



Influence of weather conditions, drugs and comorbidities on serum Na and Cl in 13 000 hospital admissions: Evidence for a subpopulation susceptible for SIADH[☆]



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ABSTRACT

Objectives: Considerable variation in serum sodium (Na) and chloride (Cl) is found in patients at hospital admission. Our goal was to quantify the respective impact of drugs, comorbidities, demographic factors and weather conditions on serum Na and Cl.

Design and methods: For 13 277 consecutive patients without terminal kidney disease admitted to the Department of Internal Medicine of the Kantonsspital St. Gallen drug history on admission, age, sex, body weight, ICD-10 diagnoses, and laboratory data were extracted from electronic medical records. Weather parameters prior to hospital admission were also integrated in a multivariate regression analysis.

Results: Both serum Na and Cl showed an asymmetric left-tailed distribution. Median (interquartile range) Na was 138 (136/140) and Cl 104 (101/106). The distribution of sodium in patients with one or more risk factors for SIADH was best explained by the presence of two populations: one population with a similar distribution as the unexposed patients and a smaller population (about 25%) shifted to lower sodium levels. Lower weight, lower blood pressure, kidney dysfunction, fever, and diabetes were associated with both lower Na and Cl. Higher ambient temperature and higher air humidity preceding admission were associated with both higher Na and Cl values.

Conclusions: Na and Cl at hospital admission are highly influenced by ambient weather conditions, comorbidities and medication. The bimodal distribution of Na and Cl in persons exposed to risk factors for SIADH suggests that SIADH may only affect a genetically distinct vulnerable subpopulation.

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Introduction

About 65% (or 2500 mmol) of total body sodium and about 85% (or 2000 mmol) of chloride are located in extracellular fluid, whereas only about 8% or 300 mmol of sodium and about 15% or 350 mmol of chloride are intracellular. The remainder of sodium (about 25–30% or 1000 mmol) is stored in bone [1,2]. Serum sodium and its accompanying anions, mainly chloride and bicarbonate, are the major osmotic active substances in the extracellular fluid [2,3]. They are therefore of paramount importance for the control of extracellular and intracellular volume statuses. Total body sodium and chloride contents are mainly balanced by oral intake and renal excretion. Losses by sweat and faeces

play a minor role, however ambient temperature and air humidity affect sweating and could thus further influence serum sodium by differential losses of electrolytes and water [2]. With the exception of acid–base disturbances changes in content or concentration of sodium are typically paralleled by similar changes of chloride [1].

Total body sodium is mainly regulated by the renin–angiotensin–aldosterone (RAA) system, the sympathetic nervous system and atrial natriuretic peptide (ANP). In contrast, serum osmolality is tightly controlled by antidiuretic hormone (ADH), which regulates free water clearance. Thus, under normal conditions, regulation of Na and Cl (and therefore extracellular volume) and regulation of water (and therefore serum osmolality) are strictly separated. However, below a certain threshold of extracellular volume depletion or expansion a non-osmotic stimulus on ADH release begins to override the osmotic one [1].

Both hyponatraemia and hypernatraemia are associated with increased mortality, especially in the presence of rapid changes of intracellular water in the central nervous system (cerebral oedema, bleeding, osmotic demyelination) [3,4]. However increased mortality is not necessarily a causal effect of electrolyte disturbance, since dysnatraemia

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may be a surrogate of severe underlying disease, which adversely affects prognosis, especially shown for heart failure and liver cirrhosis [5,6].

Several clinical conditions and drugs are associated with either increased (e.g. diabetes insipidus, hypodipsia, modulation of renal sodium and water excretion by drugs) or decreased (e.g. syndrome of inappropriate secretion of ADH (SIADH), congestive heart failure, liver cirrhosis) serum sodium concentrations [3,4,7]. SIADH is considered to be the leading cause for hyponatraemia and hypochloraemia and can be induced by drugs or comorbidity. SIADH is defined by decreased serum osmolality, coexisting urine osmolality above 100 mOsm/kg, urinary sodium above 40 mmol/L, euvoalaemia, and the absence of other causes for hyponatraemia. At least three mechanisms are described: i) increased (hypothalamic) production of ADH, ii) a reset of the so called osmostat (reduction of the hypothalamic osmolality threshold for ADH release) and iii) a syndrome mimicking SIADH with gain of function mutations in the V2 vasopressin receptor (NSIAD) [8–10].

