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Clinical Research Article

Diuretic Use and Serum Phosphate: Rotterdam Study and UK Biobank

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Abstract

Purpose: Hypophosphatemia (serum phosphate < 0.80 mmol/L) leads to musculoskeletal complaints. The most common drugs linked to hypophosphatemia are thiazide and loop diuretics, but studies in the general population are lacking. Our aim was to study associations between diuretic use and serum phosphate in the Rotterdam Study (RS), a population-based cohort study, with replication in UK Biobank (UKBB).

Methods: Associations between thiazide and loop diuretic use and serum phosphate and odds of hypophosphatemia were analyzed with cross-sectional multivariate linear and logistic regression in participants without chronic kidney disease in the RS and UKBB. Analyses were adjusted for age, sex, and body mass index (BMI) and pooled in 3 RS cohorts with further adjustment for cohort and serum potassium, which was not available in UKBB.

Results: Thiazide diuretics were associated with lower serum phosphate in both sexes. This association lost significance in RS females after adjustment for BMI and in males after adjustment for serum potassium. Thiazide diuretics increased odds of hypophosphatemia in females in both cohorts and in males in UKBB only. Loop diuretics were associated with lower serum phosphate in females but not males. Adjustment for BMI attenuated these associations. Associations between loop diuretics and increased odds of hypophosphatemia in females lost significance after BMI adjustment.

Conclusion: Thiazides, but not loop diuretics, and increased BMI and decreased serum potassium should be considered as contributing factors in subjects with hypophosphatemia. Further studies are needed to replicate the findings and elucidate the potential role of hypokalemia as a mediator of this effect.

Key Words: phosphate, hypophosphatemia, thiazide diuretics, loop diuretics

Hypophosphatemia, defined as a serum phosphate concentration < 0.80 mmol/L (2.5 mg/dL), is associated with various musculoskeletal conditions such as myopathy, rickets in children, and osteomalacia in adults [1, 2] and increased mortality in hospitalized patients [3]. Phosphate homeostasis is maintained through the control of intestinal absorption of phosphate from the diet, phosphate release from bone, and renal excretion [4]. These processes are mediated by PTH, 1,25 dihydroxyvitamin D, and fibroblast growth factor 23 (FGF23). In the kidney, phosphate is reabsorbed by the sodium-phosphate transporters 2A (NPT2A) and 2C (NPT2C) primarily at the level of the proximal tubule. Both PTH and FGF23 downregulate the expression of NPT2A and NPT2C and thereby increase renal phosphate excretion [4]. A recent review stated that thiazide and loop diuretics are among the most common drugs that have been linked to hypophosphatemia, but a trial on the use of hydrochlorothiazide in hypertension did not show an effect on serum phosphate [5]. It has been hypothesized that thiazide diuretics cause renal phosphate wasting by blocking the action of carbonic anhydrase and diminishing renal tubular absorption of phosphate [6-8]. Moreover, thiazide diuretics can induce hypokalemia and hypomagnesemia, which have both been associated with renal phosphate wasting [6, 9]. It is known that magnesium is necessary for PTH secretion and that hypomagnesaemia can also induce PTH resistance [10]. Loop diuretics act on the loop of Henle, which is not involved in renal phosphate handling, but they also have a mild inhibiting effect on carbonic anhydrase and can also induce hypokalemia and hypomagnesemia [6]. The effects of thiazide or loop diuretics on phosphate handling and the prevalence of hypophosphatemia have been studied mainly in specific patient groups such as hospitalized patients, patients with congestive heart failure, or patients with other electrolyte disturbances [11-13]. Consequently, the reported association between thiazide or loop diuretic use and hypophosphatemia may actually reflect an association with diuretic use-related comorbidities and not a direct effect of diuretic use on serum phosphate concentration. For example, obesity is strongly associated with hypertension and cardiovascular disease, and a recent Mendelian

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randomization study indicated a causal association between higher body mass index (BMI) and lower serum phosphate [14, 15]. The effect of thiazide or loop diuretics on serum phosphate in the general population and the prevalence of hypophosphatemia in users of these diuretics is currently unknown. Therefore, our aim was to study whether use of thiazide or loop diuretics is associated with serum phosphate and odds of hypophosphatemia in the Rotterdam Study (RS), a population-based cohort study. UK Biobank (UKBB) was used as a replication cohort.

Materials and Methods

All analyses were performed within the RS, and findings were replicated in UKBB. All participants with serum phosphate measurements and data on loop and thiazide diuretics use and BMI were included in this study. Phosphate excretion takes place primarily in the kidney, which is why patients with advanced chronic kidney disease develop hyperphosphatemia. For this reason, we performed all analyses in participants without chronic kidney disease stage 3 or higher, defined as an estimated glomerular filtration rate >60 mL/min/1.73 m^2, calculated using the Chronic Kidney Disease Epidemiology Collaboration equations based on creatinine concentrations [16].

Study Population

The RS is a population-based study of elderly males and females aged 45 years or more and recruited from the district of Ommoord, Rotterdam, the Netherlands. The first cohort initiated in 1989, named RS-I, with 7983 participants. RS-II, RS-III, and RS-IV followed in 2000 (n = 3011), 2005 (n = 3932), and 2017 (n = 4000), respectively. Participants have been followed through several visits since recruitment. All visits are similar in design and data collection. The rationale and the design of the RS have been described in more detail elsewhere [17].

UKBB is a major biomedical database with over half a million participants who were recruited in 2006-2010 in 22 assessment centers throughout the UK. At inclusion, participants were between 40 and 69 years old. Participants consented to collection and storage of genetic, lifestyle, and health information [18]. This research has been conducted using the UK Biobank Resource under application number 48264.

