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Summary

BACKGROUND: Nutritional factors play an important role in the regulation of blood pressure and in the development of hypertension. In this analysis, we explored the associations of 24-hour urinary Na^+, K^+ and urea excretion with blood pressure levels and the risk of hypertension in the Swiss population, taking regional linguistic differences into account.

METHODS: The Swiss Survey on Salt is a population based cross-sectional study that included 1336 subjects from the three main linguistic regions (French, German and Italian) of Switzerland. Blood pressure was measured with a validated oscillometric Omron HEM 907 device. Hypertension was defined as current antihypertensive treatment or a mean systolic blood pressure >140 mm Hg and/or diastolic >90 mm Hg, based on eight blood pressure measurements performed at two visits. Na^+, K^+ and urea excretion were assessed in 24-hour urine collections. We use multiple logistic/linear regressions to explore the associations of urine Na^+, K^+ and urea with blood pressure / hypertension, taking into account potential confounders and effect modifiers.

RESULTS: The prevalence of hypertension was 30%, 26% and 17% in the German-, French- and Italian-speaking regions respectively, (p-value across regions <0.001). In the Swiss adult population, besides age, sex, and body mass index, urinary Na^+ excretion was positively associated with systolic blood pressure and hypertension. Urinary K^+ excretion tended to be negatively associated with blood pressure but this was not significant (p = 0.08). Hypertensive people had a higher 24-hour urinary Na^+/K^+ ratio than normotensive people (p = 0.003). Urinary urea excretion was associated with neither blood pressure nor hypertension. Participants from the German-speaking region had a higher likelihood of having a high systolic blood pressure.

CONCLUSIONS: We confirm a high prevalence of elevated blood pressure in Swiss adults, including regional differences. In Switzerland, urinary Na^+ excretion is associated positively with blood pressure and hypertension, independently of urinary K^+ and urea excretion. The observed differences in blood pressure levels across linguistic regions are independent of the urinary Na^+, K^+ and urea excretion.

Key words: nutrition; sodium; potassium; proteins; hypertension; population

Introduction

Among the many physiological and pathogenic factors that participate in the regulation of blood pressure and contribute to the development of hypertension, nutritional factors have

been shown to play an important role. Indeed, a high salt intake [1], moderate but sustained alcohol consumption [2], and overweight and obesity [3] are clearly associated with higher blood pressure in epidemiological surveys. In contrast, high intakes of potassium [1], magnesium and calcium, as well as of fibre and protein were found to be inversely associated with blood pressure in observational studies [4–6]. Although several of these associations are well established, some remain unclear, for example the role of protein intake on blood pressure and the risk of developing hypertension [5, 7]. Interventional studies on nutrition have also demonstrated favourable blood pressure effects of modifying dietary patterns, essentially of reducing sodium and increasing intake of potassium, unsaturated fats and protein [8–12]. Therefore, most international hypertension guidelines have introduced these nonpharmacological interventions as the first step in the management of newly diagnosed hypertensive patients [13–15].

Dietary patterns may vary considerably between populations. Indeed, the quality of food intake is subject to many influences, including the availability of healthy food products, regional dietary habits, social environment and, of course, the local cost of food. Thus, salt intake has recently been shown to vary markedly between regions of the world: in some countries individuals consume on average more than 20 g NaCl/day, whereas in others it may be well below 10 g NaCl/day [16]. Similarly, potassium intake is highly heterogeneous among populations, with a rather low intake in Asian populations, probably because the main component of the Asiatic diet(white rice) has very low potassium content (between 10 and 110 mg K^+/100 g) [16]. Therefore, the regional patterns of food intake might have an impact on population blood pressure levels and on the risk of developing hypertension. In this context, we explored the associations of 24-hour urinary Na^+, K^+ and urea excretion with the blood pressure level and the risk of hypertension in the Swiss population, taking into account the three linguistic regions of Switzerland with their specific food habits: the German, French and Italian regions.

Subjects and methods

The Swiss Survey on Salt is a cross-sectional population-based survey conducted in 9 out of 26 cantons (Vaud, Geneva, Valais, Fribourg, Luzern, Basel, Zürich, St Gallen and Ticino), which covered the three main linguistic regions of Switzerland. This survey was part of a nationwide programme of the Swiss Federal Office of Public Health that aimed at reducing salt intake in the population. To be included, participants had to be permanent residents of Switzerland and aged 15 years or older. Recruitment took place from January 2010 to March 2012 and was based on a two-level sampling strategy similar to the one used for the Swiss Health National Surveys conducted every five years [17]. The Swiss Statistical Office provided a list of randomly selected households from the Swisscom fixed-line phone directory, which is updated every 3 months, separately for each canton. (Swisscom is a major telecommunication provider in Switzerland, mainly owned by the Swiss state.) This directory is the largest and most complete directory of the country and covers the majority of Swiss households. In a first step, we contacted these households by sending an information letter followed by phone calls with a maximum of three attempts on different days. In a second step, we randomly selected, during the phone call, one person from the household to take part in the study, using a computer-

generated random number. We recruited participants in eight predefined sex- and age-strata (men and women aged 15–29, 30–44, 45–59 and ≥60 years). Because of difficulties to recruit young and middle-aged people, limited convenience sampling was used in selected centres. Two hundred and seventy-seven participants out of 1515 who completed the survey (18%) were recruited by convenience sampling (primarily using leaflets targeting secondary or professional schools or universities). Overall participation rate was 10%. This means that we could include one participant in 10% of the contacted households. Compared with the overall population, subjects from the Italian region were slightly overrepresented in order to have a clinically relevant number of results.