The aim of this study was to determine the relative contributions of drugs, comorbidities, and environmental factors on serum sodium and chloride in a large, and unselected cohort of patients admitted to a representative tertiary referral centre. Special emphasis was placed on determinants of SIADH.

Methods

Patients

The Kantonsspital St. Gallen is the main tertiary referral centre in eastern Switzerland. All consecutive patients admitted to the Department of Internal Medicine between January 2002 and July 2004 were retrospectively included in this study. Patients on dialysis and those with an estimated glomerular filtration rate (eGFR) < 10 mL/min/1.73 m² were excluded. We have previously published predictors of potassium in the same cohort [11]. Complete drug history on admission, age, sex, body weight, blood pressure, and comorbidities (ICD-10-diagnoses: congestive heart failure, liver cirrhosis, diabetes, diarrhoea, vomiting, malabsorption, gastrointestinal bleeding, pancreatitis, malignant diseases, sepsis, pneumonia, COPD, hyperventilation, acidosis, psychosis, and stroke) were derived from the electronic patient record (Phoenix®, Parametrix, Lachen, Switzerland). The institutional review board (Ethikkommission des Kantons St. Gallen) approved the study and waived the need for written informed consent from the participants.

Drug history and defined daily doses

Drugs with the alleged potential to increase or decrease sodium and/or chloride were recorded: thiazides (6 generic substances), loop diuretics (2), K-sparing diuretics (3), carbonhydrase inhibitors (1), angiotensin-converting enzyme inhibitors (ACEIs; 12), angiotensin receptor blockers (ARBs; 4), digitalis (1), betablockers (14), β_2 -mimetics (5), theophylline (1), non-steroidal antiinflammatory drugs (NSAID; 18), corticosteroids (5), calcineurin inhibitors (2), L-Dopa or dopamine agonists (4), antiepileptics (27), antidepressants (15), neuroleptics (17), heparins (4), laxatives (>10), Insulin, and other antidiabetics (12). In drug classes with different mechanisms of actions (e.g. antiepileptics, antidepressants, etc.) subclasses were also defined. To standardize doses within a class or subclass the daily dose of a given substance was expressed as multiples of a defined daily dose (DDD) according to the world health organization WHO (http://www.whocc.no/atc_ddd_index/).

Definition of SIADH-risk factors

We searched Medline for reports of SIADH associated with drug exposure (e.g. amiodarone, morphine, tricyclic antidepressants, selective

serotonin reuptake inhibitors, and others) or comorbidity (e.g. nausea, pneumonia, lung cancer, and others). All predictors were consequently classified as being potential “SIADH-risk factors”.

Laboratory analysis

Creatinine and electrolyte values were extracted from the laboratory database. Glomerular filtration rate (eGFR) was estimated according the Modification of Diet in Renal Disease MDRD-short formula ($186 \times (\text{Scr})^{\text{exp} - 1.154} \times (\text{age})^{\text{exp} - 0.203} \times 0.742$ (if the subject is female) [12]. Correction for African descent was not done because this information was not available and less than 1% of the local population is from African descent.

Weather conditions

From the Swiss Meteorological Institute (MeteoSchweiz, Kloten, Switzerland) we obtained tables of weather conditions for the city of St. Gallen. These daily summary reports (including minimal, average, and maximal daily temperature and humidity) were used as single measurement for the day preceding hospital admission or averaged over a period of 1 week, and 1 month before hospital admission. Since we expected a short to intermediate effect of ambient temperature and air humidity on electrolytes we compared the model performance for all three measuring points.

Statistical analysis

Statistical analysis was performed using SAS release 9.2 (SAS institute Inc., Cary, NC, USA) and MATLAB (Version 7.11.0.584 (R2010b), The MathWorks, Inc., Natick USA). Continuous variables are presented as means and standard deviations (SD), or as medians and interquartile ranges (IQR), and categorical variables as percentages (%) and rates. Missing values for body weight were imputed using a regression model with the variables sex and age. If the strength of the drug or the exact dosing schedule was not reported or ambiguous, the daily intake of 1 DDD was assumed. If the drug was taken “on demand” the daily intake of 1/2 DDD was assumed.

A mixed-effects regression model, controlled for clustering by repeated admissions of individual patients was developed. To adjust for their alleged effects on electrolytes all variables were included in the multivariate model, irrespective of their statistical significance. Predefined interactions (with sex, age, heart-, liver-, and kidney-function) were only tested on univariately significant variables and included in the final model if their p-value was <0.05. In order to detect non-linear effects and for the exact graphical presentation we finally introduced classes of essential predictors (e-GFR, age, weight, blood pressure, body temperature).

