a common complication of CKD, characterized by disorders in calcium, phosphate, parathyroid hormone (PTH), or vitamin D metabolism, and is associated with increased morbidity and mortality.[1] There is growing evidence that abnormalities in mineral biomarkers could be involved in CKD progression. Indeed, multiple observational studies have shown an association between both hyperphosphatemia and hyperparathyroidism and a higher risk of CKD progression.[2–14] Studies in patients with CKD have failed to show an association between hypercalcemia and CKD progression,[2,4,13] although in patients with primary hyperparathyroidism, chronic hypercalcemia may lead

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Lay Summary

Chronic kidney disease often leads to a condition known as mineral and bone disorder, where patients experience imbalances in phosphate, calcium, and parathyroid hormone levels. Our study investigates how these imbalances can affect the progression of chronic kidney disease in older adults across Europe who have advanced stages of the disease but are not yet on dialysis, thus creating a vicious circle. Using data from 1709 patients older than 65 years, we found that high phosphate, especially when combined with low calcium and high parathyroid hormone levels, was linked to a faster decline in kidney function and a higher risk of progressing to kidney failure, necessitating the initiation of dialysis. These findings indicate that managing mineral disorders could be vital for slowing the progression of chronic kidney disease.

to nephrolithiasis and nephrocalcinosis.[15] Conversely, it has been suggested that hypocalcemia could be a risk factor for CKD progression,[14,16,17] although discerning whether this represents a causal association remains challenging because of the complex interplay with other mineral disorders (i.e., hyperphosphatemia and hyperparathyroidism).

Previous studies on the association between CKD-MBD and CKD progression share some potential limitations. First, most studies focused only on a single biomarker, whereas calcium, phosphate, and PTH influence each other in a maladaptive feedback loop, and guidelines suggest that they should always be considered jointly.[1] Second, not all studies accounted for informative censoring and the competing risk of death when analyzing the risk of CKD progression. Finally, most studies assessed the effect of a single baseline measurement whereas longitudinal analyses could be more informative, for instance, by showing the cumulative effect of mineral abnormalities over time. However, longitudinal analyses require careful consideration of time-varying confounding and potential treatment-confounder feedback bias.[18,19]

Furthermore, although CKD progression seems to be more rapid in males than in females,[20–22] biological sex differences in the association between CKD-MBD and disease progression remain unknown.

In the present study, we aim to assess the individual and combined effect of longitudinal CKD-MBD biomarkers (PTH, phosphate, and calcium) on CKD progression in a European cohort of older patients with CKD stages 4 and 5 not on dialysis, using G-methods to avoid bias due to informative censoring, competing events, and time-varying confounding. Moreover, we explore whether these associations differ between males and females.

METHODS

Study design and population

The European Quality (EQUAL) study is an ongoing prospective cohort study in patients with CKD stages 4 and 5 from Germany, Italy, the Netherlands, Poland, Sweden, and the United Kingdom; the study started in March 2012 and is fully described elsewhere.[23] Patients ≥65 years or older were included after an incident drop in estimated glomerular filtration rate (eGFR) to ≤20 ml/min per 1.73 m^2. Exclusion criteria were eGFR drop due to an acute event or previous kidney replacement therapy. EQUAL participants were selected who had at least 1 measurement of either phosphate, PTH, or calcium during 4 years of follow-up (Supplementary Figure S1). Patients were followed for up to 4 years or until kidney transplantation, death, dialysis initiation, refusal for further participation, or loss to follow-up. The study received approval from the medical ethics committees or institutional review boards of all participating countries. Written informed consent was obtained from all patients.

Data collection

Data on demographics, preexisting comorbid conditions, primary kidney disease (classified by the European Renal Association coding system[24]), and medications were collected at baseline. Laboratory data were collected at baseline and updated at each study visit, scheduled at 3- to 6-month intervals.[23] The measurement of phosphate, PTH, and calcium was performed according to local practice and was not standardized across centers. Total calcium was corrected for albumin levels using Payne's formula.[25] eGFR was calculated from serum creatinine levels standardized to isotope dilution mass spectrometry by using the CKD Epidemiology Collaboration 2009 equation. All biochemical measurements are expressed as SI units, after conversion using the following conversion factors: serum creatinine (mg/dl to μmol/l) × 88.4, urea (mg/dl to mmol/l) × 0.166, phosphate (mg/dl to mmol/l) × 0.323, parathyroid hormone (mg/l to ng/l) × 1, calcium (mg/dl to mmol/l) × 0.25, and albumin (g/dl to g/l) × 10.

Statistical analysis

Data were reported as numbers (percentages), means ± SDs, or medians and interquartile range, as appropriate. Phosphate and PTH were log-transformed to improve normality. Mean imputation was used for missing baseline variables (Table 1), whereas missing longitudinal data (Supplementary Figure S2) were handled by carrying forward the last available observation for a maximum of 2 years. Patients with missing data on any mineral biomarkers or eGFR for longer than 2 consecutive years were censored 2 years after the date of their last available observation for that missing variable.

The associations between repeated measurements of CKD-MBD biomarkers and CKD progression were investigated using the g-computation formula (also known as "g-formula"). The analysis was performed using the "gfoRmula" R package.[26] Age, sex, country, primary kidney disease, baseline Charlson Comorbidity Index, and baseline medications (vitamin D analogues, calcium supplements, phosphate binders, and calcimimetics) were included as time-fixed confounders and eGFR and albumin levels as time-varying confounders. Potentially informative censoring

