The Effect of Thiazide Diuretics on Urinary Prostaglandin Estradiol Excretion and Serum Sodium in the General Population

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Abstract

Context: Thiazide-induced hyponatremia is one of the most common forms of hyponatremia, but its pathogenesis is incompletely understood. Recent clinical data suggest links with prostaglandin E2 (PGE2) and a single nucleotide polymorphism (SNP) in the prostaglandin transporter gene (*SLCO2A1*), but it is unknown if these findings also apply to the general population.

Objective: To study the associations between serum sodium, thiazide diuretics, urinary excretions of PGE2, and its metabolite (PGEM), and the rs34550074 SNP in *SLCO2A1* in the general population.

Design: Prospective population-based cohort study (Rotterdam Study).

Setting: General population.

Participants: 2178 participants (65% female, age 64 ± 8 years)

Intervention(s): None.

Main Outcome Measure(s): Serum sodium levels.

Results: Higher urinary PGE2 excretion was associated with lower serum sodium: difference in serum sodium for each 2-fold higher PGE2 −0.19 mmol/L [95% confidence interval (CI) −0.31 to −0.06], PGEM −0.29 mmol/L (95% CI −0.41 to −0.17). This association was stronger in thiazide users (per 2-fold higher PGE2 −0.73 vs −0.12 mmol/L and PGEM −0.6 vs −0.25 mmol/L, *P* for interaction <.05 for both). A propensity score matching analysis of thiazide vs non-thiazide users yielded similar results. The SNP rs34550074 was not associated with lower serum sodium or higher urinary PGE2 or PGEM excretion in thiazide or non-thiazide users.

Conclusion: Serum sodium is lower in people with higher urinary PGE2 and PGEM excretion, and this association is stronger in thiazide users. This suggests that PGE2-mediated water reabsorption regulates serum sodium, which is relevant for the pathogenesis of hyponatremia in general and thiazide-induced hyponatremia specifically.

Key Words: electrolyte disorders, hyponatremia, single nucleotide polymorphism

Thiazide diuretics are widely used antihypertensive drugs (1) that exert their effect by inhibiting the sodium chloride cotransporter in the kidney distal convoluted tubule (2). Although thiazide diuretics reduce cardiovascular risk (3), these drugs can also cause serious adverse effects including hyponatremia, typically defined as serum sodium <135 mmol/L (4-6). Thiazide-induced hyponatremia (TIH) is the most common form of drug-induced hyponatremia requiring hospitalization and is reported in 14% of people using thiazide diuretics in a primary care setting and up to 30% of people using it in an outpatient clinic setting (4, 7-9).

Prostaglandin E2 (PGE2) is an essential lipid mediator modulating several aspects of kidney function via its effects on 4 PGE2 receptors: EP1 to EP4. Under certain conditions, PGE2 can stimulate aquaporin-2 mediated water reabsorption in the kidney collecting duct independent of the antidiuretic hormone vasopressin (10-15). Although the pathogenesis of TIH remains incompletely understood, increased water reabsorption due to the actions of PGE2 via its EP4 receptor has been reported as a possible cause (9). Patients with TIH had higher urinary PGE2 excretion compared to patients who used thiazide diuretics but remained

normonatremic (9). The risk of TIH was also increased in patients who carried a single nucleotide polymorphism (SNP) in *SLCO2A1* encoding a prostaglandin transporter in the collecting duct (9). It was therefore postulated that the SNP in *SLCO2A1* reduced PGE2 transport and therefore allowed PGE2 to increase water reabsorption.

Because the previous study was conducted in patients with TIH, the role of PGE2 in regulating serum sodium in the general population with and without thiazides remains unknown. We hypothesized that higher urinary excretions of PGE2 and its metabolite (PGEM) are associated with a lower serum sodium concentration and that this association is stronger in people using thiazide diuretics. To address this hypothesis, we assessed the association between the urinary excretions of PGE2 and PGEM with serum sodium in the general population both in participants using thiazides and those without thiazides. Finally, we tested whether the previously identified SNP in *SLCO2A1* was associated with higher urinary PGE2 and lower serum sodium concentrations.

Materials and Methods

General Population Cohort

The study was embedded in the Rotterdam Study, an ongoing prospective population-based cohort study. The rationale and design of the Rotterdam Study have been described in detail elsewhere (16). For the current study, participants from the second cohort (RS-II) were included when a baseline spot urine sample and serum sodium measurement were available. Participants using nonsteroidal anti-inflammatory drugs at the time of sample collection were excluded because they inhibit PGE2 synthesis. RS-II started in 2000 and included 3011 participants aged 55 years and older. All participants were examined at baseline, and follow-up examinations were conducted every 3 to 5 years. The Rotterdam Study was 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). All participants provided written informed consent to participate in the study.