Data collection

The study was conducted for the primary purpose of estimating dietary salt intake and hypertension prevalence in the Swiss adult population. Participants were told that the study was about "lifestyle and blood pressure" and specific care was taken not to mention salt intake at the time of enrolment, to avoid a change in dietary habits before urine collection. The study participants attended the study centre on two occasions: one baseline visit before and one follow-up visit after completion of the urine collection (within 24 hours).

Trained healthcare professionals collected data. At the baseline visit, participants filled in a questionnaire about socio-demographic factors, medical history, lifestyle and medication. Questions about alcohol intake were asked, including units of wine, beer and spirits consumed in the past 7 days. A standard unit was defined as a glass of wine, a bottle of beer or a shot of spirits, approximating 10–12 g ethanol [18]. We classified participants into three mutually exclusive categories according to the total number of alcohol units reported in the past 7 days (0, 1–6, ≥7 units per week). Smoking status was classified as current smoker versus nonsmoker.

Weight was measured in light indoor clothing to the nearest 100 g with a medical scale and height was measured to the nearest centimetre with a wall-mounted stadiometer. Body mass index (BMI) was calculated as weight divided by height in metres squared. Overweight was defined as BMI ≤25 kg/m² and <30 kg/m², and obesity as BMI ≥30 kg/m². Blood pressure was measured five times at each visit in the left arm after at least 5 minutes rest in the seated position, with a clinically validated automated oscillometric device (Omron® HEM-907, Matsusaka, Japan) with a standard cuff, or a large cuff if arm circumference was ≥33 cm [19]. The average of eight blood pressure readings (the second to fourth reading at each visit) was used for analysis. Hypertension was defined as mean systolic blood pressure ≥140 mm Hg or mean diastolic blood pressure ≥90 mm Hg or use of antihypertensive medication.

Participants were given two 3-litre plastic bottles and standard instructions on how to collect a 24-hour urine specimen. When brought back at the second visit, urine was weighed, mixed, sampled in small aliquots and immediately frozen (–20°C) at each study centre. During the second visit an optional nonfasting blood sample was collected. Urine and blood samples were subsequently sent to the Central Chemical Laboratory of Lausanne University Hospital (CHUV, Lausanne, Vaud, Switzerland) for centralised analyses with use of standard methods and stringent internal quality controls. This Central Chemical Laboratory is ISO/CEI 17025 and ISO 15189 accredited and is regularly checked by the "Centre Suisse de Contrôle de Qualité" (CSCQ – Swiss Centre for Quality Control).

Plasma and urinary electrolytes were measured by means of indirect potentiometry; urine urea was measured with the urease-GLDH method and serum and urinary creatinine with the Jaffé kinetic compensated method. We measured Na^+ excretion in 24-hour urine and used the following conversion factor to estimate 24-hour urinary salt excretion: 1 mmol of Na^+ corresponds to 0.0584 g of salt (NaCl). Protein intake was estimated by using the Maroni formula [20], based on measured 24-hour urinary urea excretion, a method considered as a valid biomarker [21, 22]. Twenty-four-hour urinary K^+ excretion was used to estimate dietary K^+ intake [23]. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula.

The quality of 24-hour urine collections was verified from the urinary creatinine excretion adapted for sex and weight. The reproducibility of urinary Na^+ excretion was verified in a small subset of participants (n = 57) who made two collections. The coefficient of correlation between the two collections was 0.69 for Na^+ excretion and 0.71 for urinary volume. For the analysis, 97 subjects were excluded because of incomplete urine collection. Criteria for exclusion were: a urinary volume less than 300 ml/24 h (n = 3), participants reporting not having collected all 24-hour urine (n = 29) and a urinary creatinine excretion equal to or below the sex-specific fifth percentile: 0.121 mmol/kg/24 h in men and 0.082 mmol/kg/24 h in women (n = 77).

Participants answered the following questions at the end of the visit:

- "Do you consider that a diet rich in salt has an impact on your health" (possible answers: yes, no, do not know);
- "According to you, for which diseases is there a direct link with salt intake?" (arterial hypertension, cardiac diseases, diabetes, irritable bowel syndrome, no disease, overweight/obesity, myocardial infarction, stroke, tuberculosis, other);
- "Which type of salt do you use at home?" (salt without supplements, iodised salt, salt enriched with iodine and fluoride, spicy salt, do not know);
- "Do you usually try to limit your dietary salt intake?" (yes/no);
- "Are you usually interested in your daily dietary salt intake?" (yes/no);
- "What is the maximum amount of salt a Swiss adult should eat on a daily basis?" (5 g, 7.5 g, 10 g, 15 g, do not know);
- "Do you usually add salt to your meals at home / outside of home?" (always, usually, occasionally, rarely);
- "Rank the following items with respect to their salt content, taking portion size into account" (one tea spoon of dressing sauce [15 g], one medium-sized bowl of soup [300 ml], one medium-sized slice of bread [30 g], one tea spoon of Knorr Aromat [19 g]);
- "What is the main source of salt in the daily diet of a standard person living in Switzerland?" (salt added to the meal at the table, fast foods or processed meals, mineral waters, breads, meat and cold cuts, cheeses, soups, do not know).

Ethics

The ethics committee of each centre approved the study. Every participant gave written informed consent; for participants under the age of 18, the written informed consent of a parent was also obtained. Each participant received compensation of 20 Swiss Francs (about 20 Euros or US dollars) upon completion of the study.