Table 1 | Baseline characteristics of the overall cohort and by sex

Characteristic	Overall (*N* = 1709)	Males (n = 1121)	Females (n = 588)	Missing, %
Sociodemographic factors				
Age, yr	76.3 ± 6.7	75.9 ± 6.4	77.0 ± 7.1	0.0
Country				0.0
Germany	147 (8.6)	85 (7.6)	62 (10.5)	
Italy	409 (23.9)	269 (24.0)	140 (23.8)	
The Netherlands	263 (15.4)	185 (16.5)	78 (13.3)	
Poland	93 (5.4)	60 (5.4)	33 (5.6)	
Sweden	304 (17.8)	214 (19.1)	90 (15.3)	
United Kingdom	493 (28.8)	308 (27.5)	185 (31.5)	
Medical history				
Primary kidney disease				0.8
Glomerular disease	156 (9.2)	115 (10.3)	41 (7.1)	
Tubulointerstitial disease	146 (8.6)	80 (7.2)	66 (11.4)	
Diabetes mellitus	347 (20.5)	242 (21.7)	105 (18.1)	
Hypertension	610 (36.0)	389 (34.9)	221 (38.0)	
Other/unknown	436 (25.7)	288 (25.9)	148 (25.5)	
Charlson Comorbidity Index	7.0 [6.0–8.0]	7.0 [6.0–8.0]	7.0 [6.0–8.0]	2.1
Physical examination				
Body mass index, kg/m^2	27.8 [24.6–31.4]	27.8 [24.7–30.9]	28.1 [24.2–32.5]	7.8
Systolic blood pressure, mm Hg	143 ± 22	143.1 ± 21.7	141.7 ± 22.6	2.0
Diastolic blood pressure, mm Hg	74 ± 11	74.1 ± 11.4	73.5 ± 11.1	2.0
Heart rate (beats/min)	71 ± 12	70.3 ± 12.1	72.3 ± 12.9	11.2
Biochemical data				
CKD-EPI eGFR, ml/min per 1.73 m^2	17.2 ± 5.3	16.9 ± 5.1	17.7 ± 5.5	1.1
Creatinine, μmol/l	274 [230–336]	301 [265–354]	230 [194–265]	0.8
Urea, mmol/l	19.3 [15.4–24.3]	19.8 [16.1–24.7]	18.1 [14.2–23.3]	4.2
uACR, mg/g	34.1 [4.9–152.3]	41.4 [7.2–156.3]	21.9 [3.2–138.1]	55.5
Phosphate, mg/dl	1.26 [1.10–1.45]	1.26 [1.10–1.42]	1.29 [1.13–1.45]	5.7
PTH, ng/l	145 [87–225]	150 [90–233]	135 [83–215]	19.6
Corrected calcium, mmol/l	2.35 ± 0.17	2.33 ± 0.17	2.38 ± 0.17	11.1
Albumin, g/ll	38 ± 5	38 ± 5	38 ± 5	10.1
Medications				1.1
Vitamin D analogues	352 (20.8)	209 (18.8)	143 (24.6)	
Calcium supplements	245 (14.5)	147 (13.2)	98 (16.9)	
Phosphate binders	232 (13.7)	157 (14.1)	75 (12.9)	
Calcimimetics	15 (0.9)	9 (0.8)	6 (1.0)	

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; PTH, parathyroid hormone; uACR, urinary albumin-to-creatinine ratio.
Data are reported as mean ± SD for normal continuous variables, median [interquartile range] for nonnormal continuous variables, and number (percentage) for categorical variables. For each variable, the proportion of missing data is reported.
Conversion factors for units: To convert serum creatinine values from mg/dl to μmol/l, × 88.4; to convert urea values from mg/dl to mmol/l, × 0.167; to convert phosphate values from mg/dl to mmol/l, × 0.323; to convert PTH values from pg/ml to pmol/l, × 0.106; to convert calcium values from mg/dl to mmol/l, × 0.250; to convert albumin values from g/dl to g/l, × 10.

was modeled by conditioning on the same covariate set. Confidence intervals (CIs) were computed by repeating the analysis in 500 bootstrapped samples. Nonlinearity was explored using restricted cubic splines with knots at 10th, 50th, and 90th percentiles. Analyses were stratified by sex. All analyses were performed with R version 4.1.1 (R Foundation for Statistical Computing).

The g-formula

The g-formula is a statistical tool for causal inference, particularly designed to deal with time-varying exposures in the presence of time-varying confounders that are affected by previous exposure.[27,28] This approach helps mitigate bias due to informative censoring, competing events, time-varying confounding, and treatment-confounder feedback bias.

A *time-varying confounder* is defined as a covariate that changes over time and affects both the outcome and the subsequent exposure. Treatment-confounder feedback bias occurs when prior values of an exposure influence future values of a time-varying confounder, which in turn affects subsequent exposure levels, potentially

biasing standard regression analyses (Supplementary Figure S3).

The g-formula addresses these biases by explicitly modeling the evolution of exposures, confounders, and outcomes over time. Briefly, it fits separate regression models for each time-varying exposure and confounder and subsequently models the outcome of interest as a function of the exposure, confounders, previous exposure, and confounder history and the probability of remaining uncensored over time, using—when appropriate—a subdistribution hazard model to account for the competing risk of death. This allows the simulation of counterfactual scenarios in which individuals are exposed to different risk factors. By comparing the outcomes under these different exposure scenarios, we can estimate the causal effect of the exposure on the outcome. Further details are provided in Supplementary Methods.

Simulated phenotypes

The g-formula can be used to simulate user-specified threshold exposures sustained over time (see Supplementary Methods). For instance, we simulated sustained hyperphosphatemia by setting a threshold at 1.45 mmol/l. This means that if the value of phosphate at any time is <1.45 mmol/l for a patient, it is artificially replaced with 1.45 mmol/l; otherwise, it remains unchanged. Thus, with "hyperphosphatemia" we are simulating a patient whose phosphate levels remained ≥1.45 mmol/l during the entire follow-up period. Technical details on this procedure can be found elsewhere.[26]