Assessment of Urinary PGE2 Excretion, Serum Sodium, and Thiazide Use

Urinary PGE2 and PGEM were measured using commercially available competitive immunoassays (Cayman chemical, RRID: AB_2924719 and AB_2876793, respectively, Ann Arbor, MI, USA), following the manufacturer's instructions, using an Opentrons OT-2 liquid handling device (Opentrons, New York City, NY, USA). PGE2 and PGEM were normalized to urinary creatinine and log2 transformed prior to analysis. Log2 transformation was performed because no reference values for PGE2 and PGEM are available and because this facilitates interpretation of the data (1-unit difference in log2 transformed PGE2 or PGEM corresponds to a 2-fold difference in urinary PGE2 or PGEM excretion) (17). Serum sodium was measured with indirect ion-selective electrodes using a Cobas 8000 ISE analyzer (Roche Diagnostics, Mannheim, Germany). Serum sodium as a continuous variable was used as outcome for the main analyses. Thiazide and nonsteroidal anti-inflammatory drugs dispensing data, including prescribed daily dose, Anatomical Therapeutic Chemical code, dispensing date, and the amount

prescribed were obtained from all pharmacies in the study district (18).

Assessment of Covariates

Covariates in our models included age, sex, body mass index (BMI), estimated glomerular filtration rate (eGFR), systolic blood pressure, use of angiotensin converting enzyme (ACE)-inhibitors or angiotensin receptor blockers (ARB), smoking status, and presence of diabetes (19, 20). BMI was calculated using height and weight measurements performed during examinations at the research center. Serum creatinine was measured by the Department of Clinical Chemistry at the Erasmus University Medical Center using an enzymatic assay. eGFR was calculated using the CKD-EPI 2009 equation using serum creatinine and without the race coefficient (21), which is currently the recommended eGFR assessment for European populations (22). Systolic blood pressure was measured at the right brachial artery with the participant in a sitting position. The mean of 2 consecutive measurements was used. ACE inhibitor and ARB use, dispensing date, and the prescribed dosage were obtained from all pharmacies in the study district. Smoking status was derived from home interviews and categorized into never smoker, former smoker, and current smoker. Assessment of diabetes mellitus has been described in detail elsewhere (23, 24).

Analysis of the SNP in *SLCO2A1*

The association between the rs34550074 SNP in *SLCO2A1* and urinary PGE2, PGEM, and serum sodium was tested in participants from RS-II with available genetic data. DNA was extracted from peripheral blood mononuclear cells. Genotyping was done using Illumina Infinium II HumanHap550 or 610-Quad Genotyping BeadChi and performed by the Human Genotyping Facility, Genetic Laboratory Department of Internal Medicine, Erasmus MC (Rotterdam, The Netherlands). Imputation of SNPs was performed using the Haplotype Reference Consortium 1.1 as a reference panel (25). In more detail, imputation was conducted using the Michigan Imputation server, which uses the SHAPEIT2 software to phase the data and Minimac 4 for imputation to the Haplotype Reference Consortium reference panel (v1.1). We extracted dosage information of the previously identified SNP rs34550074 in *SLCO2A1* (9).

Statistical Analysis

Continuous variables were expressed as mean with SD or median with interquartile range (IQR) for skewed data. Categorical variables were expressed as numbers of participants and percentage. Multivariable linear regression models were made to analyze the association of urinary PGE2 and PGEM excretions with serum sodium as a continuous measure. Because of the low incidence of overt hyponatremia, we selected 2.5% of participants with the lowest serum sodium levels and tested differences in urinary PGE2 and PGEM excretions compared to the other participants using *t*-tests. We then tested the effect of thiazide use on urinary PGE2 and PGEM excretions using linear regression models adjusting for confounders. Nonlinearity was tested modeling urinary PGE2 or PGEM excretions as restricted cubic splines with 3 knots. Our main analysis of interest was the effect modification of thiazide use on the association between urinary

PGE2 or PGEM excretion and serum sodium. For this, we performed multivariable linear regression analysis with thiazide use as the interaction term (considering a *P*-value <.1 as significant). As a sensitivity analysis, we also analyzed the interaction term for other classes of antihypertensive drugs (β-blockers, calcium antagonists, ACE inhibitors, or ARBs). All regression analyses were first performed with age, sex, and BMI as covariates and then additionally with baseline eGFR, systolic blood pressure, diastolic blood pressure, smoking status, use of ACE inhibitor or ARB, and presence of diabetes. As a secondary analysis, we analyzed the association of urinary PGE2 and PGEM excretions and serum sodium in thiazide users compared to propensity score-matched controls. Thiazide users were matched on the covariates mentioned previously, extended with serum potassium using 1:1 nearest neighbor matching with a generalized linear model fit with the "MatchIt" package in R. Balance between the cases and controls was assessed using plots of the standardized mean difference. All covariates had <5% missing data. Missing variables were multiply imputed 20 times using chained equations from the Multivariate Imputation by Chained Equation "MICE" package in R. Analyses were performed with R statistical software (R-project, Institute for Statistics and Mathematics, R Core Team 2013, Vienna, Austria, version 4.1.0).