Assessment of Serum Phosphate

In the RS, fasting serum phosphate concentrations have been measured during the second follow-up visit of RS-I and the baseline visits of RS-II and RS-III using a method based on the formation of ammonium phosphomolybdate, which is directly proportional to the inorganic phosphate concentration [19].

In UKBB, serum phosphate concentrations were measured during the initial assessment visit between 2006 and 2010 and during the first repeat assessment visit between 2012 and 2013. For the current study, we analyzed data from the initial assessment visit. Serum phosphate concentrations were also measured by phosphomolybdate complex analysis (Beckman Coulter AU5800, Beckman Coulter UK, Ltd.). Blood samples were drawn regardless of fasting status. There is no data on urinary phosphate excretion in RS or in UKBB.

Medication Use

In the RS, drug exposure has been monitored since January 1, 1991, through linkage with the pharmacies within the district. The following Anatomical Therapeutic Chemical codes were used: C03A, C07B, and C09BA for thiazide diuretics; C03CA for loop diuretics.

In UKBB, data on medication use was collected from self-reports and during interviews. For this study, we considered all drug treatments that included either a thiazide diuretic or a loop diuretic.

Covariates

BMI (kg/m^2) was calculated from weight and height. In the RS, weight and height are measured during all visits. In UKBB, weight and height were measured during the initial assessment center visit. In the RS, serum sodium and potassium concentrations were determined using ion-selective electrodes. Serum total calcium concentrations (mg/dL) were determined through a colorimetric o-cresolphthalein complexone method (Roche). Serum magnesium concentrations were determined based on the complex formation of magnesium with xylidyl blue. Serum 25-hydroxyvitamin D [25(OH)D] (nmol/L) concentrations were measured using an electrochemiluminescence immunoassay (Roche). Concentrations of serum creatinine were measured through an enzymatic colorimetric assay based on the formation of sarcosine. In UKBB, serum creatinine concentrations were measured by enzymatic analysis (Beckman Coulter AU5800, Beckman Coulter UK, Ltd.). Serum potassium and magnesium concentrations have not been measured in UKBB.

Statistical Analysis

We explored potential sex differences in the association between diuretics use and serum phosphate by building interaction terms with sex. There was evidence of an interaction between loop diuretics use and serum phosphate across sexes (P interaction <.001) but not between thiazide diuretics and serum phosphate (P interaction .277). A previous study from our group found that serum phosphate concentrations are higher in adult women compared to men [20]. Because of the interaction between loop diuretic use and serum phosphate across sexes and the differences in serum phosphate concentration between sexes across all cohorts, we performed all analyses in the total population and sex stratified. Distribution of continuous variables was determined by visual inspection of frequency distribution histograms and Q-Q plots. Differences in continuous variables between 2 groups were assessed using student T tests. Differences in categorical variables between groups were tested with Chi-square test or Fisher's exact test. Multivariable linear regression models were used to study the association between serum phosphate and current thiazide and loop diuretic use. Multivariable logistic regression models were used to study the association between use of each diuretic drug with the odds of hypophosphatemia. Analyses were adjusted for age, sex, and BMI. Analyses in the RS were further adjusted for cohort. Outliers in serum phosphate of >6 SD were removed from analysis. No adjustments were made for multiple testing

because only 2 diuretics were analyzed and 2 large independent cohorts were used to minimize risk of chance findings.

Sensitivity Analysis

To study the role of serum potassium, magnesium, and 25(OH)D concentrations on the association between diuretics use and serum phosphate, we further adjusted our analyses for serum potassium and magnesium and 25(OH)D in the RS. All analyses were performed with IBM SPSS software, version 28.0.0.0 and R version 3.6.1 (Vienna, Austria).

Ethics

The RS has been approved by the Medical Ethics Committee of the Erasmus MC (registration number MEC 02.1015) and by the Dutch Ministry of Health, Welfare and Sport (Population Screening Act WBO, license number 1071272-159521-PG). The Rotterdam Study Personal Registration Data collection is filed with the Erasmus MC Data Protection Officer under registration number EMC1712001. The RS has been entered into the Dutch Trial Register (NTR; https://onderzoekmetmensen.nl) and into the World Health Organization International Clinical Trials Registry Platform (https://apps.who.int/trialsearch/) under shared catalog number NL6645/NTR6831. All participants provided written informed consent to participate in the study and to have their information obtained from treating physicians. UK Biobank has been approved by the North West Multi-centre Research Ethics Committee.

Results

A total of 8744 participants from 3 cohorts within the RS had an estimated glomerular filtration rate >60 mL/min/1.73 m^2, serum phosphate measurements and data on loop and thiazide diuretics use, and BMI (Fig. 1). The general characteristics are depicted in Table 1. The mean age was 63.9 years, and 56.3% were female. Phosphate was higher in females than in males ($P < .001$), and hypophosphatemia was more prevalent in males than in females (5.7% vs 0.7%, $P < .001$). Thiazide and loop diuretic use was more prevalent in females with hypophosphatemia compared to females without hypophosphatemia but not in males. BMI was higher in females with hypophosphatemia compared to females without hypophosphatemia.