We defined mutually exclusive CKD-MBD phenotypes on the basis of thresholds for phosphate, calcium, and PTH. For phosphate, the threshold of 1.45 mmol/l was used to separate the reference range (<1.45 mmol/l) and hyperphosphatemia (≥1.45 mmol/l). For calcium, 2.13 to 2.63 mmol/l was considered the reference range, with hypocalcemia and hypercalcemia defined as calcium <2.13 and >2.63 mmol/l, respectively. Because the optimal PTH level to be maintained in patients with CKD not on dialysis is unknown,[1,29] we used a threshold of 150 ng/l[30] to distinguish normal to mildly increased PTH (<150 ng/l, reference) from moderate-to-severe hyperparathyroidism (≥150 ng/l). The combined effect of these simulated exposures was investigated by including 3-way interactions among the biomarkers, yielding 12 possible CKD-MBD phenotypes, as depicted in Supplementary Table S1. After excluding unrealistic phenotypes that were very uncommon throughout follow-up, with a prevalence <2% at every time point (Supplementary Figure S4), the final simulated exposures included in our analysis were as follows:

- *Reference phenotype:* All biomarkers in the reference range (phosphate <1.45 mmol/l, calcium 2.13–2.63 mmol/l, and PTH <150 ng/l)
- *Isolated hyperphosphatemia:* Phosphate ≥1.45 mmol/l with calcium 2.13–2.63 mmol/l, and PTH <150 ng/l
- *Isolated hyperparathyroidism:* PTH ≥150 ng/l with phosphate <1.45 mmol/l and calcium 2.13–2.63 mmol/l
- *Isolated hypercalcemia:* Calcium >2.63 mmol/l with phosphate <1.45 mmol/l and PTH <150 ng/l
- *Combined hyperphosphatemia and hyperparathyroidism:* Phosphate ≥1.45 mmol/l and PTH ≥150 ng/l, with calcium 2.13–2.63 mmol/l
- *Combined hypocalcemia and hyperparathyroidism:* Calcium <2.13 mmol/l and PTH ≥150 ng/l, with phosphate <1.45 mmol/l
- *Combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism:* Phosphate ≥1.45 mmol/l, calcium <2.13 mmol/l, and PTH ≥150 ng/l.

In addition, the "average trajectory" was simulated by not artificially replacing any of the estimated exposures. This represents the average outcome trajectory observed in the cohort after accounting for informative censoring due to death and dialysis initiation.

Outcomes

The primary end point was eGFR trajectory over time, accounting for informative censoring. Dialysis initiation, transplantation, and death were considered as informative censoring events, whereas patient's decision to withdraw from the study, transfer to a non-EQUAL center, or completion of follow-up were treated as noninformative. The trajectories were drawn on the basis of the point estimates of eGFR after 1, 2, and 3 years of follow-up. The point estimate of eGFR at 4 years from baseline was excluded from the analysis because of a lack of statistical power. Secondary end points included the risk of dialysis initiation, accounting for the competing risk of death, as well as the risk of the composite outcome of death or dialysis initiation during 4 years of follow-up.

Sensitivity analyses

Data on urinary albumin-to-creatinine ratio were missing in more than half of the cohort, which would have notably limited overall statistical power. We therefore performed a sensitivity analysis adjusting for baseline and time-varying urinary albumin-to-creatinine ratio in the subset of patients with available data.

Another sensitivity analysis was performed by imputing missing longitudinal data (Supplementary Figure S2) by carrying forward the last available observation for a maximum of only 1 year (instead of 2), after which patients were considered lost to follow-up.

Finally, we evaluated the absence of model misspecification by comparing the outcomes obtained with the "average trajectory" simulation and the nonparametric estimate of the outcome provided by the "g-formula" package itself. The latter estimate is obtained from the observed data using nonparametric methods, such as inverse probability weighting, and should be similar to the parametric g-formula estimate under the "average trajectory" in the absence of model misspecification.[31]