Results

Higher Urinary PGE2 and PGEM Excretions Are Associated With Lower Serum Sodium

A total of 2178 participants were enrolled in the study with available serum sodium values. Of these, 2130 urinary PGE2 and another 2130 urinary PGEM measurements were available for analysis (Supplementary Fig. S1) (26). The majority of this cohort was female (54%) with a mean age of 64.3 ± 7.7 years and an eGFR of 80.9 ± 13.5 mL/min/1.73 m^2 (Table 1). The mean serum sodium concentration in the included participants was 141.3 ± 2.2 mmol/L, and the median urinary PGE2 and PGEM excretions were 81.4 pg/mmol (IQR 60.6-114.4) and 48.2 pg/mmol (IQR 33.7-67.3), respectively (Table 1, Supplementary Fig. S2) (26). In total, 10 participants (0.5%) had hyponatremia (serum sodium <135 mmol/L), including 4 who were using thiazides (2.1% of thiazide users) and 6 who were not using a thiazide (0.3% of non-thiazide users) (Table 1). Higher urinary PGE2 and PGEM excretions were associated with lower serum sodium. The difference in serum sodium per 2-fold higher urinary PGE2 excretion was −0.21 mmol/L [95% confidence interval (CI) −0.33 to −0.09] and for urinary PGEM excretion −0.31 mmol/L (95% CI −0.43 to −0.20) (Fig. 1A). This effect did not change after adjusting for age, sex, and BMI (PGE2 −0.23 mmol/L, 95% CI −0.35 to −0.10, PGEM −0.34 mmol/L, 95% CI −0.45 to −0.21) or other confounders such as baseline eGFR, systolic blood pressure, diastolic blood pressure, smoking status, use of ACE inhibitor or ARB, and presence of diabetes (PGE2 −0.19 mmol/L, 95% CI −0.31 to −0.06, PGEM −0.29 mmol/L, 95% CI −0.41 to −0.17, Fig. 1B). There was no significant nonlinearity in these associations (PGE2 *P* = .7, PGEM *P* = .5). Participants with the lowest 2.5% of serum sodium measurements (serum sodium ≤ 137 mmol/L, n = 72) had higher urinary PGE2 and PGEM excretion compared to the other participants (difference in log2 PGE2 excretion 0.22 pg/mmol, 95% CI 0.03 to 0.40, PGEM 0.40 pg/mmol 95% CI 0.21 to 0.59, Supplementary Fig. S3).

Table 1. Baseline characteristics

Characteristic[a]	Non-thiazide users (n = 1988)	Thiazide users (n = 190)	Total (n = 2178)	*P*-value
Sex, female, n (%)	1054 (53.0)	123 (64.7)	1177 (54.0)	.002
Age, years	64.2 ± 7.6	65.5 ± 8.7	64.3 ± 7.7	.03
BMI, kg/m^2	27.0 ± 3.9	28.4 ± 4.1	27.1 ± 4.0	<.001
Baseline eGFR, mL/min/1.73 m^2	81.1 ± 13.3	77.9 ± 15.0	80.9 ± 13.5	.002
Hypertension, n (%)	1178 (59.3)	182 (95.8)	1360 (62.5)	<.001
Systolic BP, mmHg	141.9 ± 21.4	153.1 ± 21.8	142.8 ± 21.7	<.001
Diastolic BP, mmHg	78.0 ± 10.5	83.5 ± 11.5	78.5 ± 10.7	<.001
Use of ACE-i or ARB, n (%)	190 (9.6)	55 (28.9)	245 (11.2)	<.001
Serum sodium, mmol/L	141.3 ± 2.2	140.9 ± 2.7	141.3 ± 2.2	.007
Hyponatremia, n (%)	6 (0.3)	4 (2.1)	10 (0.5)	<.001
Serum potassium, mmol/L	4.3 ± 0.3	4.0 ± 0.3	4.2 ± 0.3	<.001
Smoking status, n (%)				.09
never smoker	602 (30.4)	64 (33.7)	666 (30.7)	
former now nonsmoker	977 (49.3)	100 (52.6)	1077 (49.6)	
current smoker	402 (20.3)	26 (13.7)	428 (19.7)	
Diabetes, n (%)	260 (13.1)	27 (14.2)	287 (13.2)	.66
History of cardiovascular disease, n (%)	203 (10.2)	20 (10.5)	223 (10.2)	.89
Urinary PGE2 excretion, pg/mmol	81.4 (60.5-113.9)	81.9 (61.4-122.2)	81.4 (60.6-114.4)	.98
Urinary PGEM excretion, pg/mmol	48.3 (33.7-67.4)	47.7 (33.4-64.5)	48.2 (33.7-67.3)	.79