In UKBB, a total of 420 768 participants had serum phosphate measurements and data on thiazide and loop diuretic use and BMI (Fig. 1). The general characteristics of UKBB are also depicted in Table 1. Mean age was 56.5 years, and 53.7% were female. Similar to the RS, serum phosphate was higher in females than males ($P < .001$) and hypophosphatemia was more prevalent in males ($P < .001$). BMI was higher in both males and females with hypophosphatemia compared to participants without hypophosphatemia of the same sex. Thiazide diuretic but not loop diuretic use was more prevalent in males with hypophosphatemia compared to males without hypophosphatemia (Table 2). In females, thiazide diuretic use was also more prevalent in participants with hypophosphatemia compared to participants without hypophosphatemia. Loop diuretic use tended to be more prevalent in females with hypophosphatemia compared to females without hypophosphatemia, but this difference was borderline significant.

Next, we compared thiazide diuretic users with nonusers for males and females separately (Table 3). In the RS, serum phosphate concentrations were lower in thiazide diuretic users compared to nonusers in both sexes. Hypophosphatemia was more prevalent in female thiazide diuretic users compared to nonusers but not in males. Moreover, in both sexes potassium and magnesium concentrations were lower in thiazide diuretic users compared to nonusers, while BMI was higher. In UKBB, serum phosphate was lower and BMI higher in thiazide diuretics users compared to nonusers in both sexes, and prevalence of hypophosphatemia was higher in thiazide diuretic users.

Likewise, we compared loop diuretic users with nonusers in males and females separately in the RS (Table 4). Male loop diuretic users were older than male nonusers, but phosphate concentrations and prevalence of hypophosphatemia were not significantly different. Female loop diuretic users were older, with higher BMI than female nonusers. Female loop diuretic users had lower phosphate levels than female nonusers, and

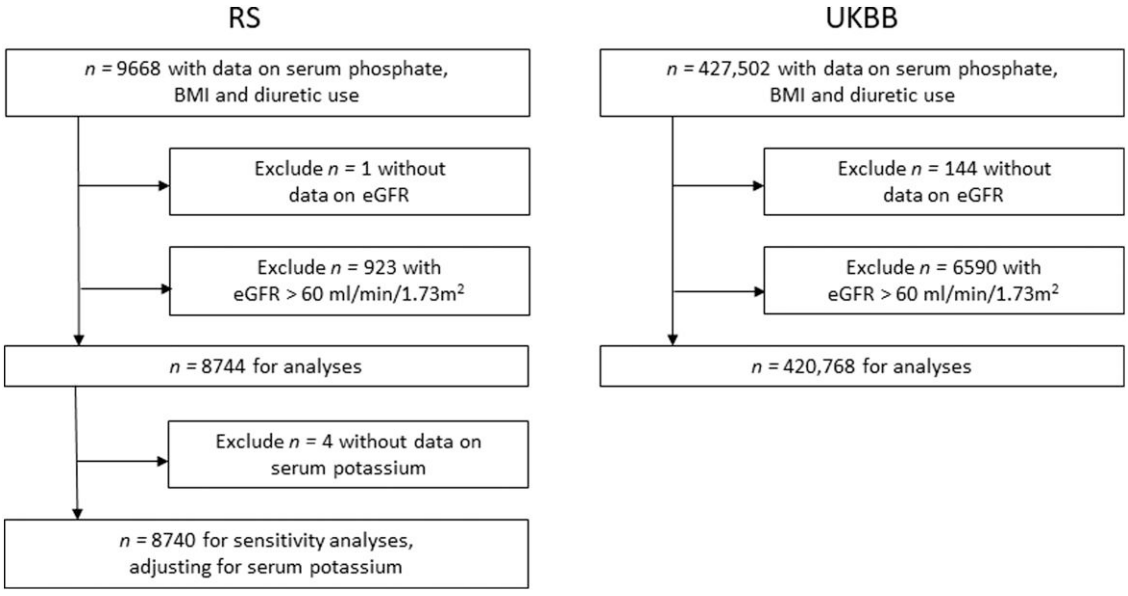

Figure 1. Participant flowchart summarizing sample sizes for the different analyses.

Abbreviations: eGFR, estimated glomerular filtration rate.

Table 1. General characteristics of the study population in RS and UKBB

	Total population	Male	Female	*P*-value	Normal values
RS					
n	8744	3825	4919		
Age, years	63.9 (9.1)	63.6 (8.8)	64.1 (9.4)	.008	
Female (%)	4919 (56.3)				
Phosphate, mmol/L	1.11 (0.16)	1.02 (0.15)	1.17 (0.15)	<.001	0.80-1.40
Hypophosphatemia (%)	255 (2.9)	219 (5.7)	36 (0.7)	<.001	
Sodium, mmol/L	142.1 (3.1)	142.0 (3.1)	142.2 (3.1)	<.001	136-145
Potassium, mmol/L	4.34 (0.33)	4.35 (0.34)	4.35 (0.33)	.352	3.5-5.1
Magnesium, mmol/L	0.84 (0.06)	0.84 (0.06)	0.84 (0.06)	.036	0.70-1.05
eGFR, mL/min/1.73 m^2	82.5 (13.0)	83.3 (11.5)	82.5 (11.7)	<.001	
BMI, kg/m2	27.2 (4.2)	27.09 (3.6)	27.4 (4.6)	.002	
Loop diuretics (%)	156 (1.8)	70 (1.8)	86 (1.7)	.775	
Thiazide diuretics (%)	198 (2.3)	78 (2.0)	120 (2.4)	.212	
UKBB					
n	420 768	194 103	226 665		
Age, years	56.5 (8.1)	56.6 (8.2)	56.3 (8.0)	<.001	
Female (%)	226 665 (53.7)				
Phosphate, mmol/L	1.16 (0.16)	1.12 (0.16)	1.19 (0.15)	<.001	
Hypophosphatemia (%)	6412 (1.5)	5049 (2.6)	1363 (0.6)	<.001	
eGFR, mL/min/1.73 m^2	97.4 (14.3)	99.7 (16.3)	95.4 (12.0)	<.001	
BMI, kg/m2	27.4 (4.8)	27.8 (4.2)	27.0 (5.2)	<.001	
Loop diuretic use (%)	3900 (0.9)	1799 (0.9)	2101 (0.9)	.998	
Thiazide diuretic use (%)	27 219 (6.5)	11 560 (6.0)	15 659 (6.9)	<.001	