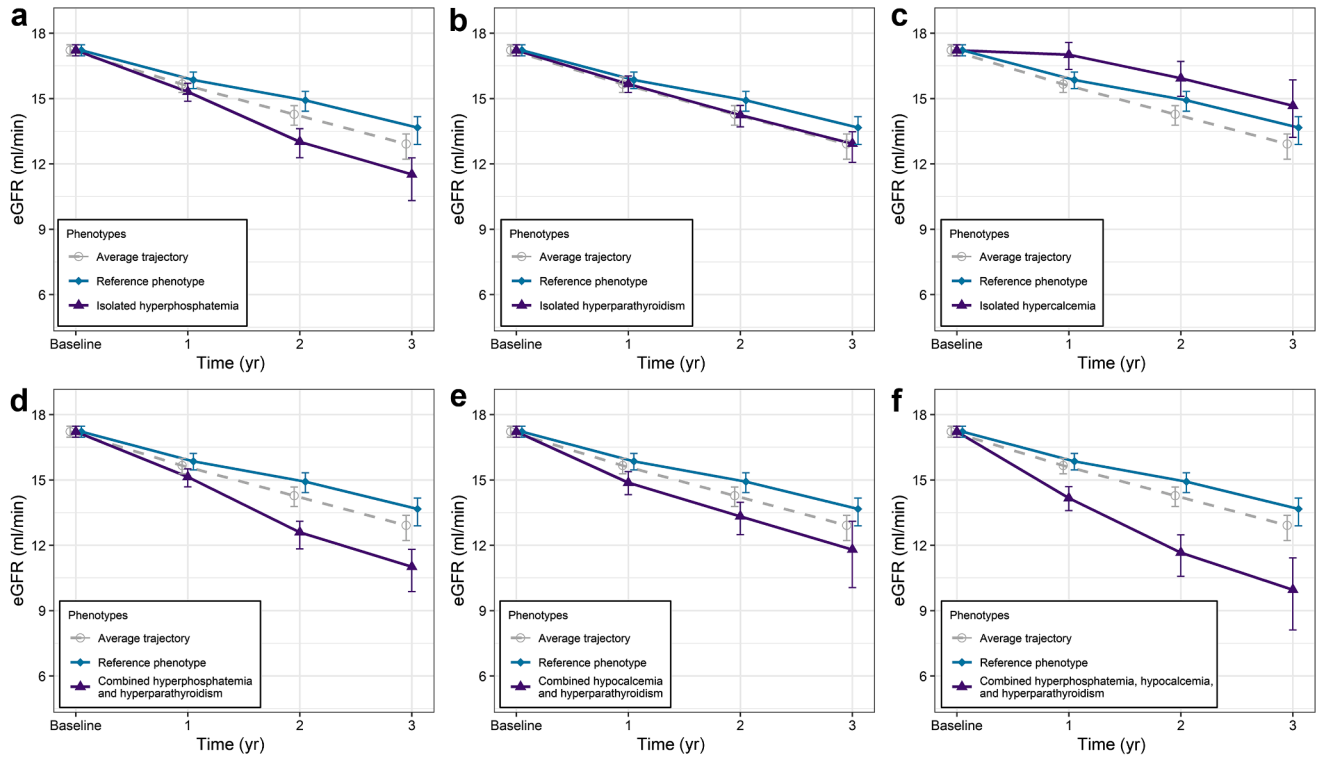

Figure 1 | Estimated glomerular filtration rate (eGFR) trajectories under different simulated chronic kidney disease–mineral and bone disorder phenotypes. In each panel, the gray dashed line with open circles represents the average trajectory, that is, the eGFR trajectory observed in the entire cohort after accounting for informative censoring. The colored solid lines represent eGFR trajectories under specific exposures, with the light blue line indicating the reference phenotype (phosphate <1.45 mmol/l, parathyroid hormone <150 ng/l, and calcium 2.13–2.63 mmol/l), and the purple line indicating specific phenotypes for comparison: (**a**) isolated hyperphosphatemia, (**b**) isolated hyperparathyroidism, (**c**) isolated hypercalcemia, (**d**) combined hyperphosphatemia and hyperparathyroidism, (**e**) combined hypocalcemia and hyperparathyroidism, and (**f**) combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism. Trajectories are drawn on the basis of point estimates of eGFR after 1, 2, and 3 years of follow-up (represented by the dots along the line and corresponding confidence intervals). We included age, sex, country, primary kidney disease, baseline Charlson Comorbidity Index, and baseline medications (vitamin D analogues, calcium supplements, phosphate binders, and calcimimetics) as time-fixed confounders and eGFR and albumin levels as time-varying confounders.

RESULTS

Patient characteristics

The baseline characteristics of the 1709 patients included in the study are reported in Table 1, both overall and stratified by sex. The mean age was 76.3 ± 6.7 years, with males representing 66% of the cohort (N = 1121). At baseline, males had a slightly lower mean eGFR (16.9 ml/min per 1.73 m^2 vs. 17.7 ml/min per 1.73 m^2) and higher median PTH levels (150 ng/l vs. 135 ng/l) whereas females had marginally higher phosphate (1.29 mmol/l vs. 1.26 mmol/l) and calcium (2.38 mmol/l vs. 2.33 mmol/l) levels. The distribution of primary kidney diseases and comorbidities was similar across sexes. Use of CKD-MBD–related medications showed some variation, with a higher proportion of females receiving vitamin D analogues and calcium supplements.

Table 2 | Mean differences in eGFR between different CKD-MBD phenotypes and the reference phenotype at each time point

CKD-MBD phenotypes	After 1 yr (*n* = 1256)	After 2 yr (*n* = 804)	After 3 yr (*n* = 423)
Isolated hyperphosphatemia	−0.54 (−0.84 to −0.24)	−1.90 (−2.61 to −1.28)	−2.15 (−3.10 to −1.27)
Isolated hyperparathyroidism	−0.18 (−0.45 to 0.05)	−0.68 (−1.05 to −0.34)	−0.74 (−1.37 to −0.15)
Isolated hypercalcemia	1.16 (0.58 to 1.68)	1.01 (0.23 to 1.79)	1.00 (−0.21 to 2.25)
Combined hyperphosphatemia and hyperparathyroidism	−0.72 (−1.08 to −0.35)	−2.32 (−3.02 to −1.76)	−2.66 (−3.72 to −1.74)
Combined hypocalcemia and hyperparathyroidism	−0.98 (−1.43 to −0.51)	−1.59 (−2.30 to −1.02)	−1.87 (−3.51 to −0.45)
Combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism	−1.69 (−2.18 to −1.16)	−3.26 (−4.25 to 2.38)	−3.71 (−5.44 to −2.15)

CKD-MBD, chronic kidney disease–mineral and bone disorder; eGFR, estimated glomerular filtration rate; *n*, number of uncensored patients; PTH, parathyroid hormone. Mean differences in eGFR (ml/min per 1.73 m^2) between each simulated CKD-MBD phenotype and the reference phenotype (phosphate <1.45 mmol/l, parathyroid hormone <150 ng/l, and calcium 2.13–2.63 mmol/l) are reported with their 95% confidence intervals.

eGFR trajectory over time

The median follow-up time was 2.1 years (interquartile range 0.9–3.6 years). After 1, 2, and 3 years of follow-up, the mean eGFR was 15.7, 14.3, and 12.9 ml/min per 1.73 m^2, respectively. The eGFR trajectories under the different CKD-MBD phenotypes are shown in Figure 1, and the mean differences between exposures at each time point are reported in Table 2. Compared with the reference phenotype, all tested phenotypes except for isolated hypercalcemia were associated with a steeper decline in eGFR. In particular, the steepest eGFR trajectory was observed for the combination of hyperphosphatemia, hypocalcemia, and hyperparathyroidism, with a mean eGFR difference of −3.71 ml/min per 1.73 m^2 (95% CI −5.44 to −2.15 ml/min per 1.73 m^2) after 3 years, compared to the reference phenotype. Most of this effect is likely attributable to hyperphosphatemia, as the phenotype characterized by isolated hyperphosphatemia showed a mean eGFR difference of −2.15 ml/min per 1.73 m^2 (95% CI −3.10 to −1.27 ml/min per 1.73 m^2) after 3 years compared with the reference phenotype, and this difference further increased only to −2.66 ml/min per 1.73 m^2 (95% CI −3.72 to −1.74 ml/min per 1.73 m^2) when hyperphosphatemia was combined with hyperparathyroidism. A milder effect was also observed in the presence of isolated hyperparathyroidism (mean difference after 3 years −0.74 ml/min per 1.73 m^2; 95% CI −1.37 to −0.15 ml/min per 1.73 m^2) as well as for the combination of hypocalcemia and hyperparathyroidism (−1.87 ml/min per 1.73 m^2; 95% CI −3.51 to −0.45 ml/min per 1.73 m^2).