P-values from *t*-tests or χ^2 test where applicable.
Abbreviations: ACE-i, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; PGE2, prostaglandin estradiol; PGEM, prostaglandin metabolite.
[a]Continuous variables are expressed as mean ± SD or median with interquartile range for skewed data and n (%) for categorical variables.
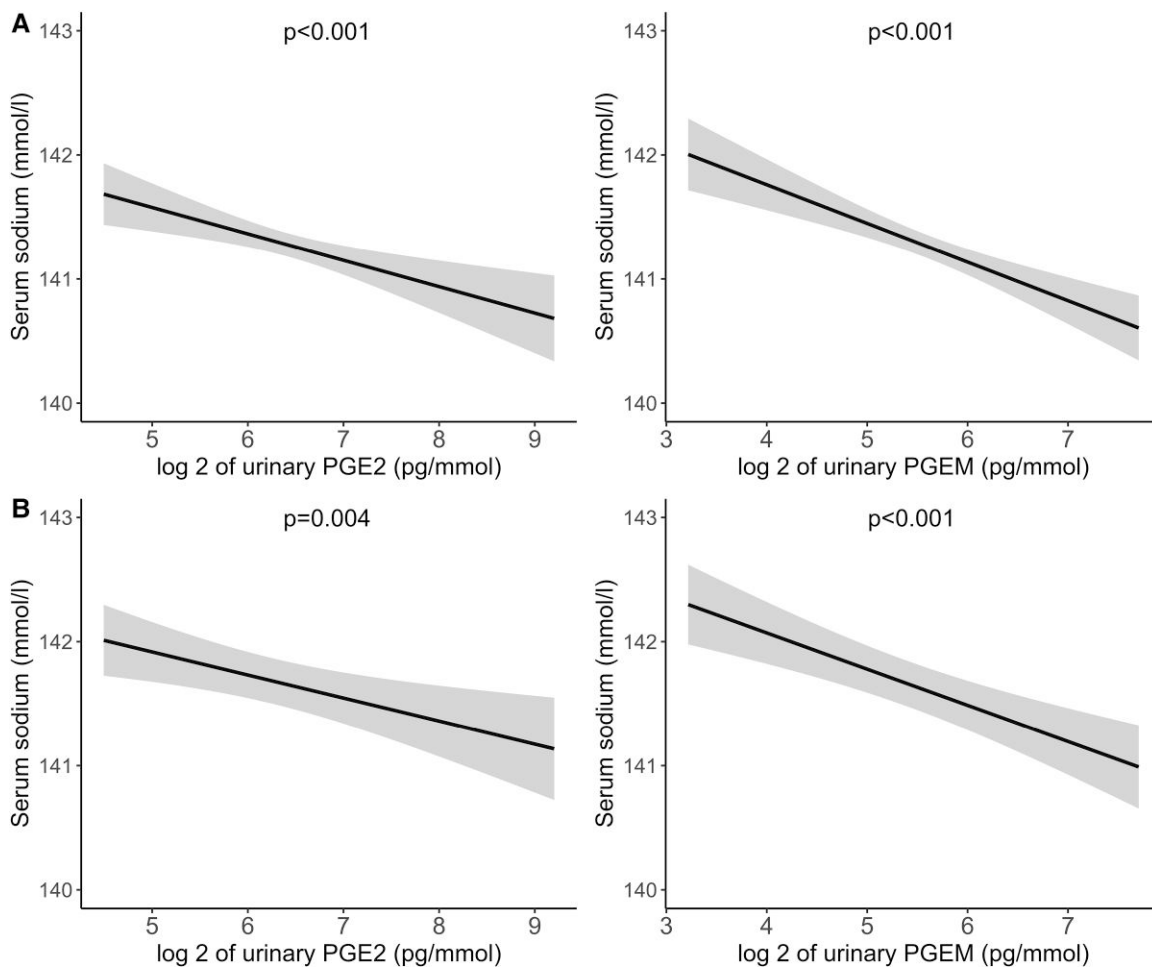
Figure 1. Multivariable regression model for the association between serum sodium and urinary PGE2 and PGEM excretion. (A) Uncorrected analyses. (B) Analyses corrected for sex, age, BMI, baseline eGFR, smoking status, systolic blood pressure, and ACE-i/ARB-use.