In order to determine the best model for the effect of exposure with one or more SIADH-risk factor(s) the following hypotheses were generated: a) the distribution of exposed persons has a similar shape as the distribution of unexposed persons but it's globally shifted to the left (with or without an additional stretching-factor) and b) the observed distribution is the sum of two separate distributions one of which is identical to the distribution of the unexposed persons, and a second distribution, which is shifted to the left (with or without an additional stretching factor). The optimal values for the parameters in question were found using least squares methods. The models were ranked according to the Akaike Information Criterion.

Results

From the original cohort of 15 000 cases 283 were excluded due to dialysis or eGFR <10 mL/min/1.73 m², 571 were excluded due to “haemolytic” serum, and 675 due to missing data for sodium or chloride. The present analysis is based on the data of 13 277 admissions in 9767

patients. 5507 (41%) were females and 7770 (59%) males. Mean (\pm SD) age was 63.3 (\pm 16.0) years, body weight was 70.3 (\pm 15.7) kg, and eGFR was overall 74 (\pm 33) mL/min/1.73 m². On a yearly basis the average (\pm SD) intensity of solar radiation was 127.2 (\pm 95.3) W/m², mean ambient temperature was 8.9 (\pm 7.6) °C, and mean air humidity 74.9 (\pm 13.8) %.

Distribution of electrolytes and SIADH risk factors

Overall, both electrolytes showed a skewed, left-tailed distribution with a median (5%, 25%, 75%, and 95% percentiles) of 138 (130, 136, 140, 143) mmol/L for sodium and 104 (94, 101, 106, 107) mmol/L for chloride. 7380 (56%) took a drug or suffered from a condition with the potential to induce SIADH. Depending on the degree of exposure with SIADH-risk-factors the left tail became more prominent, whilst the position of the peak of the distribution remained almost unchanged as outlined in Fig. 1A and B. This might be explained by a superposition of two distinct distributions. Indeed we found strong evidence for a double-peaked distribution of Na and even clearer for Cl, in persons exposed to one or more SIADH-risk factors. According to our mathematical model about 75% of the exposed patients had a sodium-distribution which was identical to the distribution of the unexposed group, and about 25% of the exposed persons were part of a second distribution, which was on average shifted by 4 mmol/L to the left (lower values) and additionally stretched by a stretching factor of 0.92 from an anchoring point of 143 mmol/L. Almost identical results were found for

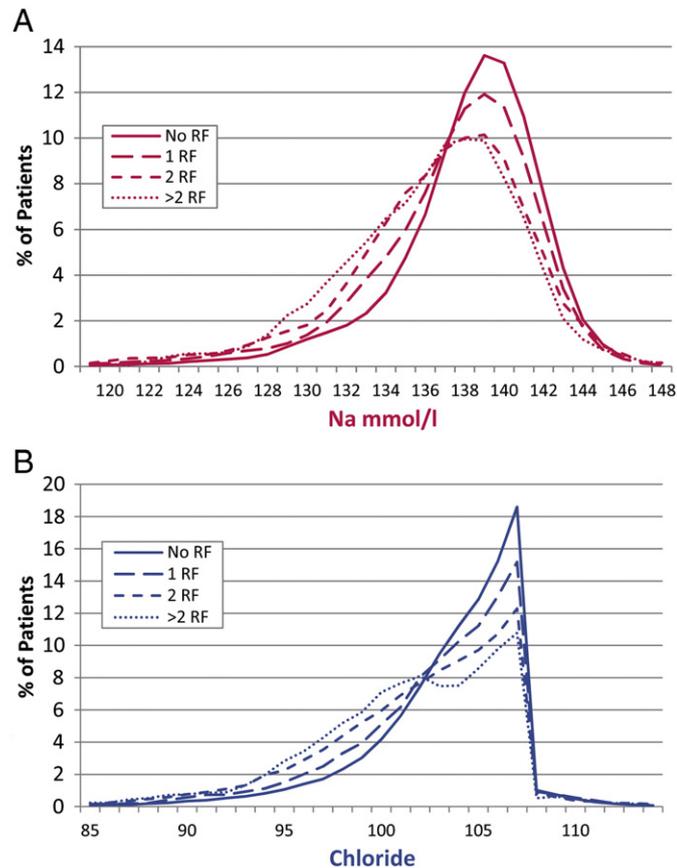


Fig. 1. A. Distribution of sodium according to presence of SIADH-risk factors. Unadjusted distributions of serum sodium in patients as a function of exposure to SIADH-risk factors. All distributions are relative distributions within subgroups and the lines are smoothed using directly adjacent observations at each point. B. Distribution of chloride according to presence of SIADH-risk factors. Unadjusted distributions of serum chloride in patients as a function of exposure to SIADH-risk factors. All distributions are relative distributions within subgroups and the lines are smoothed using directly adjacent observations at each point.

chloride. In Fig. 2A and B the distribution of all exposed patients is presented as the superposition of the two modelled populations.