Continuous values are displayed as mean (SD); categorical variables are displayed in absolute counts (%). Differences between males and females were analyzed using an independent *t*-test for continuous variables and χ^2 test for categorical variables.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; RS, Rotterdam Study; UKBB, UK Biobank.

hypophosphatemia was more prevalent in the loop diuretic users. In both sexes, BMI was significantly higher in loop diuretic users compared to nonusers. Serum potassium was lower in loop diuretic users in females only. Male and female loop diuretic users in UKBB were older and had higher BMI than nonusers of the same sex. Serum phosphate concentrations were slightly lower in loop diuretic users compared to nonusers in both sexes, but prevalence of hypophosphatemia was not significantly different.

Association Between Diuretic Use and Serum Phosphate Concentrations

The use of thiazide diuretics was associated with lower serum phosphate levels in the total population in both the RS and UKBB. Adjustment for BMI attenuated the association in both studies, but it remained significant. The inverse association between thiazide diuretic use and serum phosphate was significant in both sexes. Adjustment for BMI attenuated the association in males, but it remained significant. In females, the association between thiazide diuretic use and serum phosphate lost significance in RS but not in UKBB after adjustment for BMI [RS: β: −0.019, 95% confidence interval (CI): −.045 to .007; $P = .144$; UKBB: β: −0.027, 95% CI: −.029 to −.024; $P < .001$] (Table 5).

The use of thiazide diuretics was associated with an increased odds of hypophosphatemia in the total population in both the RS and UKBB (Table 6). Adjustment for BMI attenuated this association in both studies, but it remained significant in UKBB. Sex-stratified analyses showed that the use of thiazide diuretics was associated with an increased odds of hypophosphatemia in females in both the RS and UKBB [RS: odds ratio (OR): 6.17, 95% CI: 2.27 to 16.77; $P < .001$; UKBB: OR: 2.47, 95% CI: 2.06 to 2.94; $P < .001$]. This association was attenuated but remained significant after adjustment for BMI. In males, this association was significant only in UKBB, and it remained significant after adjustment for BMI (RS: OR: 1.15, 95% CI: .46 to 2.90; $P = .769$; UKBB: OR, 1.26; 95% CI: 1.13 to 1.40; $P < .001$).

Sex-stratified analyses showed a significant inverse association between loop diuretic use and serum phosphate in females only (RS: β: −0.064, 95% CI: −.095 to −.033; $P < .001$; UKBB: β: −0.025, 95% CI: −.031 to −.018; $P < .001$). Adjustment for BMI attenuated but did not abolish this association (RS: β: −0.049, 95% CI: −.080 to −.019; $P = .002$; UKBB: β: −0.007, 95% CI: −.014 to −.001; $P = .031$). The association between loop diuretic use and serum phosphate was not significant in males (Table 7).

In females, the use of loop diuretics was associated with an increased odds of hypophosphatemia in both the RS and UKBB. This association lost significance after adjustment for BMI in both studies. In males, the association between loop diuretic use and hypophosphatemia was significant in UKBB only, and it lost significance after adjustment for BMI (Table 8).

Sensitivity Analyses

As previously mentioned, serum potassium and magnesium levels were available in the RS cohort but not in UKBB.

Table 2. General characteristics of males and females with and without hypophosphatemia in RS and UKBB

	Males without hypophosphatemia	Males with hypophosphatemia	*P*-value	Females without hypophosphatemia	Females with hypophosphatemia	*P*-value
RS						
n	3606	219		4883	36	
Age, years	63.6 (8.9)	63.4 (8.0)	.739	64.1 (9.4)	64.6 (11.5)	.778
Phosphate, mmol/L	1.04 (0.13)	0.74 (0.05)	<.001	1.18 (0.14)	0.76 (0.03)	<.001
Sodium, mmol/L	142.0 (3.1)	141.6 (2.4)	.048	142.2 (3.1)	141.4 (2.4)	.110
Potassium, mmol/L	4.36 (0.33)	4.21 (0.39)	<.001	4.35 (0.33)	4.19 (0.39)	.006
Calcium, mmol/L	2.42 (0.10)	2.39 (0.11)	<.001	2.44 (0.10)	2.45 (0.20)	.773
Magnesium, mmol/L	0.84 (0.06)	0.84 (0.06)	.317	0.84 (0.06)	0.93 (0.06)	.180
Vitamin D, nmol/L	60.1 (27.8)	60.4 (28.5)	.911	54.5 (27.2)	46.8 (27.1)	.090
eGFR, mL/min/1.73 m^2	83.3 (11.5)	84.0 (11.5)	.330	82.5 (11.7)	80.7 (12.0)	.360
BMI, kg/m2	27.1 (3.6)	27.4 (3.2)	.197	27.3 (4.6)	32.9 (6.8)	<.001
Loop diuretics (%)	68 (1.9)	2 (0.9)	.436	83 (1.7)	3 (8.3)	.024
Thiazide diuretics (%)	73 (2.0)	5 (2.3)	.793	115 (2.4)	5 (13.9)	.002
UKBB						
n	189 504	5049		225 302	1363	
Age, years	56.7 (1.1)	55.9 (0.7)	<.001	56.3 (8.0)	52.4 (8.2)	<.001
Phosphate, mmol/L	1.13 (0.15)	0.73 (0.06)	<.001	1.20 (0.15)	0.74 (0.05)	<.001
eGFR, mL/min/1.73 m^2	99.7 (16.3)	101.1 (16.2)	<.001	95.3 (12.0)	98.3 (12.3)	<.001
BMI, kg/m2	27.8 (4.2)	28.6 (4.4)	<.001	27.0 (5.2)	29.3 (6.2)	<.001
Loop diuretic use (%)	1741 (0.9)	58 (1.1)	.10	2082 (0.9)	19 (1.4)	.07
Thiazide diuretic use (%)	11 182 (5.9)	378 (7.5)	<.001	15 511 (6.9)	148 (10.9)	<.001