Risk of dialysis initiation

During the study period, 570 patients started dialysis, while 397 died before having the chance to start kidney replacement therapy. At 4 years of follow-up, the observed risks were 38% for dialysis initiation and 68% for the composite end point of death or dialysis initiation.

The risk of dialysis initiation over time under the different CKD-MBD phenotypes is shown in Figure 2, with corresponding hazard ratios (HRs) reported in Table 3. In line with the primary end point, isolated hyperphosphatemia was associated a higher risk of dialysis initiation compared to the reference phenotype (HR 1.34; 95% CI 1.15–1.54). This risk increased further with the combination of hyperphosphatemia and hyperparathyroidism (HR 1.43; 95% CI 1.23–1.75), and the highest risk was observed under the phenotype of combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism (HR 1.75; 95% CI 1.35–2.10). Isolated hyperparathyroidism was also associated with a mild risk increase compared to the reference phenotype (HR 1.17; 95% CI 1.05–1.28), with concomitant hypocalcemia increasing this association (HR 1.44; 95% CI 1.16–1.72). The risk under isolated hypercalcemia did not differ significantly from that under the reference phenotype. Similar results were observed for the composite outcome of death or dialysis initiation, as shown in Figure 3 and Table 3.

Sex differences

The distribution of different CKD-MBD phenotypes over time in males and females is shown in Supplementary Figure S5. Compared with females, males had a lower baseline eGFR (16.9 ml/min per 1.73 m^2 vs. 17.7 ml/min per 1.73 m^2) and a steeper decline, with a mean eGFR at 1, 2, and 3 years of follow-up of 15.0, 13.2, and 11.6 ml/min per 1.73 m^2 in males and 16.7, 15.8, and 14.5 ml/min per 1.73 m^2 in females. However, the effect of abnormal mineral biomarkers on eGFR trajectory was similar in both sexes (Supplementary Figure S6).

Compared with females, males had a higher risk of dialysis initiation (observed risk at year 4 43% vs. 28%) and of the composite outcome (73% vs. 57%). As shown in Supplementary Figure S7, the effect of abnormal mineral biomarkers on the risk of dialysis initiation seemed more pronounced in males than in females. For instance, males with combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism had an 85% higher risk of dialysis initiation compared to the reference phenotype, whereas this was not evident in females. In contrast, the associations between the different CKD-MBD phenotypes and the composite outcome of death or dialysis initiation did not differ by sex (Supplementary Figure S8).

Sensitivity analyses

After adjusting for baseline and time-varying urinary albumin-to-creatinine ratio, in the subset of patients with data available, the associations between CKD-MBD biomarkers and CKD progression were similar, although reduced in effect size (Supplementary Table S2).

Similarly, results were mostly unchanged when missing longitudinal data were imputed by carrying forward the last available observation for a maximum of only 1 year instead of 2 years (Supplementary Table S3).

Finally, in all analyses the parametric g-formula under the "average trajectory" closely replicated the nonparametric outcome estimate (Supplementary Figure S9), which supports the absence of gross model misspecification.

DISCUSSION

In this study, we describe the effects of specific CKD-MBD phenotypes on CKD progression in a large European cohort of older patients with advanced CKD not on dialysis, using causal inference methodology to avoid bias due to informative censoring, competing risks, and time-varying confounding. Our results show that hyperphosphatemia and moderate-to-severe hyperparathyroidism—both alone or in combination—and their co-occurrence with hypocalcemia are associated with a higher risk of CKD progression, even at this late stage of the disease (eGFR ≤20 ml/min per 1.73 m^2).

Our findings align with several previous observational studies that identified hyperphosphatemia and hyperparathyroidism at baseline as risk factors for CKD progression in patients with various stages of CKD.[2–8,10–13,32] This knowledge was recently expanded by D'Arrigo *et al.*,[14] who