Statistical analyses

Sample size calculation was based on the primary outcome of interest, namely dietary salt intake, aiming at being able to detect (with 80% power at a 5% two-sided type 1 error rate) a 10% difference in salt intake in each sex strata, in the four prespecified age groups (15–29 years, 30–44 years, 45–59 years, ≥60 years) and in the two larger linguistic regions (German vs French). Mean and standard deviation were used to describe unadjusted continuous variables, and percentages to describe dichotomous or categorical variables. Prevalence was described proportions across sex and age groups. Analysis of variance (ANOVA) and the chi-squared test were used to compare the characteristics of groups where appropriate. Multiple logistic regression was conducted with hypertension as the dependent variable, including linguistic region, age, sex, smoking status, alcohol consumption, BMI, eGFR, serum urea, serum uric acid, serum Na^+, serum K^+, corrected serum Ca^{++}, urinary excretion (Na^+, K^+, urea, creatinine) and urine volume. Multiple linear regression was conducted with systolic blood pressure as the dependent variable, including linguistic region, age, sex, smoking status, alcohol consumption, BMI, eGFR, serum urea, serum uric acid, serum Na^+, serum K^+, urinary excretion (Na^+, K^+, urea, creatinine) and urinary volume. To ease interpretation of the findings, sex-specific tertiles of serum and urine Na^+, K^+ and urea were used instead of continuous covariates. For both models, a backward procedure was used, starting with a full model, and then removing, one at a time, nonsignificant covariates. Age, sex, BMI, urine volume and duration of urine collection as well as urinary creatinine excretion were forced into the models. The choice of covariates was based on clinical knowledge and previous research, as well as an interest in exploring the available nutrition biomarkers. A nonparametric test was used to assess trend (nptrend function in Stata) across sex-specific quintiles of systolic blood pressure.

Results

The characteristics of the 1336 subjects enrolled in the survey are shown, by linguistic region, in table 1 . The prevalence of hypertension was 30%, 25% and 17% in the German-, French- and Italian-speaking regions, respectively (p-value for differences across regions <0.001). Hypertension prevalence by sex and age groups is presented in figure 1.
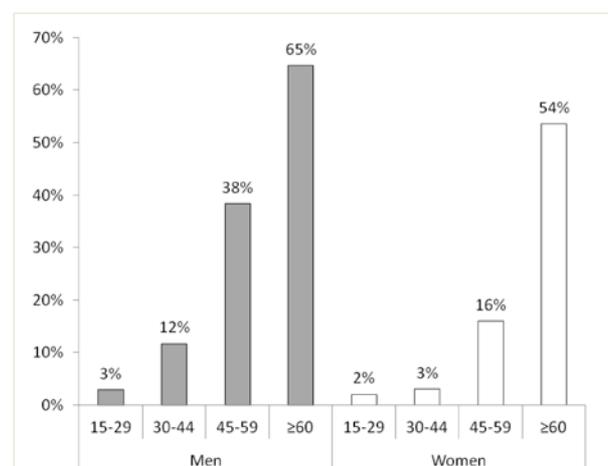

Figure 1: Hypertension prevalence by sex and age groups.

Table 1: Participants' characteristics by linguistic region (n = 1336).

	German	French	Italian	p-value
No.	709	428	199	
Age (years)	48.8 (18)	47.8 (18.1)	45.3 (18.4)	0.06
Sex (% women)	0.51 (0.5)	0.52 (0.5)	0.51 (0.5)	0.92
Current smoking (%)	0.29 (0.45)	0.3 (0.46)	0.26 (0.44)	0.40
Regular alcohol consumption (%)	0.84 (0.36)	0.86 (0.35)	0.78 (0.42)	0.04
Education level (%)*				0.02
Basic	13.8	16.8	18.6	
Intermediate	42.9	43.7	51.3	
High	43.3	39.5	30.1	
BMI (kg/m^2)	25.3 (4.3)	25.5 (5.1)	24.5 (4.2)	0.03
Hypertension (%)	0.30 (0.46)	0.26 (0.44)	0.17 (0.38)	0.001
SBP (mm Hg)	126.1 (15.9)	122.5 (14.9)	120.5 (15)	<0.001
DBP (mm Hg)	75.5 (10.2)	74.2 (9.8)	69.9 (9.9)	<0.001
Serum Na$^+$ (mmol/l)	141.7 (1.9)	142.0 (2.1)	142.2 (1.9)	<0.001
Serum K$^+$ (mmol/l)	4.25 (0.45)	4.12 (0.34)	4.05 (0.31)	<0.001
Corrected serum Ca^{++} (mmol/l)	2.3 (0.09)	2.28 (0.12)	2.28 (0.09)	<0.001
Serum urea (mmol/l)	5.4 (1.77)	5.6 (2.07)	5.8 (1.71)	0.02
Serum uric acid (µmol/l)	305 (82)	309 (90)	293 (80)	0.08
Serum creatinine (µmol/l)	80 (16.9)	79 (19.3)	80 (16.3)	0.50
eGFR† (ml/min/1.73m^2)	89 (19.5)	91 (19)	91 (20.1)	0.13
Urine volume (ml/1440 min)	2139 (943)	1747 (796)	1668 (805)	<0.001
Urine creatinine (mg/kg/24 h)	19.0 (5)	19.1 (5.1)	20.1 (5.7)	0.03
Urine Na$^+$ (mmol/1440 min)	160 (66)	151 (71)	158 (72)	0.09
Urine K$^+$ (mmol/1440 min)	68.0 (24.8)	65.7 (24.1)	63.3 (27.3)	0.05
Urine Ca^{++} (mmol/1440 min)	4.0 (2.34)	4.21 (2.5)	4.18 (2.57)	0.25
Urine urea (mmol/1440 min)	362 (136)	371 (146)	387 (152)	0.12

BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; SBP = systolic blood pressure
Data are means (standard deviation) unless specified otherwise.
* Basic = mandatory school or less; intermediate = apprenticeship or high school; high = higher specialized education or university.
† Based on Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation.