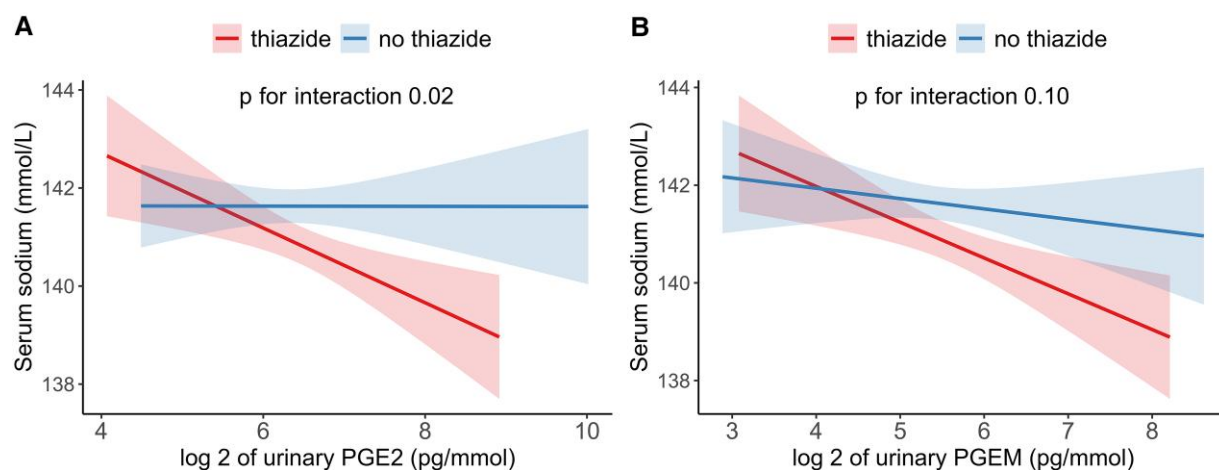### Serum Sodium and Urinary PGE2 Excretion in Thiazide Users

A total of 190 participants were using thiazides (8.7%) for a mean of 37 weeks with a mean defined daily dose of 0.88 (Supplementary Table S1) (26). Compared to the rest of the cohort, thiazide users were predominantly female, were older, and had a higher BMI and blood pressure and a lower eGFR (Table 1). Serum sodium was 0.45 mmol/L (95% CI 0.12 to 0.78) lower in thiazide users. A higher defined daily dose of thiazides or increasing duration of its use were not significantly associated with a lower serum sodium (difference in serum sodium per unit change in daily dose −3.8 mmol/L, 95% CI −9.2 to 1.5) or with increasing duration of thiazide use (difference in serum sodium per month of thiazide use −0.03 mmol/L, 95% CI −0.08 to 0.03). There was no difference in urinary PGE2 or PGEM excretion between thiazide users and non-thiazide users (difference in log2 transformed excretion for PGE2 0.03 pg/mmol 95% CI −0.09 to 0.14 and for PGEM −0.03 pg/mmol 95% CI −0.16 to 0.09). When defining thiazide use as participants using thiazides for longer than 3 months, the results were similar (n = 146, serum sodium difference 0.79 mmol/L, 95% CI 0.42 to 1.16, urinary PGE2 excretion 0.07 pg/mmol 95% CI −0.06 to 0.2, urinary PGEM excretion 0.02 pg/mmol, 95% CI −0.11 to 0.16, Supplementary Table S2) (26).

Stronger Association Between Urinary PGE2 Excretion and Serum Sodium in Thiazide Users