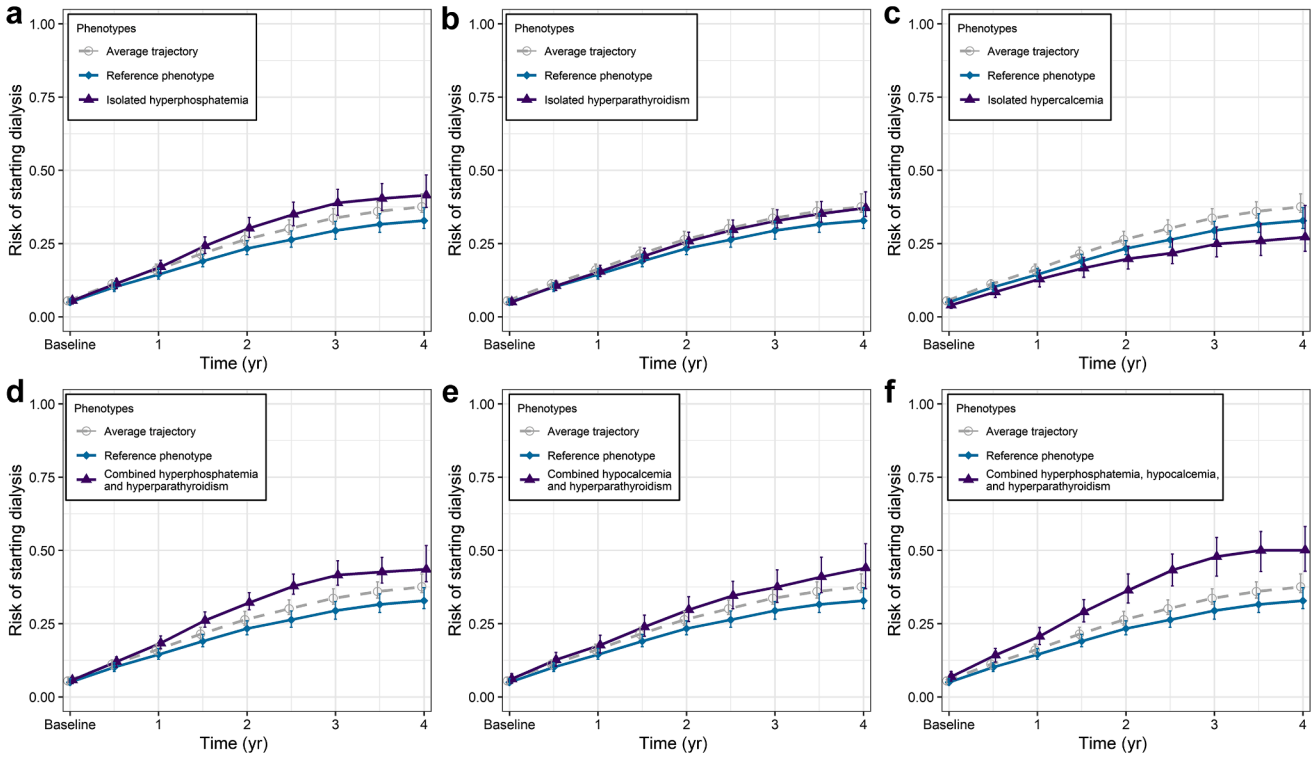

Figure 2 | Risk trajectories for dialysis initiation under different simulated chronic kidney disease–mineral and bone disorder phenotypes. In each panel, the gray dashed line with open circles represents the average trajectory, that is, the risk trajectory observed in the entire cohort accounting for the competing risk of death. The colored solid lines represent risk trajectories under specific exposures, with the light blue line indicating the reference phenotype (phosphate <1.45 mmol/l, parathyroid hormone <150 ng/l, and calcium 2.13–2.63 mmol/l), and the purple line indicating specific phenotypes for comparison: (**a**) isolated hyperphosphatemia, (**b**) isolated hyperparathyroidism, (**c**) isolated hypercalcemia, (**d**) combined hyperphosphatemia and hyperparathyroidism, (**e**) combined hypocalcemia and hyperparathyroidism, and (**f**) combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism. Trajectories are drawn on the basis of the conditional probability, at each time point, of the outcome occurring in the following 6-month interval (represented by the dots along the line and corresponding confidence intervals). We included age, sex, country, primary kidney disease, baseline Charlson Comorbidity Index, and baseline medications (vitamin D analogues, calcium supplements, phosphate binders, and calcimimetics) as time-fixed confounders and estimated glomerular filtration rate and albumin levels as time-varying confounders.

analyzed the association between repeated measurements of CKD-MBD biomarkers over time and CKD progression in an Italian cohort of patients with CKD stages 2 to 5. Their findings indicate that increases in phosphate and PTH levels, as well as decreases in calcium levels, are associated with a higher risk of reaching the composite end point, which included either a 30% decrease in eGFR or initiation of kidney replacement therapy. Our study expands on their work in several key ways. First, we used the g-formula to adjust for time-varying eGFR, addressing confounding by declining kidney function over time. Second, we accounted for biases from informative censoring and competing risks. Third, we analyzed CKD-MBD biomarkers as phenotypes, capturing the interplay between phosphate, calcium, and PTH, providing a more comprehensive understanding of how these interrelated biomarkers collectively influence CKD

Table 3 | Hazard ratios for the risk of dialysis initiation and of the composite outcome (death or dialysis initiation) between different CKD-MBD phenotypes and the reference phenotype

CKD-MBD phenotypes	Dialysis	Composite outcome (death or dialysis initiation)
Isolated hyperphosphatemia	1.34 (1.15–1.54)	1.35 (1.20–1.51)
Isolated hyperparathyroidism	1.17 (1.05–1.28)	1.13 (1.03–1.23)
Isolated hypercalcemia	0.81 (0.65–1.13)	0.89 (0.73–1.08)
Combined hyperphosphatemia and hyperparathyroidism	1.43 (1.23–1.75)	1.40 (1.24–1.59)
Combined hypocalcemia and hyperparathyroidism	1.44 (1.16–1.72)	1.28 (1.12–1.59)
Combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism	1.75 (1.35–2.10)	1.64 (1.37–2.06)

CKD-MBD, chronic kidney disease–mineral and bone disorder; PTH, parathyroid hormone.
Hazard ratios for the risk of dialysis initiation and of the composite outcome (death or dialysis initiation) between each simulated CKD-MBD phenotype and the reference phenotype (phosphate <1.45 mmol/l, parathyroid hormone <150 ng/l, and calcium 2.13–2.63 mmol/l) are reported with corresponding 95% confidence intervals.