Note the very high prevalence in men and women aged ≥60 years (65 and 54%, respectively). Several other differences were observed across linguistic regions: the level of education was lower in Italian-speaking subjects; systolic and diastolic blood pressure, urinary volume, serum potassium and urinary potassium excretion were higher in German-speaking participants. Urinary salt excretion was 7.2 ± 3.1, 8.1 ± 3.4 and 7.6 ± 3.2 g/24 h in women and 10.3 ± 4.3, 10.7 ± 4.1 and 10.5 ± 4.3 g/24 h in men from the French-, German- and Italian-speaking regions, respectively.

Nutritional factors and their association with blood pressure

Table 2 shows the results of the multiple linear regressions for systolic blood pressure in the entire set of subjects. As expected, age, sex, BMI and smoking were significantly associated with blood pressure. In addition, a high education level was associated with a lower blood pressure. Systolic blood pressure was significantly higher in participants from the German-speaking area than in those from the French- and Italian-speaking regions.

Table 2: Multiple linear regression for systolic blood pressure (n = 1336).

Variables		Beta coefficient	95% confidence limits	p-value
Age (years)		0.37	0.31; 0.44	<0.001
Sex (men vs women)		−9.53	−11.46; −7.6	<0.001
Language	French	ref.		
	German	2.91	1.34; 4.47	<0.001
	Italian	−0.86	−2.98; 1.26	0.43
Current smoking (yes/no)		−1.63	−3.15; −0.1	0.04
Antihypertensive treatment (yes/no)		4.12	2.02; 6.21	<0.001
Body mass index (kg/m^2)		0.33	0.13; 0.53	<0.001
Alcohol consumption	<1 unit/week	ref.		
	<1 unit/day and >1 unit/week	0.56	−1.13; 2.24	0.52
	≥1 unit/day	0.57	−1.52; 2.65	0.60
Education	Basic	ref.		
	Medium level	−2.3	−4.29; −0.32	0.02
	High level	−3.5	−5.55; −1.45	0.001
Serum uric acid	Tertile 1*	ref.		
	Tertile 2	0.88	−0.78; 2.53	0.30
	Tertile 3	1.86	0.04; 3.68	0.05
Serum urea (mmol/l)	Tertile 1	ref.		
	Tertile 2	−1	−2.75; 0.74	0.26
	Tertile 3	−1.35	−3.38; 0.68	0.19
Estimated protein intake	Tertile 1	ref.		
	Tertile 2	−0.52	−2.41; 1.38	0.59
	Tertile 3	−0.03	−2.46; 2.4	0.98
Serum Ca^{++}	Tertile 1	ref.		
	Tertile 2	0.23	−1.42; 1.89	0.78
	Tertile 3	0.96	−0.76; 2.68	0.27
Urine Ca^{++}	Tertile 1	ref.		
	Tertile 2	2.01	0.28; 3.74	0.02
	Tertile 3	1.11	−0.78; 3	0.25
Serum Na$^+$	Tertile 1	ref.		
	Tertile 2	0.4	−1.34; 2.13	0.65
	Tertile 3	0.88	−0.74; 2.5	0.29
Urine Na$^+$	Tertile 1	ref.		
	Tertile 2	0.45	−1.28; 2.18	0.61
	Tertile 3	2.81	0.81; 4.81	0.01
Serum K$^+$	Tertile 1	ref.		
	Tertile 2	−0.89	−2.47; 0.69	0.27
	Tertile 3	−0.99	−2.73; 0.75	0.27
Urine K$^+$	Tertile 1	ref.		
	Tertile 2	−0.84	−2.62; 0.95	0.36
	Tertile 3	−1.89	−3.98; 0.19	0.08
Urine volume (ml/24 h)		0.54	−0.32; 1.4	0.22
Urine creatinine (mg/kg/24 h)		0.06	−0.16; 0.29	0.59

The p-values from the likelihood ratio test are: p = 0.0001 for linguistic region; p = 0.004 for education level; p = 0.07 for urine Ca^{++} tertiles; p = 0.01 for urine Na$^+$ tertiles; p = 0.08 for urine K$^+$ tertiles; p >0.10 for tertiles of serum Ca^{++}, K$^+$, Na$^+$, uric acid and urea, for alcohol consumption and estimated protein intake.