Continuous values are displayed as mean (SD); categorical variables are displayed in absolute counts (%). Differences between participants with and without hypophosphatemia were analyzed using an independent *t*-test for continuous variables and χ^2 test for categorical variables.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; RS, Rotterdam Study; UKBB, UK Biobank.

The association between thiazide diuretic use and serum phosphate lost significance after adjustment for serum potassium in the total RS population and in males. In RS females, the association between thiazide diuretic use and serum phosphate had already lost significance after adjustment for BMI, but the direction of the association completely reversed after further adjustment for serum potassium (Supplementary Table S1 [21]). The association between thiazide diuretic use and odds of hypophosphatemia in the total population lost significance after adjustment for serum potassium. The association in females attenuated but remained significant after adjustment for serum potassium (OR: 3.21, 95%CI: 1.13 to 9.11; $P = .029$) (Supplementary Table S2 [21]). Adjustment for serum magnesium or 25(OHD) did not change results (data not shown). Adjustment for serum potassium in the RS did not change the association between loop diuretic use and serum phosphate in females. (Supplementary Tables S3 and S4 [21]).

Discussion

This study in 2 large population-based cohorts showed that thiazide diuretic use was associated with lower serum phosphate concentrations in both sexes and with increased odds of hypophosphatemia in females. This association may be partly explained by a difference in BMI. For loop diuretic use the results were less consistent, but there was an inverse association between loop diuretic use and serum phosphate concentrations in females. These results are in line with a randomized cross-over study in postmenopausal osteopenic women, which showed that thiazide diuretics caused a dose-dependent decrease in serum phosphate concentrations [22]. In contrast, a randomized controlled trial in healthy elderly persons did not find a significant difference in serum phosphate in thiazide diuretic users compared to placebo [23]. In linear regression analyses we show that BMI is an important confounder in the association between thiazide diuretic use and serum phosphate. In addition, serum potassium concentrations may also play a role in the observed differences in serum phosphate concentration between thiazide diuretic users and nonusers. Hypophosphatemia in general can be caused by either an intracellular shift, impaired intestinal absorption of phosphate or intake, or renal phosphate wasting [22]. However, the cause of the hypophosphatemia cannot always be identified [24]. Our findings may be relevant for health care professionals who analyze and treat patients with hypophosphatemia. Thiazide diuretics have been prescribed to patients with X-linked hypophosphatemia (XLH), the most common monogenetic cause of chronic hypophosphatemia, to decrease drug-induced urinary calcium excretion and to prevent nephrocalcinosis [25]. In a small cohort study in pediatric XLH patients, thiazide diuretic use decreased urinary calcium excretion, but it also decreased serum phosphate, which would suggest a causal relationship. Therefore, caution is warranted when prescribing thiazide diuretics to XLH patients [26].

There are several mechanisms that may explain a difference in serum phosphate between thiazide diuretic users and nonusers. One pathophysiological mechanism relates to PTH. PTH regulates serum phosphate concentration by induction

Table 3. Characteristics of thiazide diuretic users and nonusers in RS and UKBB stratified by sex

	Male thiazide nonuser	Male thiazide user	*P*-value	Female thiazide nonuser	Female thiazide user	*P*-value
RS						
n	3747	78		4799	120	
Age, years	63.6 (8.9)	60.3 (6.7)	<.001	64.1 (9.4)	62.0 (9.2)	.014
Phosphate, mmol/L	1.02 (0.15)	0.99 (0.15)	.034	1.17 (0.14)	1.14 (0.16)	.010
Hypophosphatemia, n (%)	214 (5.7)	5 (6.4)	.803	31 (0.6)	5 (4.2)	.002
Sodium, mmol/L	142.0 (3.1)	142.1 (3.9)	.794	142.2 (3.1)	141.7 (2.8)	.057
Potassium, mmol/L	4.36 (0.33)	4.17 (0.34)	<.001	4.35 (0.33)	4.14 (0.36)	<.001
Calcium, mmol/L	2.42 (0.10)	2.43 (0.09)	.105	2.44 (0.10)	2.47 (0.10)	.005
Magnesium, mmol/L	0.85 (0.06)	0.82 (0.07)	.006	0.84 (0.06)	0.82 (0.07)	.002
Vitamin D, nmol/L	60.2 (27.8)	57.3 (27.3)	.364	54.5 (27.2)	53.1 (26.3)	.584
eGFR, mL/min/1.73 m^2	83.2 (11.5)	86.1 (10.8)	.028	82.5 (11.7)	82.5 (11.1)	.995
BMI, kg/m^2	27.0 (3.6)	29.4 (4.4)	<.001	27.3 (4.6)	30.3 (5.4)	<.001
UKBB						
n	182 543	11 560		211 006	15 659	
Age, years	56.3 (8.2)	61.4 (6.0)	<0.001	55.9 (8.0)	61.2 (6.0)	<0.001
Phosphate, mmol/L	1.12 (0.16)	1.11 (0.17)	<0.001	1.20 (0.15)	1.17 (0.15)	<0.001
Hypophosphatemia (%)	4671 (2.6)	378 (3.3)	<0.001	1215 (0.6)	148 (0.9)	<0.001
eGFR, mL/min/1.73 m^2	100.1 (16.3)	94.7 (16.3)	<0.001	95.6 (12.0)	91.6 (12.0)	<0.001
BMI, kg/m2	27.7 (4.2)	29.8 (4.8)	<0.001	26.8 (5.0)	30.0 (5.7)	<0.001