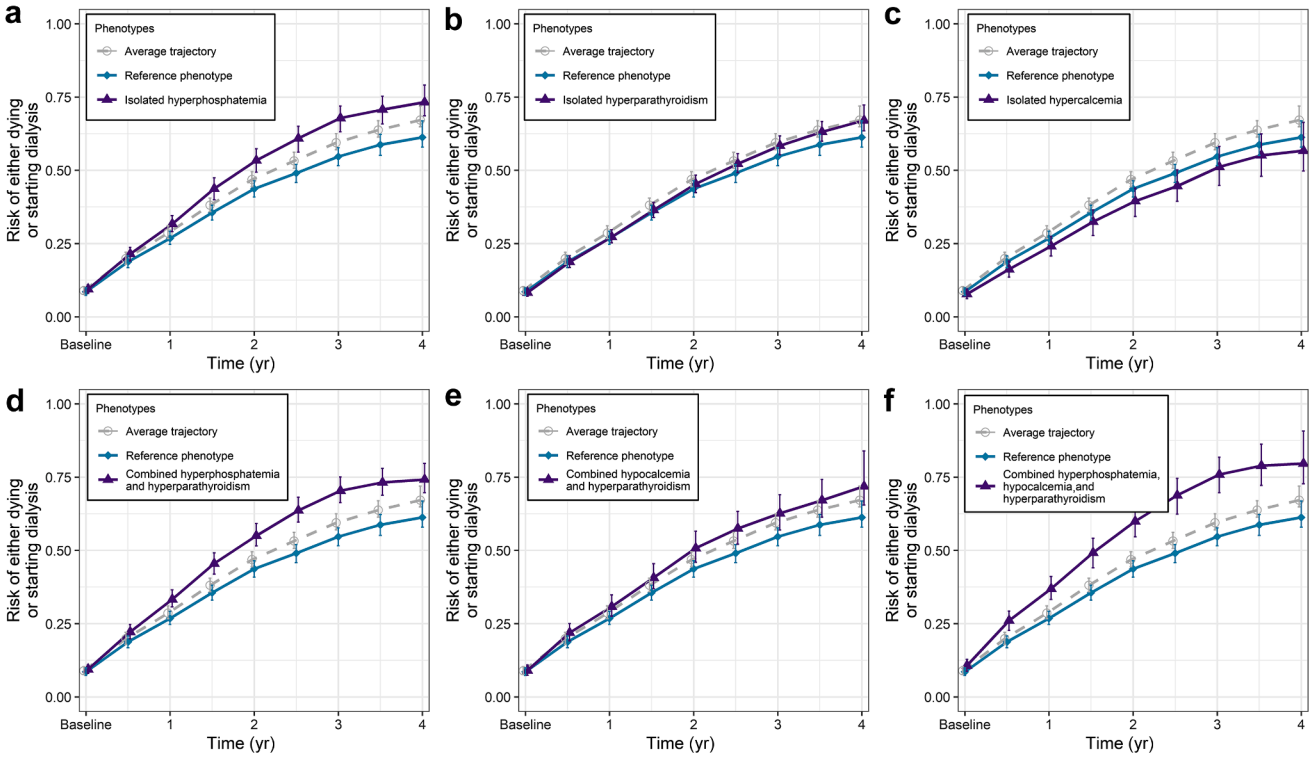

Figure 3 | Risk trajectories for the composite outcome of death or dialysis initiation under different simulated chronic kidney disease–mineral and bone disorder phenotypes. In each panel, the gray dashed line with open circles represents the average trajectory, that is, the risk trajectory observed in the entire cohort. The colored solid lines represent risk trajectories under specific exposures, with the light blue line indicating the reference phenotype (phosphate <1.45 mmol/l, parathyroid hormone <150 ng/l, and calcium 2.13–2.63 mmol/l), and the purple line indicating specific phenotypes for comparison: (**a**) isolated hyperphosphatemia, (**b**) isolated hyperparathyroidism, (**c**) isolated hypercalcemia, (**d**) combined hyperphosphatemia and hyperparathyroidism, (**e**) combined hypocalcemia and hyperparathyroidism, and (**f**) combined hyperphosphatemia, hypocalcemia, and hyperparathyroidism. Trajectories are drawn on the basis of the conditional probability, at each time point, of the outcome occurring in the following 6-month interval (represented by the dots along the line and corresponding confidence intervals). We included age, sex, country, primary kidney disease, baseline Charlson Comorbidity Index, and baseline medications (vitamin D analogues, calcium supplements, phosphate binders, and calcimimetics) as time-fixed confounders and estimated glomerular filtration rate and albumin levels as time-varying confounders.

progression. Finally, EQUAL participants had more advanced CKD than did the cohort studied by D'Arrigo *et al.*[14] This suggests that CKD-MBD may continue to influence the progression of CKD, even in its advanced stages.

Although animal studies have already established that a higher dietary phosphate load induces tubular damage and interstitial fibrosis, especially in rats with a reduced number of nephrons,[33] the underlying mechanisms of phosphate nephrotoxicity are still uncertain, and several hypotheses have been proposed. First, hyperphosphatemia has been found to be associated with higher levels of inflammatory markers[34] and the administration of phosphate binders in a CKD rat model reduced renal inflammatory cytokines and macrophage infiltration.[35] Second, sustained hyperphosphatemia promotes the formation of secondary calciprotein particles, whose levels have been linked to a higher risk of CKD progression, likely through cell toxicity, inflammasome activation, and endothelial dysfunction.[36,37] Third, hyperphosphatemia induces increases in PTH and fibroblast growth factor 23, which have also been associated with a higher risk of CKD progression.[10,14,38] These phosphaturic hormones promote the excretion of phosphate per nephron to help maintain its homeostasis. A higher phosphate concentration in the tubular fluid leads to the formation of calcium-phosphate microcrystals, which damage tubular cells and induce interstitial fibrosis.[39] In addition to mechanisms related to its phosphaturic actions, other experimental studies suggest that PTH may have an effect on podocytes,[40,41] which express PTH receptors.[42,43] Indeed, PTH suppression in rats with CKD prevents podocyte loss, endothelial-to-mesenchymal transition, and interstitial fibrosis.[44,45]

Intuitively, one would expect that hypercalcemia contributes to CKD progression because of the precipitation of calcium-phosphate microcrystals in the microvasculature[46] and renal tubules[39] and because of a higher risk of nephrolithiasis and nephrocalcinosis.[15] However, previous clinical studies suggest that hypocalcemia, rather than hypercalcemia, may be involved in CKD progression.[2,4,13,14,16,17] For instance, Janmaat *et al.*[17] found that a 1-mg/dl increase in baseline calcium levels was associated with a slower eGFR decline, particularly in patients with advanced CKD. This result was