Serum sodium, potassium and urea were not associated with blood pressure levels but participants in the highest tertile of serum uric acid had a higher systolic blood pressure. Urinary Na$^+$ excretion was associated positively with systolic blood pressure. An inverse trend was observed with urinary K$^+$ excretion but the association did not reach statistical significance. In the fully adjusted model, the association was borderline significant (p = 0.08) (fig. 2). Urinary urea excretion was not associated with systolic blood pressure. The associations between the various clinical and nutritional factors and sex-specific quintiles of systolic blood pressure are presented in supplementary table S1 (appendix). Note that the urinary

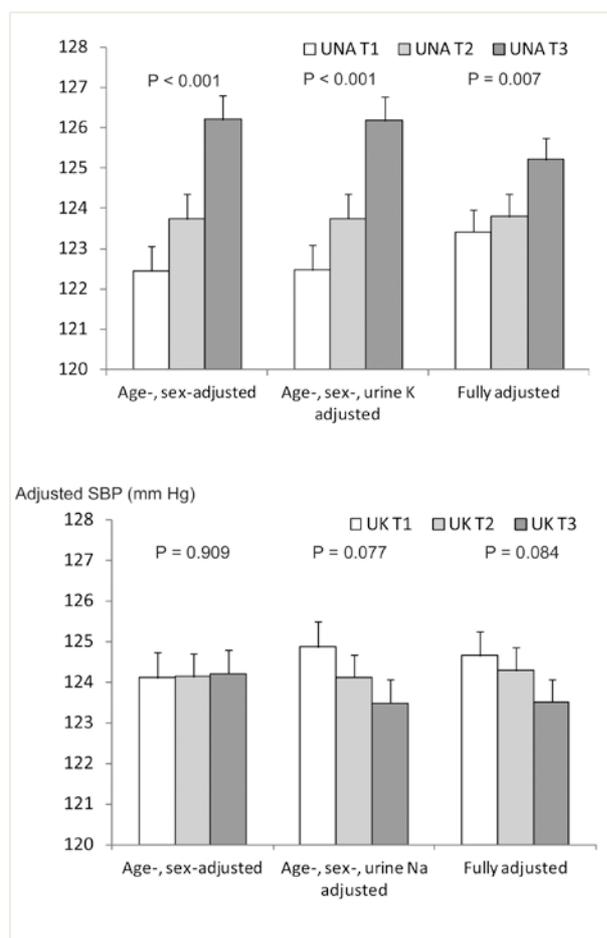Na$^+$/K$^+$ ratio was strongly associated with systolic blood pressure.

Figure 2: Adjusted systolic blood pressure (mm Hg) by sex-specific tertiles of 24-hour urinary K$^+$ (left) or Na$^+$ (right) excretion. Fully adjusted models include age, sex, linguistic region, smoking, antihypertensive treatment, body mass index, alcohol consumption, education, sex-specific serum uric acid, urea, Na$^+$, K$^+$ and Ca^{++} tertiles, sex-specific 24-hour urinary urea, Ca^{++}, Na$^+$ and K$^+$ excretion tertiles, 24-hour urine volume and urinary creatinine excretion per kg body weight. The p-values are from a test for linearity across tertiles in the corresponding model, coding tertiles using 1, 2 and 3. For 24-hour urinary Na$^+$, tertiles 1 (n = 437), 2 (n = 449) and 3 (n = 450) correspond to 93, 148 and 228 mmol, respectively. For 24-hour urinary K$^+$, tertiles 1 (n = 435), 2 (n = 459) and 3 (n =4 42) correspond to 43, 65 and 92 mmol, respectively.

Nutritional factors and their association with hypertension

In our population, the overall prevalence of hypertension was 32.3% in men and 25.6% in women. In men, the regional prevalence was 27.9%, 36.8% and 23.8% in the French, German and Italian regions respectively. For women, these figures were 18.1%, 21.4% and 12.6% respectively. Table 3 shows the multiple logistic regressions for hypertension in the entire population. Age, sex, BMI and urinary Na$^+$ excretion were positively associated with hypertension. Serum uric acid was positively associated with hypertension, but a negative association was found between serum potassium and hypertension. Urinary K$^+$ and urea excretion (estimated protein intake) and linguistic region were not independently associated with hypertension. Unadjusted selected clinical characteristics of normotensive and hypertensive participants and age-, sex-, BMI- and linguistic region-adjusted means of plasma and urinary electrolytes in normotensive subjects are described in table S2 (appendix).

Hypertensive patients were older, more frequently men, smokers and overweight. They also presented higher serum uric acid and lower urinary K$^+$ excretion. There was no difference in urinary Na$^+$ excretion between hypertensive and normotensive participants, but the Na$^+$/K$^+$ ratio was higher in hypertensive participants.