Continuous values are displayed as mean (SD); categorical variables are displayed in absolute counts (%). Differences between diuretic users and nonusers were analyzed using an independent *t*-test for continuous variables and χ^2 test for categorical variables.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; RS, Rotterdam Study; UKBB, UK Biobank.

Table 4. Characteristics of loop diuretic users and nonusers in RS and UKBB stratified by sex

	Male loop nonuser	Male loop user	*P*-value	Female loop nonuser	Female loop user	*P*-value
RS						
n	3755	70		4833	86	
Age, years	63.4 (8.8)	71.5 (9.2)	<.001	63.9 (9.3)	73.7 (11.2)	<.001
Phosphate, mmol/L	1.02 (0.15)	1.04 (0.13)	.272	1.17 (0.14)	1.10 (0.15)	<.001
Hypophosphatemia, n (%)	217 (5.8)	2 (2.9)	.436	33 (0.7)	3 (3.5)	.024
Sodium, mmol/L	142.0 (3.1)	141.1 (3.2)	.024	142.2 (3.1)	142.0 (3.1)	.412
Potassium, mmol/L	4.35 (0.33)	4.31 (0.36)	.326	4.35 (0.33)	4.23 (0.43)	.014
Calcium, mmol/L	2.41 (0.10)	2.39 (0.09)	.025	2.44 (0.10)	2.43 (0.10)	.147
Magnesium, mmol/L	0.84 (0.06)	0.85 (0.09)	.841	0.84 (0.06)	0.85 (0.06)	.067
Vitamin D, nmol/L	60.3 (27.8)	54.6 (28.1)	.095	54.7 (27.2)	38.7 (22.7)	<.001
eGFR, mL/min/1.73 m^2	83.4 (11.5)	76.6 (10.9)	<.001	82.6 (11.5)	77.9 (17.6)	<.001
BMI, kg/m^2	27.1 (3.6)	28.4 (3.8)	.003	27.3 (4.6)	29.5 (5.4)	<.001
UKBB						
n	192 304	1799		224 564	2101	
Age, years	56.6 (8.2)	62.1 (5.8)	<0.001	56.2 (8.0)	61.4 (6.1)	<.001
Phosphate, mmol/L	1.12 (0.16)	1.11 (0.17)	0.004	1.19 (0.15)	1.18 (0.16)	<.001
Hypophosphatemia (%)	4991 (2.6)	58 (3.2)	0.10	1344 (0.6)	19 (0.9)	.07
eGFR, mL/min/1.73 m^2	99.8 (16.3)	90.3 (17.3)	<0.001	95.4 (12.0)	87.7 (13.5)	<.001
BMI, kg/m2	27.8 (4.2)	32.5 (6.3)	<0.001	27.0 (5.1)	33.0 (7.0)	<.001

Continuous values are displayed as mean (SD); categorical variables are displayed in absolute counts (%). Differences between diuretic users and nonusers were analyzed using an independent *t*-test for continuous variables and χ^2 test for categorical variables.
Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate; RS, Rotterdam Study; UKBB, UK Biobank.

of bone resorption, stimulation of 1α-hydroxylase resulting in increased synthesis of calcitriol, and increasing renal phosphate excretion. The net effect is that serum phosphate levels go down [4, 27]. However, in a study of postmenopausal osteopenic women thiazide diuretics decreased urinary calcium excretion without a change in PTH [22]. Unfortunately, this

Table 5. Association between thiazide diuretic use and serum phosphate concentration in RS and UKBB in the total population and stratified by sex

	Total population			Men			Women		
	n	β (95% CI)	*P*-value	n	β (95% CI)	*P*-value	n	β (95% CI)	*P*-value
RS[a]									
Model 1	8744	−0.033 (−0.056 to −0.010)	**.005**	3825	−0.042 (−0.075 to −0.009)	**.012**	4919	−0.038 (−0.065 to −0.012)	**.005**
Model 2	8744	−0.027 (−0.048 to −0.007)	**.009**	3825	−0.038 (−0.071 to −0.005)	**.023**	4919	−0.019 (−0.045 to 0.007)	.144
UKBB									
Model 1	420 768	−0.023 (−0.025 to −0.021)	**<.001**	194 103	−0.008 (−0.011 to −0.005)	**<.001**	226 665	−0.035 (−0.038 to −0.033)	**<.001**
Model 2	420 768	−0.016 (−0.018 to −0.014)	**<.001**	194 103	−0.004 (−0.008 to −0.001)	**.005**	226 665	−0.027 (−0.029 to −0.024)	**<.001**

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and BMI. Bold values significant at $P < .05$.
Abbreviations: BMI, body mass index; CI, confidence interval; RS, Rotterdam Study; UKBB, UK Biobank.
[a]Models in RS were additionally adjusted for cohort.