confirmed in the longitudinal analysis by D'Arrigo *et al.*,[14] who found that a 1-mg/dl (equal to 0.25 mmol/l) increase in repeated measurements of calcium was associated with a 29% lower risk of CKD progression, albeit not accounting for the possible confounding effect of time-varying eGFR (i.e., the fact that worsening eGFR over time both reduces calcium levels and increases the risk of kidney failure). In our study, we could not confirm a detrimental role of isolated hypocalcemia (i.e., hypocalcemia with phosphate and PTH in their reference ranges), as this phenotype was not sufficiently represented in our cohort and therefore excluded from the present analysis. However, we did observe that hypocalcemia, when combined with other mineral abnormalities such as hyperparathyroidism, was associated with an increased risk of CKD progression. Moreover, the combination of hyperphosphatemia, hypocalcemia, and hyperparathyroidism constituted the phenotype associated with the highest risk of CKD progression, emphasizing the synergistic effect of these mineral disturbances. Conversely, isolated hypercalcemia was not associated with an increased risk of CKD progression, suggesting that mild elevations in calcium levels, when not accompanied by other mineral abnormalities, may not be detrimental to kidney function. However, this interpretation should be made with caution, given the relatively low prevalence of hypercalcemia in our cohort and the predominance of mild rather than severe cases. It is also possible that mild hypercalcemia in these patients reflects better nutritional status or more favorable levels of other relevant biomarkers, such as vitamin D or magnesium.

With regard to sex differences, our findings revealed that although a similar effect of mineral abnormalities on eGFR decline in both sexes, the associated risk of dialysis initiation was higher in males. This discrepancy might reflect a different association between CKD-MBD and specific symptoms, as previously described in our cohort,[47] and a greater tendency among elderly females to choose conservative care over dialysis.[22,48]

As deranged mineral biomarkers have been associated with higher risks of mortality and cardiovascular events in patients with advanced CKD, current international guidelines suggest lowering elevated phosphate levels toward the normal range, avoiding hypercalcemia, and evaluating modifiable risk factors for hyperparathyroidism.[1,29] However, these suggestions are based on a low grade of evidence (2C).[1,29] In addition, a recent European consensus on calcium management in CKD raised concerns about the skeletal risks associated with hypocalcemia, recommending sufficient dietary calcium intake and the treatment of acute iatrogenic hypocalcemia with calcium supplementation and/or active vitamin D derivatives.[49] Using robust methods for causal inference, our study strengthens the existing evidence that abnormal mineral biomarkers increase the risk of CKD progression and supports guideline recommendations for CKD-MBD management. In particular, our results support avoiding and treating hyperphosphatemia, and—in the presence of hyperphosphatemia—minimizing concomitant hypocalcemia and moderate-to-severe hyperparathyroidism, to slow disease progression and delay dialysis initiation, even in advanced CKD. This is especially relevant for older patients, in whom the decision to initiate maintenance dialysis must always be carefully weighed.[50] Furthermore, our phenotype-based analysis underscores the importance of assessing all 3 biomarkers collectively, which is significant for both clinical practice and future research on CKD-MBD.

The strengths of our study include a large sample size from 6 European countries, which improves the generalizability of our findings; the long follow-up time with repeated measurements of CKD-MBD biomarkers and kidney function; the implementation of G-methods to avoid bias due to informative censoring, competing events, and time-varying confounding; and the use of clinically relevant phenotypes to account for the complex interplay between mineral biomarkers. We also acknowledge some limitations. First, given the observational nature of the study, we cannot exclude the presence of unmeasured confounders, including other important mineral biomarkers such as vitamin D, fibroblast growth factor 23, and magnesium, which were not collected by the EQUAL study. In addition, although medication use was included as a confounder, we were only able to model it at baseline, limiting our ability to account for changes in treatment over time. Second, the use of different assays to measure CKD-MBD biomarkers, particularly PTH, may have reduced the accuracy of our findings. To mitigate this limitation, we adjusted for country of origin in our analysis, which indirectly accounts for some of the differences in assay practices across centers. However, residual variability likely remains. Importantly, such nondifferential misclassification bias generally biases effect estimates toward the null, resulting in more conservative findings.[51] As a result, the true causal impact of PTH on CKD may be underestimated in our analysis. Third, our cohort included patients 65 years or younger and our results may not be fully generalized to younger patients, who often present with more severe abnormalities of mineral biomarkers[52] and may have different etiologies of CKD, such as genetic disorders or glomerular diseases, which are associated with a more rapid decline in kidney function. Fourth, missing baseline values were imputed by averaging observed values, and missing longitudinal data were handled by carrying forward the last available observation. Although this simplified approach ensured feasibility, it may have introduced bias compared with more robust methods, such as multiple imputation.

In conclusion, we found that in older patients with advanced CKD not on dialysis, hyperphosphatemia, moderate-to-severe hyperparathyroidism—either alone or in combination—and their co-occurrence with hypocalcemia are associated with a higher risk of CKD progression. Thus, our findings support guideline recommendations for treating hyperphosphatemia and minimizing concomitant hypocalcemia and moderate-to-severe hyperparathyroidism to slow disease progression and delay dialysis initiation, even in patients with advanced stages of CKD.

APPENDIX

The EQUAL Study Investigators

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DISCLOSURE

Outside this work, MC declares advisory/lecture fees from Amgen, AbbVie, Shire, Vifor Pharma, and Baxter; FJC received honoraria from Baxter Healthcare; FWD reported research grants from Astellas Pharma and Vifor Pharma; ME reports payment for advisory boards and lectures by Astellas Pharma, Vifor Pharma, and AstraZeneca; ME reports institutional grants from AstraZeneca and Astellas Pharma; CW received honoraria for consultancy and lecturing were received from Amicus, AstraZeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Gilead, GSK, MSD, Sanofi-Genzyme, and Takeda; and PS received honoraria for consultancy and lecturing were received from AstraZeneca, Baxter, Novo Nordisk, Invizius, Pfizer, FMC, Vifor Pharma. The authors declare that the results presented in this paper have not been published previously. All the authors declared no competing interests with respect to the present research.

DATA STATEMENT

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

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AUTHOR CONTRIBUTIONS

LM, MC, NC, and KJ conceptualized the study. LM carried out formal analysis, investigated, and wrote the original draft. MC, NC, and KJ carried out the review. NC carried out project administration. NC and KJ supervised. KJ acquired funding. All authors contributed to data curation, reviewed the manuscript draft, and approved the final version of the article.

Supplementary material is available online at www.kidney-international.org.

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