Table 3: Multivariable logistic regression for hypertension (n = 1336).		Odds ratio	95% confidence limits	p-value
Variables				
Age (years)		1.09	1.07; 1.11	<0.001
Sex (men vs women)		0.32	0.19; 0.52	<0.001
Education level	Basic	1		
	Intermediate	0.86	0.54; 1.38	0.53
	High	0.82	0.5; 1.34	0.44
Language	French	1		
	German	1.26	0.86; 1.84	0.23
	Italian	0.72	0.42; 1.24	0.24
Current smoking (yes/no)		0.72	0.51; 1.03	0.08
Alcohol consumption	<1 unit /week	1		
	<1 unit/day and >1 unit/week	0.97	0.63; 1.47	0.88
	≥1 unit/day	0.91	0.55; 1.49	0.7
Body mass index (kg/m^2)		1.14	1.09; 1.19	<0.001
eGFR (ml/min/1.73 m^2)		1	0.99; 1.02	0.54
Serum uric acid	Tertile 1	1		
	Tertile 2	1.37	0.89; 2.1	0.15
	Tertile 3	1.79	1.16; 2.78	0.01
Serum urea (mmol/l)	Tertile 1	1		
	Tertile 2	0.77	0.49; 1.20	0.24
	Tertile 3	0.81	0.49; 1.34	0.41
Estimated protein intake	Tertile 1	1		
	Tertile 2	0.83	0.53; 1.32	0.44
	Tertile 3	0.79	0.44; 1.42	0.43
Serum Ca^{++}	Tertile 1	1		
	Tertile 2	1.01	0.67; 1.54	0.95
	Tertile 3	1.84	1.22; 2.78	0.004
Urine Ca^{++} (mmol/24 h)	Tertile 1	1		
	Tertile 2	0.78	0.51; 1.18	0.24
	Tertile 3	0.76	0.49; 1.19	0.23
Serum K$^+$	Tertile 1	1		
	Tertile 2	0.58	0.39; 0.86	0.01
	Tertile 3	0.58	0.38; 0.88	0.01
Urine K$^+$ (mmol/24 h)	Tertile 1	1		
	Tertile 2	1.13	0.73; 1.76	0.58
	Tertile 3	0.88	0.53; 1.44	0.60
Serum Na$^+$	Tertile 1	1		
	Tertile 2	0.9	0.59; 1.39	0.64
	Tertile 3	0.76	0.51; 1.13	0.18
Urine Na$^+$ (mmol/24 h)	Tertile 1	1		
	Tertile 2	1.33	0.87; 2.03	0.19
	Tertile 3	1.99	1.23; 3.23	0.01
Urine volume (ml/24 h)		0.99	0.80; 1.23	0.95
Urine creatinine (mg/kg/24 h)		0.96	0.90; 1.01	0.14

eGFR = estimated glomerular filtration rate (Chronic Kidney Disease-Epidemiology Collaboration formula)
All tertiles are sex-specific (i.e., they were generated separately for women and for men).
The p-values from the likelihood ratio test are: p = 0.09 for linguistic region; p = 0.03 for serum uric acid tertiles; p = 0.003 for serum Ca^{++} tertiles; p = 0.03 for serum urea tertiles; p = 0.01 for serum K$^+$ tertiles; p = 0.02 for urine Na$^+$ tertiles; p >0.10 for serum Na$^+$ tertiles, urine K$^+$ tertiles, urine Ca^{++} tertiles, education level, reported alcohol consumption and estimated protein intake.

When questioned on the effect of salt on health, participants from the German-speaking region were less aware of the impact of salt on blood pressure (77.3% in the German vs 84.9% in the French and 88.0% in Italian part of Switzerland) and cardiovascular complications than participants from other regions (p <0.01). Participants from the German-speaking region reported less frequently the use of salt without supplements (30.6%, p<0.05), but more frequently use of salt with iodine (42.4% vs 29% in French and 27.3% in Italian speaking participants, p<0.001) or spicy salt (46.9% vs 26.3% in French and 21.8% in Italian participants, p<0.001). They were also less inclined to try to limit the quantity of salt in their diet (54.2% in German-speaking subjects vs 61.4% and 66.8% in French- and Italian-speaking subjects, respectively).

Discussion

The main goal of this study was to assess the association of several dietary factors with blood pressure and hypertension in Switzerland, a country of 8 million inhabitants with three main linguistic areas that have specific dietary habits but a relatively comparable standard of living and economic status. The data obtained in these analyses first tend to confirm the prominent roles of age, sex, BMI and sodium and potassium intake on blood pressure and hypertension. They also confirm the association between serum uric acid and hypertension. Globally, we did not find any association between protein intake and blood pressure or hypertension. We also observed regional differences that were independent of the explored dietary factors.

Dietary factors and blood pressure

Among all components of a normal diet, sodium is certainly the most important factor because of its crucial physiological role in the regulation of blood volume and blood pressure. Large epidemiological surveys have reported an association between urinary sodium excretion, as an indirect marker of sodium intake, and blood pressure [24, 25]. This association was confirmed recently with the data of the Prospective Urban Rural Epidemiology study (PURE) in which 102 216 adults from 18 countries were investigated. Indeed, the authors found an increase of 2.11 mm Hg in systolic and 0.78 mm Hg in diastolic blood pressure for each 1-g increment in estimated sodium excretion [1]. In this latter study, the slope of association was steeper in hypertensive individuals and in subjects older than 55 years. In accordance with these observations, we also found a significant association between urinary sodium excretion and systolic blood pressure in Swiss participants.

The role of potassium in the regulation of blood pressure and in the development of hypertension has long been underestimated. However, several studies compiled in a meta-analysis published as long ago as 1997 had found that a low potassium intake plays an important role in the genesis of high blood pressure [26]. In this meta-analysis, potassium supplementation had a favourable impact on blood pressure, particularly in studies in which participants were concurrently exposed to a high sodium intake. More recent data have demonstrated that an increased potassium intake can not only reduce blood pressure in people with hypertension, but also reduce the risk of stroke [27]. In a recent large Chinese survey, a higher consumption of fresh fruit was associated with a lower blood pressure and a reduced prevalence of cardiovascular complications and mortality [6]. A *post-hoc* analysis of the ONTARGET and TRANSCEND studies has even suggested that a high potassium intake may actually retard the progression of