Table 6. Association between thiazide diuretic use and hypophosphatemia in RS and UKBB in the total population and stratified by sex

	Total population			Men			Women		
	n	OR (95% CI)	*P*-value	n	OR (95% CI)	*P*-value	n	OR (95% CI)	*P*-value
RS[a]									
Model 1	8744	2.10 (1.08 to 4.12)	**.030**	3825	1.21 (.48 to 3.05)	.353	4919	6.17 (2.27 to 16.77)	**<.001**
Model 2	8744	1.81 (.92 to 3.56)	.087	3825	1.15 (.46 to 2.90)	.769	4919	4.00 (1.43 to 11.14)	**.008**
UKBB									
Model 1	420 768	1.56 (1.42 to 1.71)	**<.001**	194 103	1.38 (1.24 to 1.53)	**<.001**	226 665	2.47 (2.06 to 2.94)	**<.001**
Model 2	420 768	1.38 (1.25 to 1.51)	**<.001**	194 103	1.26 (1.13 to 1.40)	**<.001**	226 665	1.92 (1.59 to 2.29)	**<.001**

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and BMI. Bold values significant at $P < .05$.
Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; RS, Rotterdam Study; UKBB, UK Biobank.
[a]Models in RS were additionally adjusted for cohort.

Table 7. Association between loop diuretic use and serum phosphate concentration in RS and UKBB in the total population and stratified by sex

	Total population			Men			Women		
	n	β (95% CI)	*P*-value	n	β (95% CI)	*P*-value	n	β (95% CI)	*P*-value
RS[a]									
Model 1	8744	−.023 (−.046 to .000)	.055	3825	.028 (−.007 to .063)	.118	4919	−.064 (−.095 to −.033)	**<.001**
Model 2	8744	−.012 (−.035 to .011)	.301	3825	.032 (−.003 to .067)	.073	4919	−.049 (−.080 to −.019)	**.002**
UKBB									
Model 1	420 768	−.016 (−.021 to −.011)	**<.001**	194 103	−.006 (−.014 to .001)	.096	226 665	−.025 (−.031 to −.018)	**<.001**
Model 2	420 768	−.003 (−.008 to .002)	.192	194 103	.001 (−.006 to .009)	.734	226 665	−.007 (−.014 to −.001)	**.031**

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and BMI. Bold values significant at $P < .05$.
Abbreviations: BMI, body mass index; CI, confidence interval; RS, Rotterdam Study; UKBB, UK Biobank.
[a]Models in RS were additionally adjusted for cohort.

study did not report on the effects of diuretic use on serum phosphate concentrations. Thiazide diuretics act on the sodium chloride cotransporter NCCT in the distal convoluted tubule. Mutations in the *SLC12A3* gene encoding NCCT cause Gitelman syndrome [28]. Interestingly, in a recently published cohort study, hypophosphatemia was observed in 16% of patients with Gitelman syndrome. The authors also found an association between serum phosphate levels and TmP/GFR, indicating that the hypophosphatemia was most likely related to renal phosphate wasting. In patients with Gitelman syndrome, only 6.9% had hyperparathyroidism and PTH was also not correlated with serum phosphate or with TmP/GFR. We were not able to adjust for PTH in our analyses, but these results suggest that the inverse association between thiazide diuretic use and serum phosphate concentrations is not related to increased PTH concentrations.

A second important regulator of phosphate homeostasis besides PTH is FGF23. This hormone lowers serum phosphate by increasing renal phosphate excretion and inhibiting 1α-hydroxylase [29]. Mouse studies have shown that NCCT

Table 8. Association between loop diuretic use and hypophosphatemia in RS and UKBB in the total population and stratified by sex

	Total population			Men			Women		
	n	OR (95% CI)	*P*-value	n	OR (95% CI)	*P*-value	n	OR (95% CI)	*P*-value
RS[a]									
Model 1	8744	1.12 (.45 to 2.80)	.816	3825	.50 (.12 to 2.07)	.340	4919	5.09 (1.45 to 17.92)	**.011**
Model 2	8744	.97 (.39 to 2.44)	.950	3825	.48 (.12 to 1.97)	.306	4919	3.24 (.90 to 11.69)	.072
UKBB									
Model 1	420 768	1.48 (1.17 to 1.85)	**.001**	194 103	1.34 (1.01 to 1.72)	**.032**	226 665	2.16 (1.32 to 3.31)	**.001**
Model 2	420 768	1.12 (.88 to 1.40)	.328	194 103	1.08 (.82 to 1.40)	.554	226 665	1.33 (.81 to 2.04)	.233

Model 1: adjusted for age and sex; model 2: adjusted for age, sex, and BMI. Bold values significant at $P < .05$.
Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio; RS, Rotterdam Study; UKBB, UK Biobank.
[a]Models in RS were additionally adjusted for cohort.

knockout mice have higher FGF23 concentrations than wild-type mice. However, fractional phosphate excretion was not different between knockout mice and wild-type mice. Moreover, although the FGF23 transcript was increased in the bone of the NCCT knockout mice, thiazide diuretic treatment of osteoblasts did not result in an increase in FGF23 transcription [30]. It remains to be elucidated whether thiazide diuretic use causes an increase in FGF23 resulting in lower serum phosphate concentrations.