Regression models for sodium and chloride

In multivariate regression higher body weight was associated with higher sodium and chloride levels (+0.028 mmol/L Na per kg, $p < 0.0001$; +0.0261 mmol/L Cl per kg, $p < 0.0001$; Fig. 3). In contrast higher body temperature was associated with lower electrolytes (linearized -0.1333 mmol/L Na per °C, $p < 0.0001$ and -0.079 mmol per °C, $p = 0.017$; Fig. 4). Kidney function ($p < 0.001$) as well as blood pressure ($p < 0.0001$) showed an inverse U-shaped association with sodium and chloride (Figs. 5 and 6).

Both higher air humidity (sodium: +0.017 mmol/L per % higher humidity, $p < 0.0001$; chloride: +0.015 mmol/L per % higher humidity, $p < 0.001$) and higher ambient temperature (sodium: +0.033 mmol/L per °C, $p < 0.0001$; chloride: +0.046 mmol/L per °C, $p < 0.0001$) in the week preceding admission had small albeit highly significant effects on both electrolytes (Na: Fig. 7, Cl: data not shown).

If kidney dysfunction is omitted, overall 6885 (52%) had at least one comorbidity with alleged influence on serum sodium or chloride. The following conditions were all associated with both lower Na and Cl:

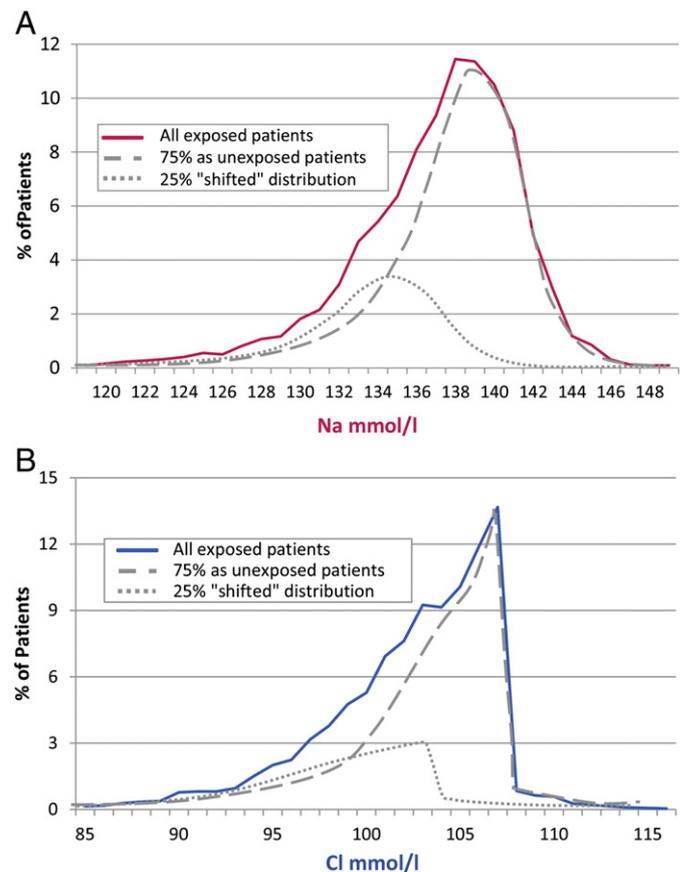


Fig. 2. A. Components of the distribution of sodium in patients exposed to SIADH-risk factor(s). All patients exposed to one or more SIADH-risk factor(s) are combined (solid red line). According to our mathematical model this distribution can be explained by the superposition of two discrete populations: approximately 75% of patients with the same distribution as unexposed patients (dashed grey line) and 25% of patients shifted to the left (dotted grey line). B. Components of the distribution of chloride in patients exposed to SIADH-risk factor(s). All patients exposed to one or more SIADH-risk factor(s) are combined (solid blue line). According to our mathematical model this distribution can be explained by the superposition of two discrete populations: approximately 75% of patients with the same distribution as unexposed patients (dashed grey line) and 25% of patients shifted to the left (dotted grey line).