chronic kidney diseases [28]. In the PURE study, urinary potassium excretion was also inversely correlated with blood pressure and the slope of the association was again steeper in older and in hypertensive subjects [1]. Moreover, the influence of potassium on blood pressure was greater in subjects with a high sodium intake. In our population, urinary potassium excretion was indeed negatively associated with blood pressure, but the association did not reach statistical significance. However, systolic blood pressure was not associated with urinary potassium excretion unless urinary sodium excretion was included in the model. In that case, systolic blood pressure was lower in the highest tertile of potassium excretion (p = 0.08). These results further suggest a strong interaction between sodium and potassium intake and blood pressure, the impact of the former being in part dependent on the background intake of the latter. In that respect, one could question whether the assessment of the urinary Na^+/K^+ ratio, which includes both factors, would not be a better index than either sodium or potassium alone in the evaluation of blood pressure outcomes and incident hypertension. Indeed, studies have suggested that the Na^+/K^+ ratio correlates better with blood pressure than urinary sodium alone [29–31], and several authors have proposed increasing potassium intake in addition to a moderate reduction of sodium intake to lower blood pressure (reviewed recently by Perez and Chang [32]). In our study, the urinary Na^+/K^+ ratio was indeed better correlated with sex-specific quintiles of systolic blood pressure than was urinary sodium excretion alone, as presented in table S1. Among the other dietary parameters investigated in our study, protein intake was not associated with systolic or diastolic blood pressure.

Dietary factors and hypertension

In epidemiological surveys, a high urinary sodium excretion is associated with hypertension. In our multivariable logistic regression for hypertension, urinary sodium excretion (besides age, sex and BMI) was positively associated with hypertension. A negative association was found with serum potassium but not urinary potassium excretion. However, when the clinical characteristics of hypertensive subjects in our population were compared with those of the normotensive subjects, a greater age, a greater proportion of men and a higher BMI characterised hypertensive subjects. Interestingly, urinary sodium excretion was comparable in normotensive and hypertensive subjects, but the urinary excretion of potassium and urea were significantly lower in hypertensive subjects. The Na^+/K^+ ratio was also higher in hypertensive than in normotensive subjects in our population. These observations are in accordance with previous publications suggesting that a low potassium intake [27] and a low protein intake are associated with a higher blood pressure and hypertension [7, 10, 33]. The precise mechanisms whereby protein intake influences blood pressure and the risk of hypertension are not completely understood. However, a secondary analysis of the PREMIER trial, a randomised clinical trial designed to determine the effect of two multicomponent lifestyle interventions on blood pressure [34], have suggested that an increased intake of plant protein rather than animal proteins may have a favourable effect in lowering blood pressure and preventing the development of hypertension [35].

The higher systolic blood pressure levels observed in the German-speaking region compared with the other linguistic regions was independent of 24-hour urinary sodium, potassium and urea excretion, which suggests that a factor other than salt, potassium and protein intake contributed to the

higher prevalence of hypertension in the German-speaking participants. Studies on the regional disparities in elevated blood pressure prevalence in the United States have shown that many factors other than salt and potassium intake may play a role, including the intake of riboflavin, niacin, iron and vitamins A, C and B6 [36]. Moreover, the environment, socio-economic status, educational level and, of course, the genetics of the population may play an important role in the development of hypertension [37] An additional factor may be the perception of the role of dietary factors in causing hypertension and cardiovascular complications, which may have an impact on attitudes to prevention within the populations.

Thus, in the 2007 Swiss Health Survey, which enrolled 17 879 subjects in seven administrative regions of Switzerland [17], cardiovascular risk factor screening and management differed between regions and the differences could not be accounted for by differences in population age, gender, educational level or migrant status, suggesting that other factors such as local habits might be at stake. In this survey, the prevalence of hypertension was higher in some areas of the German region, but detection and management was comparable in all regions. The detection and treatment of dyslipidaemia and diabetes was significantly lower in German-speaking regions than in the French- and Italian-speaking areas. However, there was no direct measurement of blood pressure, glucose or lipids in this survey and the presence of hypertension, diabetes and dyslipidaemia was based on a positive response to the question "Did a doctor or a healthcare professional tell you that you have high blood pressure, diabetes or a high cholesterol?" A recent publication by Chammartin et al. demonstrated that cardiovascular mortality is higher in the German-speaking areas of Switzerland than in the French- and Italian-speaking cantons [38]. This observation would fit with our findings, as blood pressure and hypertension are major determinants of cardiovascular morbidity and mortality.

The following limitations have to be taken into account in the interpretation of this study. First, this was a cross-sectional study, which precludes inference of causality. Second, the low participation rate limits the external validity of our findings. The low participation rate in this study may be explained by the unattractiveness of 24-hour urine collection and the two-stage sampling strategy, which reflects that fact that the person contacted by phone was not automatically the one randomly selected to enter the study. It is, however, unlikely that the observed relationships would be substantially different in nonparticipants. Dietary information was not collected via a standardised and detailed food-frequency questionnaire, which may result in incomplete and/or imprecise dietary information.

In conclusion, salt intake is high in the three linguistic regions of Switzerland but it is comparable to that of most central European countries. Our data confirm the important influence of sodium intake on blood pressure and the prevalence of hypertension in the Swiss context. We observed higher blood pressure levels in the German-speaking region, even after taking urinary sodium, potassium and urea excretion into account, which suggests that other factors, possibly dietary as well, are needed to fully explain regional differences in blood pressure.

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Appendix: Supplementary tables

Table S1: Participants' characteristics by sex-specific quintiles of systolic blood pressure (n = 1336).