The association between urinary PGE2 excretion and serum sodium was stronger in thiazide users compared to the participants not using thiazides after correction for confounders (change in serum sodium per 2-fold higher urinary PGE2 excretion −0.73 mmol/L, 95% CI −1.25 to −0.21 vs −0.12 mmol/L, 95% CI −0.26 to −0.001, P for interaction = .002, Fig. 2A). Results for the association between urinary PGEM excretion and serum sodium were similar (thiazide users: −0.6 mmol/L, 95% CI −1.08 to −0.13, non-thiazide users −0.25, 95% CI −0.37 to −0.13, P for interaction = .02, Fig. 2B). This interaction did not change when only selecting participants with over 3 months of thiazide use [PGE2: P for interaction = .0008, PGEM: P for interaction = .006, Supplementary Fig. S4A (26)] or excluding normotensive participants from the analysis [PGE2: P for interaction = .005, PGEM: P for interaction = .02, Supplementary Fig. S4B (26)]. The stronger association between urinary PGE2 or PGEM excretion and serum sodium was specific to users of thiazide diuretics since there was no significant interaction when stratifying by use of ACE inhibitors or ARBs, calcium antagonist, or β-blockers (Supplementary Fig. S5) (26).
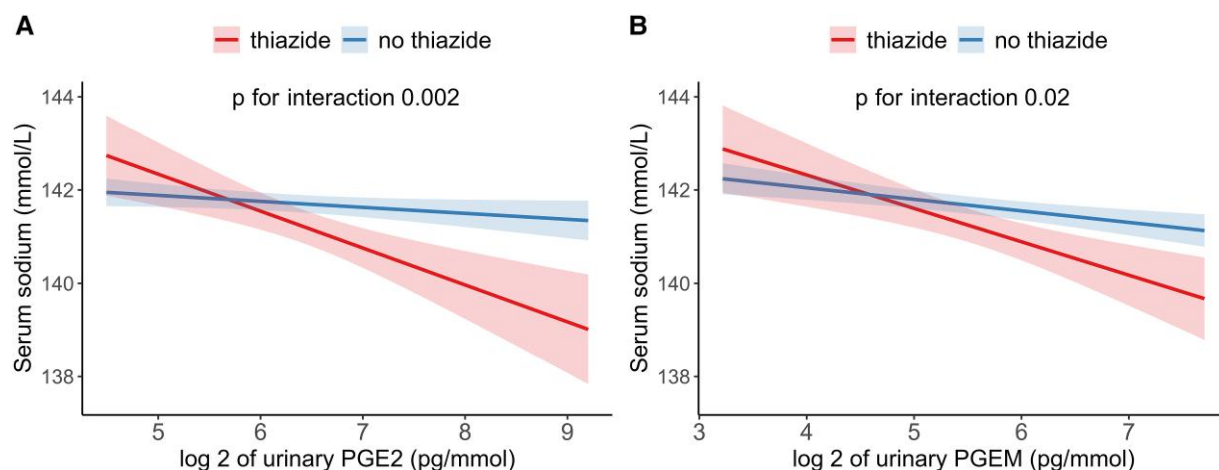
Figure 2. Association between urinary PGE2 and PGEM excretion and serum sodium and thiazide use. Effect plots for the interaction of thiazide use on the association between urinary PGE2 (A) and PGEM (B) and serum sodium from a multivariable model correcting for sex, age, BMI, baseline eGFR, smoking status, systolic blood pressure, and ACE-i/ARB-use.

Figure 3. Association between urinary PGE2 and PGEM excretion and serum sodium and thiazide use after propensity score matching. Effect plots for the interaction of thiazide use on the association between urinary PGE2 (A) and PGEM (B) and serum sodium from a multivariable model correcting for sex, age, BMI, baseline eGFR, smoking status, systolic blood pressure, ACE-i/ARB-use, serum potassium and diabetes status.

Propensity Score-matched Analysis

Propensity score matching on thiazide use resulted in a cohort of 181 matched participants using thiazides and 181 matched participants not using thiazides (Supplementary Table S3, Supplementary Fig. S6) (26). There was no difference in the distribution of covariates between the thiazide users and their matched controls (Supplementary Table S3) (26). The propensity score-matched analysis also showed that serum sodium was significantly lower in thiazide users compared to non-thiazide users (140.8 ± 2.7 mmol/L vs 141.6 ± 2.3 mmol/L, difference −0.80 mmol/L, 95% CI −1.31 to −0.28, Supplementary Table S3) (26). The propensity-matched analysis showed the same effect of thiazides on the association between urinary PGE2 excretion and serum sodium (*P* for interaction = .02) but was no longer statistically significant for urinary PGEM excretion, possibly due to loss of power (*P* for interaction = .10, Fig. 3).

Analysis of *SLCO2A1* SNP rs4550074

Genetic data was available from 1793 participants with urinary PGE2 and PGEM measurements. The allele frequency of

the previously described variant in *SLCO2A1* rs4550074 was 0.20. There was no statistically significant difference in serum sodium, urinary PGE2 excretion, or urinary PGEM excretion between carriers of 0, 1, or 2 alleles of rs4550074 (Supplementary Table S4, Fig. 4) (26). In addition, the association between urinary PGE2 and PGEM excretion and serum sodium did not differ between carriers of 0 or 1 or 2 alleles of rs4550074 (Supplementary Fig. S7) (26). Similarly, there was no difference when repeating the analysis in participants using thiazides or those not using thiazides.