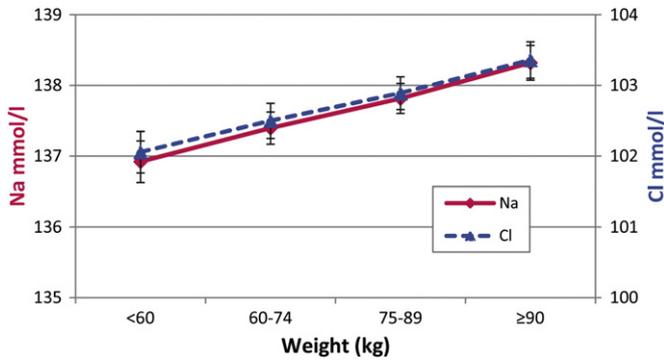


Fig. 3. Weight and Na/Cl. Linear association between higher weight and higher Na and Cl (adjusted model; $p = 0.001$ for sodium and $p < 0.0001$ for chloride). Error bars stand for 95% confidence limits.

diabetes, liver cirrhosis, alcohol abuse, vomiting, diarrhoea, pancreatitis, as well as several infections and cancers. The prevalence of comorbidities and their association with electrolytes is summarized in Table 1.

9212 (69%) took at least one drug with the potential to modify sodium or chloride as outlined in Table 2. Thiazide diuretics, potassium sparing diuretics but not loop diuretics were associated with significantly lower Na, whereas beta blockers seemed to increase both Na and Cl. A significant interaction between thiazide diuretics and age was identified. In patients older than 65 years, the sodium and chloride lowering effect of thiazide diuretics was significantly stronger (-1.61 mmol/L Na; $p < 0.0001$ and -2.34 mmol/L Cl; $p < 0.0001$ per DDD) than in younger patients (-0.80 mmol/L Na; $p = 0.003$ and -1.25 mmol/L Cl; $p < 0.0001$ per DDD). Antiepileptics with alleged SIADH-potential were associated with lower Na and Cl, whereas other antiepileptics were not.

Discussion

In an unselected population admitted to a representative tertiary referral centre several drugs, comorbidities, demographic factors, and weather conditions before admission have significant effects on serum sodium and chloride levels.

Distribution of electrolytes and syndrome of inappropriate ADH secretion (SIADH)

A large number of diseases, drugs and other precipitating causes for SIADH have been reported [8,13]. The occurrence and severity of SIADH seem to vary with the type of causative drugs: the prevalence is considered to be especially high in persons taking antidepressants [14], particularly serotonin reuptake inhibitors [15,16], antiepileptic drugs, especially carbamazepine and oxcarbazepine [17,18] and opioids [19,20].

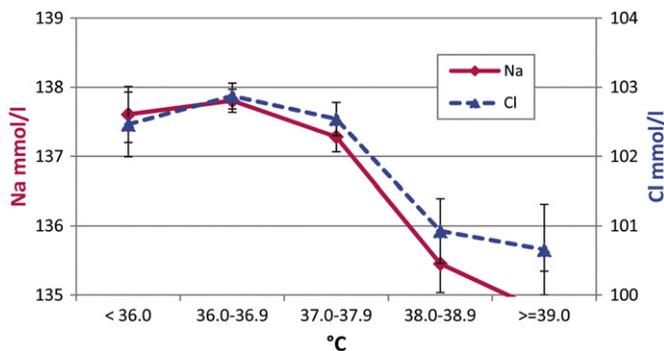


Fig. 4. Body temperature and Na/Cl. Na and Cl both decline above a threshold body temperature (adjusted model; $p < 0.0001$ for sodium and $p = 0.01$ for chloride). Error bars stand for 95% confidence limits.

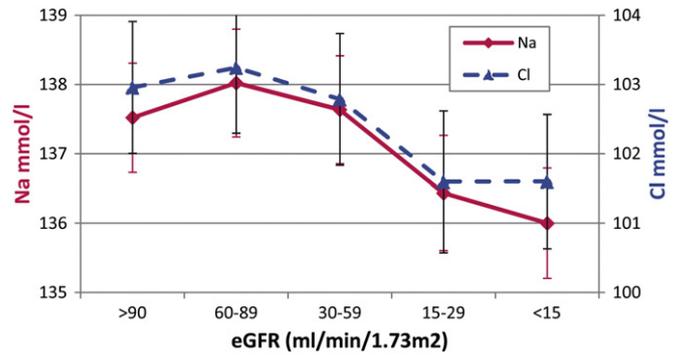


Fig. 5. Kidney function and Na/Cl. Na and Cl decline with worsening kidney function with a possible U-shaped association (adjusted model $p < 0.001$ for both electrolytes). eGFR: estimated glomerular filtration rate in mL/min/1.73 m². Error bars stand for 95% confidence limits.