It has also been hypothesized that thiazide and loop diuretics affect serum phosphate concentration due to inhibition of carbonic anhydrase (CA) [7, 8]. Inhibition of CA causes a decrease in secretion of H+, leading to natriuresis and diuresis [31]. CA inhibition can also cause metabolic acidosis, during which urinary phosphate excretion increases [32, 33, 34]. The increase in sodium delivery to the distal tubule together with a diuretic induced stimulation of the renin-angiotensin-aldosterone cascade causes an increase in distal potassium secretion, leading to hypokalemia [33]. Rat studies have shown that potassium deficiency is associated with a decrease in sodium phosphate transporters type IIc in the proximal tubular brush border membrane [35]. In addition, a recent dietary-controlled randomized trial showed that potassium supplementation leads to a decrease in FGF23 and an increase in plasma phosphate and TmP/GFR [36]. These results suggest that there may be a relation between potassium and phosphate, potentially mediated by FGF23. It has been shown that thiazide diuretics induce more hypokalemia than loop diuretics, despite the direct action of loop diuretics in Henle's loop [37]. In the RS, thiazide diuretic users had lower serum potassium than nonusers. The inverse association between thiazide diuretic use and serum phosphate in the total population and in males lost significance after adjustment for serum potassium. This association in females had already lost significance after adjustment for BMI, but further adjustment for serum potassium completely reversed the direction of the association. By contrast, serum potassium was not significantly different in male loop diuretic users, and in female users it was decreased but to a lesser extent. Unfortunately these findings could not be replicated in UKBB because of lack of data on serum potassium, but our results suggest that serum potassium may be a mediator in the association between thiazide diuretic use and serum phosphate.

The association between thiazide diuretic use and serum phosphate may also reflect an association between diuretic use-related comorbidities and serum phosphate. In this study we found that thiazide diuretic users from both sexes and female loop diuretic users had higher BMI than nonusers of the same sex. Obesity is strongly associated with hypertension and cardiovascular disease [15]. Previous studies have reported an inverse association between BMI and serum phosphate concentrations [14, 38, 39]. Furthermore, a Mendelian randomization study from our group reported a suggested causal effect of BMI on serum phosphate [14]. A higher BMI may lead to higher FGF23 concentrations, possibly through leptin, resulting in increased renal phosphate excretion [14, 40-43]. Also, it has been shown that BMI is associated with PTH [44, 45]. Therefore, PTH may play a role in the association between BMI and phosphate. Indeed, adjustment for BMI attenuated the association between thiazide diuretic use and serum phosphate concentrations in males in the RS and UKBB and in females in UKBB. In the RS, the association between thiazide diuretic use and serum phosphate lost significance in females after adjustment for BMI. The association between serum phosphate and odds of hypophosphatemia attenuated but remained significant in both sexes in UKBB and in females in RS after adjustment for BMI. These results suggest that BMI is an important confounder in these associations. Lastly, the association between loop diuretic use and serum phosphate was only significant in females. A possible explanation for this sex difference is that female loop diuretic users had lower serum 25(OH)D concentrations than female nonusers, although results did not change after adjustment for 25(OH)D. It is likely that 25(OH)D only influences phosphate homeostasis at the extremes of its concentrations [46].

This study has several limitations. We performed cross-sectional analyses, which refrains us from drawing conclusions on the effect of initiation, duration, and dose of diuretics use on serum phosphate concentrations. Due to the design of the study, no adjustments were made for multiple testing; however, a Bonferroni correction would not have changed the significance for thiazide diuretics but it would for loop diuretics, supporting our conclusion that thiazide diuretics and not loop diuretics are associated with serum phosphate in men. As mentioned previously, blood samples were drawn nonfasting in UKBB. Moreover, medication use in UKBB is self-reported, which is susceptible to errors. Interestingly, despite lower age in UKBB, loop diuretic use was lower and thiazide diuretic use was higher in UKBB compared to the RS, suggesting national differences in prescription. Still, results from association analyses were similar. We had no availability

of PTH or FGF23 concentrations and also no data on comorbidities or use of other drugs. Also, serum potassium has not been measured in UKBB. However, drugs that are known to affect serum phosphate (eg, antriretrovirals, anticancer drugs, and calcineurin inhibitors) are not often used in the general population, and we are not aware of any disorders that are associated with both diuretic use and serum phosphate. Malnutrition or alcohol abuse as the cause of lower phosphate concentrations in diuretic users seems unlikely because in our study BMI was higher and there is no literature data showing that use of diuretics is associated with alcohol abuse. There are several strengths, such as the availability of 2 large well-characterized population-based cohorts and the ability to replicate the findings.

In conclusion, this study in 2 population-based cohorts showed that thiazide diuretic users have lower serum phosphate concentrations than nonusers in both sexes. Hypophosphatemia was more prevalent in female thiazide diuretics users than in female nonusers. Loop diuretic use was not associated with serum phosphate or with hypophosphatemia in males, while in females there was an inverse association between loop diuretic use and serum phosphate. BMI appears to be an important confounder of these associations, while serum potassium may be a mediator. Thiazide diuretic use, but not loop diuretics, and increased BMI and decreased serum potassium should be considered as contributing factors in patients with hypophosphatemia. Further studies are needed to replicate the findings and elucidate the potential role of hypokalemia as a mediator of this effect.

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N.C., C.K., and B.S. have nothing to declare. The institution of M.C.Z. has received a research grant from Kyowa Kirin and M.C.Z. is an unpaid board member of the steering committee of the Kyowa Kirin International XLH registry.

Data Availability

RS data can be obtained upon request. Requests should be directed towards the management team of the Rotterdam Study (datamanagement.ergo@erasmusmc.nl), which has a protocol for approving data requests. Because of restrictions based on privacy regulations and informed consent of the participants, data cannot be made freely available in a public repository. The data from UK Biobank is open source and available to researchers after acceptance of a research proposal and payment of an access fee.

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