Discussion

In this study, we show that in the general population, higher urinary PGE2 and PGEM excretions are associated with lower serum sodium concentration and that this association is stronger in thiazide users. The interaction was confirmed in a propensity score-matched analysis for PGE2 and not observed with other antihypertensive drug classes. We also analyzed the rs4550074 SNP in *SLCO2A1*, which was previously reported to increase the risk of thiazide-induced hyponatremia in a cohort of patients presenting to the emergency room (9).
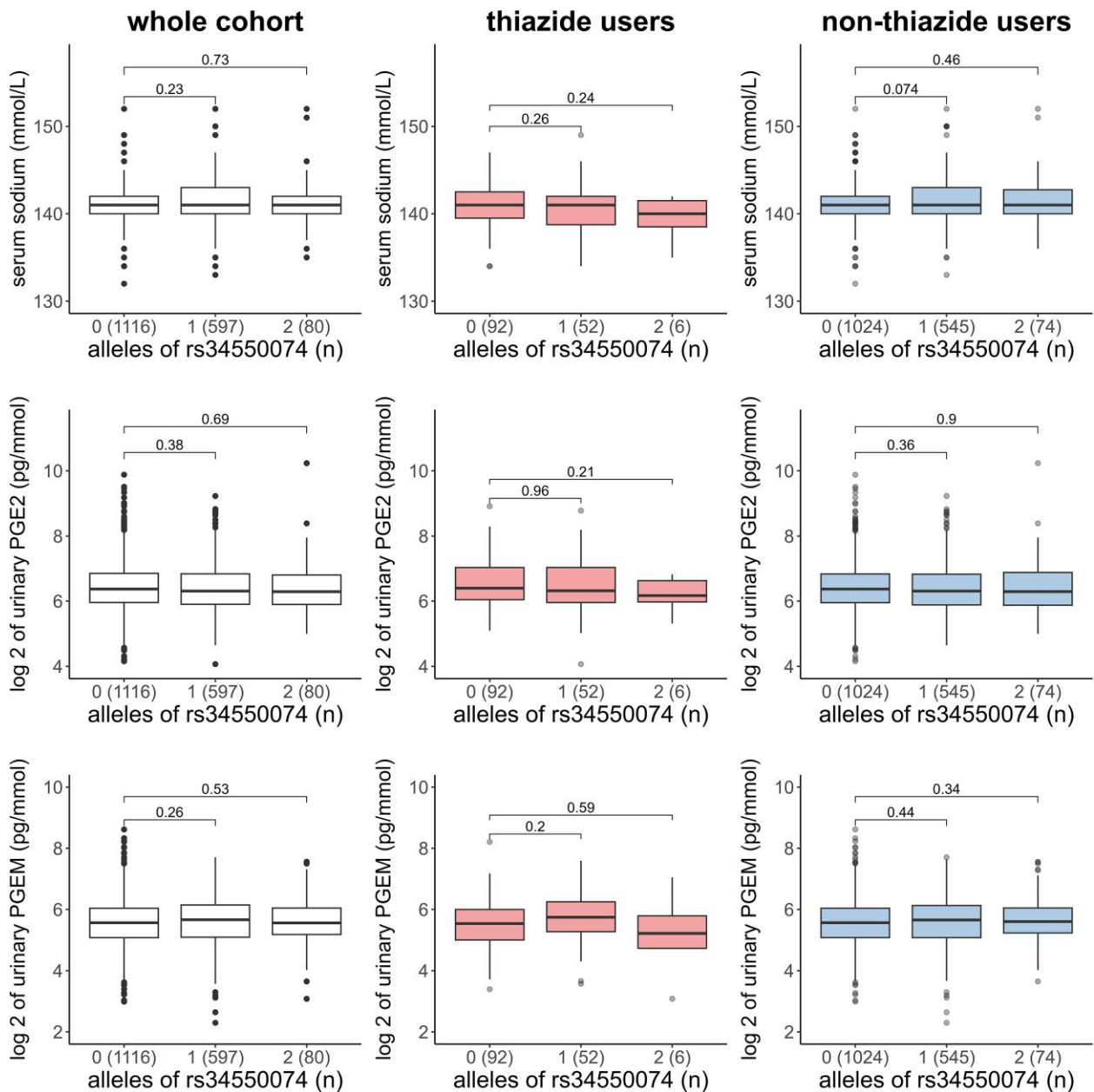
Figure 4. The association of SNP rs34550074 with serum sodium and urinary PGE2 or PGEM. White bars represent the whole cohort, red represents thiazide users and blue represents non-thiazide users.

In our general population cohort, we were unable to identify an association between this SNP and lower serum sodium concentrations or higher urinary PGE2 or PGEM excretions. Our results, together with previous observations, suggest that PGE2 plays a role in regulating serum sodium levels. This is relevant for understanding the factors contributing to hyponatremia in general and thiazide-induced hyponatremia specifically.