Conversely the effect of SIADH can be abolished by vasopressin receptor antagonists (vaptans) which induce aquaresis [21]. As expected we were able to demonstrate significantly lower sodium in most of the aforementioned conditions. Nevertheless the average effect in the population was rather mild, which raises the question if only a predisposed subpopulation is vulnerable to develop SIADH or if the whole population is vulnerable. In the case of global susceptibility the whole distribution curve would be expected to shift to the left in exposed persons, whereas a bimodal distribution should result, if only a subset of the population reacts to the stimulus. Indeed we found strong evidence for such a bimodal distribution in our population with a subset of about 25% of exposed persons being at risk for the development of SIADH. It can be speculated, that a genetic variant is responsible for this differential reaction to SIADH risk factors. It is even conceivable, that these vulnerable persons could have somewhat lower sodium values even without exposure to a SIADH-risk factor. This could in part explain the clearly asymmetric distribution of the unexposed persons, which remained evident, even when patients with other sodium-lowering exposures were excluded from the analysis (data not shown). Further studies are needed to confirm these findings and to possibly identify a susceptibility locus in a genome-wide association study to predict this vulnerability for an individually tailored pharmacotherapy.

Weather conditions preceding admission

This is the first study to show a positive synergistic effect of both higher ambient temperature and higher air humidity during the week preceding measurement on sodium and chloride levels. In Switzerland

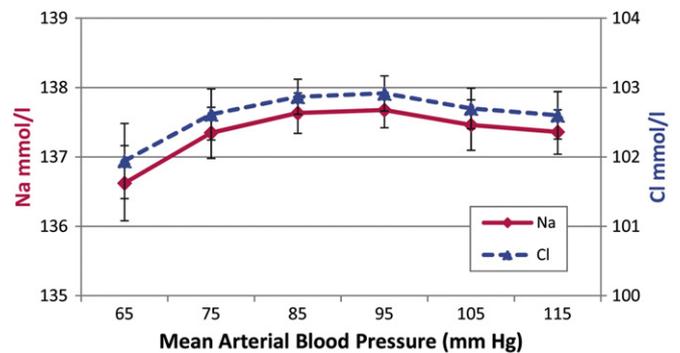


Fig. 6. Blood pressure and Na/Cl. Evidence for lower Na and Cl below a threshold blood pressure with a possible U-shaped association (adjusted model $p < 0.0001$ for both electrolytes). Mean arterial blood pressure is calculated by adding 1/3 of the difference between systolic and diastolic blood pressure to the diastolic blood pressure. Error bars stand for 95% confidence limits.

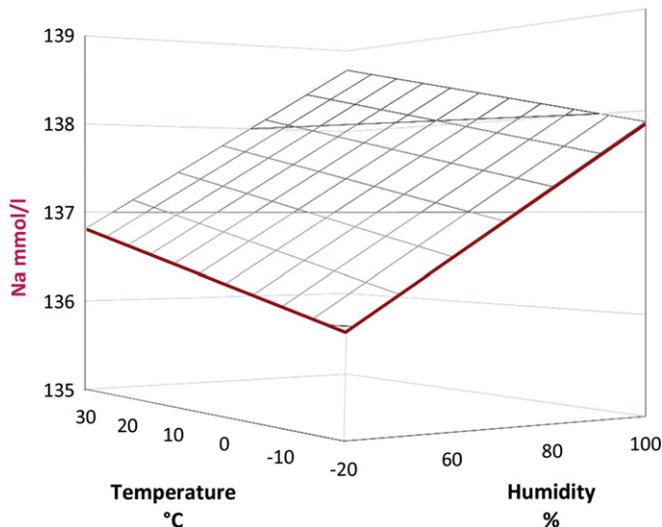


Fig. 7. Air humidity and ambient temperature. This figure shows the associations between sodium and air humidity (adjusted model; $p < 0.0001$) as well as ambient temperature ($p < 0.0001$) averaged over one week before hospital admission (solid red lines). The graph also shows the additive effect of these two parameters (grey grid). Similar results were obtained for chloride (data not shown).

all homes have heating in wintertime, but air conditioning is used only very rarely. Patients do not seem to sufficiently correct fluid losses by sweating and are hence expected to be slightly exsiccated in summer. We were not able to demonstrate an interaction between ambient temperature and drugs (e.g. diuretic use).