Covariate	Q1 (n = 265)	Q2 (n = 262)	Q3 (n = 268)	Q4 (n = 269)	Q5 (n = 272)	p-value trend
Serum Na$^+$ (mmol/l)*	141.8 (141.6; 142)	141.9 (141.7; 142.1)	141.7 (141.5; 141.9)	142 (141.7; 142.2)	141.9 (141.6; 142.2)	0.45
Serum K$^+$ (mmol/l)*	4.21 (4.17; 4.25)	4.19 (4.14; 4.23)	4.17 (4.12; 4.22)	4.17 (4.13; 4.22)	4.17 (4.12; 4.22)	0.23
Serum Ca^{++} (corrected) (mmol/l)*	2.29 (2.28; 2.31)	2.30 (2.29; 2.31)	2.30 (2.29; 2.31)	2.31 (2.30; 2.32)	2.30 (2.29; 2.31)	0.06
Serum urea (µmol/l)*	5.34 (5.17; 5.51)	5.29 (5.13; 5.45)	5.23 (5.06; 5.4)	5.31 (5.14; 5.49)	5.16 (5; 5.31)	0.07
Serum uric acid (µmol/l)*	287 (280; 294)	292 (285; 300)	293 (285; 301)	297 (290; 305)	296 (289; 304)	0.08
eGFR (ml/min/1.73 m^2)	90.9 (89.3; 92.6)	89.2 (87.6; 90.8)	89.3 (87.8; 90.8)	89.2 (87.7; 90.7)	90.9 (89.4; 92.5)	0.83
Urine Na$^+$ (mmol/24 h)*	143 (136; 150)	143 (137; 151)	152 (144; 159)	155 (148; 162)	154 (148; 161)	0.003
Urine K$^+$ (mmol/24 h)*	63.3 (60.7; 66)	64.9 (62.1; 67.8)	65.8 (63.2; 68.4)	64.2 (61.6; 66.8)	62.8 (60.2; 65.5)	0.63
Urine Na$^+$/K$^+$ ratio	2.32 (2.21; 2.44)	2.27 (2.16; 2.38)	2.36 (2.24; 2.47)	2.48 (2.38; 2.59)	2.53 (2.42; 2.65)	<0.001
Urine urea (mmol/24 h)*	345 (332; 358)	353 (340; 367)	361 (348; 375)	361 (348; 375)	354 (341; 367)	0.29
Urine Ca^{++} (mmol/24 h)*	3.55 (3.31; 3.79)	3.70 (3.45; 3.97)	3.77 (3.51; 4.03)	3.84 (3.58; 4.11)	3.86 (3.59; 4.14)	0.05
Urine volume (l/24 h)*	1.78 (1.68; 1.88)	1.84 (1.74; 1.94)	1.83 (1.74; 1.93)	1.90 (1.81; 2.00)	1.87 (1.77; 1.97)	0.22
Urine creatinine (mg/kg/24 h)*	18.4 (17.9; 18.9)	18.9 (18.4; 19.4)	19 (18.6; 19.4)	19.2 (18.7; 19.7)	18.7 (18.3; 19.2)	0.56

eGFR = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula); Q = quintile
Data are adjusted means and 95% confidence limits. Means are adjusted for age, sex, body mass index and linguistic region.

Table S2: Selected characteristics of normotensive and hypertensive participants.

	Normotension (n = 981)	Hypertension (n = 355)	
	Mean (SE)	Mean (SE)	p-value*
Age (years)	42.33 (0.52)	63.63 (0.7)	<0.001
Sex (proportion women)	0.57	0.37	<0.001
Current smoking (%)	26	36	<0.001
Body weight (kg)	70.8 (0.5)	80.4 (0.9)	<0.001
Body height (cm)	170.4 (0.3)	169. 5 (0.5)	0.11
BMI (kg/m^2)	24.3 (0.13)	27.9 (0.25)	<0.001
Age-, sex-, BMI- and linguistic region-adjusted means (95% confidence limits)			
Serum Na$^+$ (mmol/l)	141.9 (141.8; 142.1)	141.6 (141.4; 141.9)	0.007
Serum K$^+$ (mmol/l)	4.19 (4.17; 4.21)	4.16 (4.11; 4.2)	0.14
Serum Ca^{++} (corrected) (mmol/l)	2.3 (2.29; 2.3)	2.31 (2.3; 2.32)	0.12
Serum urea (µmol/l)	5.27 (5.19; 5.36)	5.24 (5.08; 5.4)	0.71
Serum uric acid (µmol/l)	290 (287; 294)	301 (295; 309)	0.004
eGFR (ml/min/1.73m^2)	89.9 (89.1; 90.7)	90 (88.6; 91.5)	0.85
Urine Na$^+$ (mmol/24 h)	149 (145; 158)	151 (145; 158)	0.51
Urine K$^+$ (mmol/24 h)	65.2 (63.8; 63.7)	61.4 (59.2; 63.7)	0.005
Urine Na$^+$/K$^+$ ratio	2.35 (2.29; 2.62)	2.52 (2.43; 2.62)	0.003
Urine urea (mmol/24 h)	359 (353; 354)	343 (331; 354)	0.01
Urine volume (ml/24 h)	1.86 (1.81; 1.88)	1.80 (1.72; 1.88)	0.24
Urine creatinine (mg/kg/24 h)	19 (18.8; 18.8)	18.4 (18; 18.8)	0.02

eGFR = estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration formula)
Data are unadjusted means (standard error) in the upper part and age-, sex-, BMI- and linguistic region-adjusted means in the lower part.
* p-values from t test, chi-squared test or Wald test as appropriate.