Previous studies in cells and animals have shown that PGE2 is capable of increasing water reabsorption through the water channel aquaporin-2 (AQP2) in the principal cells of the collecting duct, which in turn regulates water balance and serum sodium (12-14, 27-29). These physiological principles likely explain the association between serum sodium and urinary PGE2 excretion. Serum sodium is not always associated with urinary PGEM excretion, which may be explained by the

observation that urinary PGE2 is almost exclusively kidney-derived, whereas PGE2 from the circulation also contributes to urinary PGEM (30). The relationship between PGE2, vasopressin, and AQP2 is complex, because PGE2 stimulates water reabsorption in the absence of vasopressin but decreases it in the presence of vasopressin. This differential effect was recently explained by the involvement of different PGE2 receptors, including EP4 for vasopressin-independent AQP2 stimulation and EP1/3 for vasopressin-dependent AQP2 downregulation (12). Ware et al showed that patients with TIH had suppressed plasma vasopressin levels with high urinary PGE2 excretion, which is compatible to PGE2 stimulating EP4 and AQP2 (9). Of note, after stopping thiazide diuretics, plasma vasopressin remained lower in the patients who had TIH compared to normonatremic thiazide controls. This suggests that lower plasma vasopressin levels may facilitate PGE2-mediated water

reabsorption in the setting of increased PGE2 production, for example by thiazide diuretics. Urine osmolality, plasma vasopressin, and plasma copeptin were not available in our cohort, but these would be relevant parameters to add in future studies exploring this association.

Even though we observed a stronger association between serum sodium and urinary PGE2 excretion in thiazide users, urinary PGE2 or PGEM excretions were not higher in thiazide users vs nonusers. Why participants using thiazide diuretics have a stronger effect on serum sodium than nonusers for the same level of urinary PGE2 excretion remains unclear, but this could again point in the direction of concurrent factors facilitating PGE2-mediated water reabsorption. Of note, several previous studies, including ours, did find higher urinary PGE2 excretion during the use of thiazide diuretics. For example, in a randomized controlled trial in patients with chronic kidney disease and hypertension, we observed higher urinary PGE2 and PGEM excretion during hydrochlorothiazide/amiloride administration than during a low sodium diet (31). In this previous study, higher urinary PGE2 and PGEM excretions were also associated with a lower free water clearance. In another trial in patients with polycystic kidney disease treated with the vasopressin receptor antagonist tolvaptan, hydrochlorothiazide also increased urinary PGE2 excretion and potentially explained the observed antidiuretic effect of hydrochlorothiazide (32, 33). The discrepancy between the current study and these previous studies may be related to the fact that urinary PGE2 excretion is the net result of PGE2 secretion by several tubular segments as well as reabsorption through the prostaglandin transporter and that various factors may regulate these individual steps. Of note, low distal salt delivery in a mouse model of overactivity of the sodium chloride cotransporter actually increased PGE2 synthase and urinary PGE2 excretion, which was then *reversed* with thiazide diuretics (27). Thus, the effect of thiazide diuretics on urinary PGE2 excretion may depend on the baseline condition in which the thiazide is given.

In our study, another relevant question is what caused some participants to have higher urinary PGE2 excretion than others (if not caused by thiazide diuretics). We recently analyzed the determinants of urinary PGE2 and PGEM excretion in the Rotterdam Study and found that they were higher in older participants, those with a lower BMI, smokers, and participants with diabetes or albuminuria (17). Of interest, some of these determinants are also risk factors for the development of hyponatremia (34). Here, we also analyzed 1 genetic determinant of urinary PGE2 excretion, namely the rs34550074 SNP in *SLCO2A1* (9). However, in our cohort, this SNP was not associated with lower serum sodium, higher urinary PGE2 or PGEM excretion, or the association between urinary PGE2 excretion and serum sodium despite a similar allele frequency as in the previous study. It is conceivable that the SNP is relevant for the development of clinically overt TIH but not for milder fluctuations in serum sodium in the general population.

The main strengths of this study are the large population-based cohort with a prospective design, the high participation rate, and the use of propensity score matching. Our study also has a number of limitations. First, overt hyponatremia was relatively uncommon in our cohort and the impact of thiazide use on the decrease in serum sodium relatively modest. Although this is not unexpected in a general population cohort, this does imply that the findings of this study mainly pertain to participants with serum sodium in the normal to low-normal range and that the clinical relevance of our findings is limited. However, previous studies in the general population illustrate that small differences in serum sodium within the normal range are associated with relevant outcomes such as heart failure or mortality (35, 36). Second, the majority of the participants in the Rotterdam Study have European ancestry, limiting the generalizability of the results to other ethnicities.

In conclusion, we showed in a general population-based cohort that urinary PGE2 and PGEM excretions are higher in people with lower serum sodium and that this association is stronger in thiazide users. Although the absolute differences in serum sodium are small, this study strengthens the body of evidence supporting a regulatory role of PGE2 in body water homeostasis, even in the absence of hyponatremia, and provides further evidence for the role of PGE2 in water reabsorption in thiazide users with and without TIH.

Disclosures

The authors have nothing to disclose.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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