Renal function and blood pressure

We found an inverse U-shaped association between worsening kidney function and sodium as well as chloride. The shape of this curve suggests the presence of two competing mechanisms: sodium and chloride initially slightly increase presumably due to lower sodium and chloride excretion by the loss of functional nephrons, despite adaptive higher levels of natriuretic peptides [22]. In progressive renal

disease however, the reduced ability to reabsorb sodium and chloride by renal tubuli and the diminished capacity to dilute urine outweigh this effect and lead to a preferential retention of water compared to sodium and chloride with the net effect of hyponatraemia and hypochloreaemia [9].

Both higher body weight and higher mean blood pressure were associated with higher sodium and chloride. In an observational study it is impossible to identify, whether these associations represent causal effects or if they are induced by a common underlying mechanism. Indeed obesity, hypertension and sodium are highly interdependent: obesity raises blood pressure by: i) higher activity of the renin-angiotensin-aldosterone-axis, ii) higher activity of the sympathetic nervous system, iii) renal medullar compression (especially by visceral obesity), and iv) lower levels and efficacy of cardiac natriuretic peptides. All these factors increase renal sodium and chloride reabsorption and thus provoke a volume expansion [23,24]. Lower sodium and chloride in the highest blood pressure quantiles are best explained by pressure natriuresis overwhelming the autoregulation of the kidney [8,25].

Diuretics and antihypertensive drugs

Both thiazides and potassium-sparing diuretics showed a strong dose-dependent effect on sodium and chloride blood levels. In contrast loop diuretics had no significant effect on sodium but they also significantly albeit only mildly lowered chloride, presumably by inducing contraction alkalosis. In accordance with clinical experience the sodium-lowering effect of thiazide diuretics was significantly potentiated by older age [26].

Since ACE-inhibitors and angiotensin receptor blockers also reduce aldosterone activity it would be expected, that these drugs also induce lower sodium levels. However, after correction for the effect of lower blood pressure this effect was no longer significant. It could be speculated, that an additional inhibition of thirst and of ADH-release by these drugs may lead to mild hypovolaemia, which could counteract the aldosterone effect [27,28].

Diseases associated with oedematous states

Congestive heart failure (CHF) is often associated with non-osmotic stimulation of ADH and hyponatraemia [4,9,29,30]. Indeed in our

Table 1

Association between comorbidity and serum sodium as well as chloride in multivariate model (effect-size if disease is present).

Non-malignant diseases	N	% of patients	Association with sodium	p=	Association with chloride	p=
eGFR < 60 mL/min	3617	27.2	-0.38	<0.0001	-0.42	<0.0001
Congestive heart failure	1426	10.7	0.23	0.06	0.06	0.6
Diabetes	1799	13.5	-0.72	<.0001	-1.02	0.0001
Liver cirrhosis	249	1.9	-2.60	<.0001	-1.29	0.0002
Alcohol abuse	239	1.8	-1.05	0.0002	-2.06	<.0001
Vomiting ^a	113	0.9	-1.06	0.006	-2.85	<.0001
Diarrhoea	515	3.9	-1.47	<.0001	-1.55	<.0001
Gastrointestinal bleeding	356	2.7	-0.06	0.8	0.62	0.01
Pancreatitis	168	1.3	-0.13	0.0001	-1.38	0.0002
Sepsis	220	1.7	-1.03	<0.0001	-0.57	0.07
Pneumonia ^a	712	5.4	-1.71	<0.0001	-1.81	<.0001
COPD ^a	1351	10.2	-0.21	0.1	-0.49	0.001
Tuberculosis ^a	32	0.2	-2.27	0.005	-2.49	0.004
Malignant diseases						
Breast cancer	246	1.9	-0.36	0.2	-0.53	0.1
Lung cancer ^a	676	5.1	-1.34	<0.0001	-1.56	<0.0001
Pancreatic cancer ^a	137	1.0	-1.91	<0.0001	1.85	<0.0001
Urothelial cancer ^a	122	0.9	-0.99	0.02	0.04	0.9
Prostate cancer ^a	267	2.0	-0.58	0.04	-0.10	0.7
Ovarian cancer ^a	53	0.4	-3.09	<0.0001	-3.87	<0.0001
Myeloma	160	1.2	-1.22	0.008	0.48	0.3
Leukaemia	258	1.9	-0.47	0.2	0.08	0.8
Lymphoma	514	3.9	-0.20	0.4	-0.17	0.5

^a Stands for "SIADH-risk factor".

Table 2

Association between drug exposure and serum sodium as well as chloride in multivariate model (effect size for 1 defined daily dose [DDD] of drug).

<i>Diuretics and antihypertensive drugs</i>	N	% of patients	Association with sodium	p=	Association with chloride	p=
Thiazides	1108	8.3	−1.39	<0.0001	−2.05	<0.0001
Loop diuretics	2078	15.7	0.02	0.7	−0.48	<0.0001
Potassium sparing diuretics	933	7.0	−1.85	<0.0001	−0.98	<0.0001
Carbonhydrase inhibitors	35	0.3	2.19	0.1	4.06	0.008
Beta blockers	4001	30.1	0.57	<0.0001	0.28	0.03
ACE inhibitors	2430	18.3	−0.10	0.1	−0.03	0.7
Angiotensin II antagonists	931	7.0	−0.12	0.2	−0.10	0.4
<i>CNS-active drugs</i>						
Selective serotonin reuptake inhibitors ^a	527	4.0	−0.12	0.5	−0.10	0.6
Tricyclic antidepressants ^a	385	2.9	0.12	0.8	−0.05	0.9
Antiepileptics with SIADH-potential ^{a,b}	256	1.9	−1.04	0.02	−1.21	0.02
Antiepileptics without SIADH-potential ^c	123	0.9	−0.12	0.8	−0.02	1.0
Morphine ^a	1067	8.0	−0.17	<.0001	−0.21	<.0001
Typical neuroleptics	210	1.6	0.28	0.7	0.90	0.2
Atypical neuroleptics	80	0.6	0.23	0.5	0.42	0.2
<i>Selected other drugs</i>						
Heparinoids	862	6.5	−0.09	0.03	0.00	1.0
Calcineurin inhibitors	142	1.1	−0.51	0.004	0.24	0.3
Amiodarone ^a	264	2.0	−0.25	0.1	−0.50	0.1
Digoxin	423	3.2	−0.48	0.1	−1.10	0.001
Mycophenolate	65	0.5	−0.97	0.3	0.54	0.6
Corticosteroids	838	6.3	0.01	0.9	−0.03	0.3
Non-steroidal antiinflammatory drugs	758	5.7	0.01	1.0	0.17	0.3
Dopaminergic agents ^a	150	1.1	−0.02	1.0	−0.43	0.2
Theophylline	60	0.5	−0.42	0.4	−0.34	0.5
Insulin	528	4.0	0.56	0.02	0.24	0.3
Oral antidiabetics	956	7.2	−0.31	0.1	−0.19	0.3
Laxatives	889	6.7	0.03	0.5	0.08	0.05

^a Stands for "SIADH-risk factor".^b Antiepileptics with SIADH-potential: carbamazepine, oxcarbazepine, gabapentine, lamotrigine, levetiracetam.^c Antiepileptics without SIADH-potential: barbiturates, phenytoine, topiramate, valproic acid.

unadjusted model patients with CHF also showed lower sodium values. However after adjustment for the effect of drugs, comorbidity, kidney dysfunction and low blood pressure (partly induced by CHF) this effect was no longer detectable. In contrast liver cirrhosis was still associated with a potent additional sodium-lowering potential after adjustment for these variables. This could be explained by nitric oxide overproduction in cirrhosis, which leads to vasodilatation and secondary activation of the sympathetic nervous system and the RAAS as well as non-osmotic ADH release, which in turn leads to lower sodium levels [31,32].

Limitations of the study

This study is retrospective and strictly observational. Therefore causal inference has to be drawn with caution. The study focuses on the moment of hospital admission, which often occurs in a situation of physiologic instability. Therefore the effect size of the associations may not be representative of steady-state conditions.

Conclusions

Sodium and chloride levels at hospital admission are highly modulated by patient characteristics, drugs, and diseases. A strong additive effect of ambient temperature and air humidity on sodium and chloride levels implies that free water losses by sweat are not fully substituted by many patients. Our data further suggest that only a subgroup of about 25% of the European population show a higher susceptibility to SIADH triggers. Further studies are needed to identify the (genetic) basis of this bimodal distribution and the consequences for individual treatment decisions.

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