

# Fatal and Nonfatal Outcomes, Incidence of Hypertension, and Blood Pressure Changes in Relation to Urinary Sodium Excretion

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**T**HE EVIDENCE RELATING BLOOD pressure to salt intake in humans originates from population-based studies<sup>1</sup> and randomized clinical trials of interventions on dietary salt intake.<sup>2,3</sup> Across 52 INTERSALT centers, the median 24-hour urinary sodium excretion ranged from 0.2 to 242.1 mmol.<sup>1</sup> After standardization for sex and age and with adjustments for body mass index and alcohol intake, the cross-sectionally assessed age-related increase in systolic and diastolic blood pressure was significantly steeper with higher sodium excretion. Subsequent analyses, which accounted for regression dilution bias and included complex curve fitting, confirmed the first INTERSALT

**Context** Extrapolations from observational studies and short-term intervention trials suggest that population-wide moderation of salt intake might reduce cardiovascular events.

**Objective** To assess whether 24-hour urinary sodium excretion predicts blood pressure (BP) and health outcomes.

**Design, Setting, and Participants** Prospective population study, involving 3681 participants without cardiovascular disease (CVD) who are members of families that were randomly enrolled in the Flemish Study on Genes, Environment, and Health Outcomes (1985-2004) or in the European Project on Genes in Hypertension (1999-2001). Of 3681 participants without CVD, 2096 were normotensive at baseline and 1499 had BP and sodium excretion measured at baseline and last follow-up (2005-2008).

**Main Outcome Measures** Incidence of mortality and morbidity and association between changes in BP and sodium excretion. Multivariable-adjusted hazard ratios (HRs) express the risk in tertiles of sodium excretion relative to average risk in the whole study population.

**Results** Among 3681 participants followed up for a median 7.9 years, CVD deaths decreased across increasing tertiles of 24-hour sodium excretion, from 50 deaths in the low (mean, 107 mmol), 24 in the medium (mean, 168 mmol), and 10 in the high excretion group (mean, 260 mmol;  $P < .001$ ), resulting in respective death rates of 4.1% (95% confidence interval [CI], 3.5%-4.7%), 1.9% (95% CI, 1.5%-2.3%), and 0.8% (95% CI, 0.5%-1.1%). In multivariable-adjusted analyses, this inverse association retained significance ( $P = .02$ ): the HR in the low tertile was 1.56 (95% CI, 1.02-2.36;  $P = .04$ ). Baseline sodium excretion predicted neither total mortality ( $P = .10$ ) nor fatal combined with nonfatal CVD events ( $P = .55$ ). Among 2096 participants followed up for 6.5 years, the risk of hypertension did not increase across increasing tertiles ( $P = .93$ ). Incident hypertension was 187 (27.0%; HR, 1.00; 95% CI, 0.87-1.16) in the low, 190 (26.6%; HR, 1.02; 95% CI, 0.89-1.16) in the medium, and 175 (25.4%; HR, 0.98; 95% CI, 0.86-1.12) in the high sodium excretion group. In 1499 participants followed up for 6.1 years, systolic blood pressure increased by 0.37 mm Hg per year ( $P < .001$ ), whereas sodium excretion did not change ( $-0.45$  mmol per year,  $P = .15$ ). However, in multivariable-adjusted analyses, a 100-mmol increase in sodium excretion was associated with 1.71 mm Hg increase in systolic blood pressure ( $P < .001$ ) but no change in diastolic BP.

**Conclusions** In this population-based cohort, systolic blood pressure, but not diastolic pressure, changes over time aligned with change in sodium excretion, but this association did not translate into a higher risk of hypertension or CVD complications. Lower sodium excretion was associated with higher CVD mortality.

JAMA. 2011;305(17):1777-1785

www.jama.com

report.<sup>4</sup> In a meta-analysis of 31 trials with a minimum duration of 4 weeks, lowering 24-hour urinary sodium excretion by 75 mmol was associated with decreases in blood pressure, averag-

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ing 5.06 mm Hg for systolic and 2.70 mm Hg for diastolic among patients with hypertension; and by 2.03 mm Hg and 0.99 mm Hg, respectively, among participants without hypertension.<sup>3</sup>

Three recent reports,<sup>5-7</sup> using statistical modeling based on the aforementioned evidence and a set of complex assumptions, concluded that modest reductions in dietary salt intake, in the order of 3 g/d, could substantially reduce cardiovascular events and medical costs. However, these projections<sup>5-7</sup> ignored the inconsistency of the association between blood pressure and various indexes of salt intake in observational studies,<sup>8,9</sup> the far-reaching extrapolations from short-term intervention trials in normotensive or hypertensive volunteers to the general population,<sup>10</sup> the possible adverse effects of an indiscriminate reduction of

salt intake,<sup>11</sup> and the doubtful feasibility of a generalized limitation of salt consumption.<sup>12,13</sup> The assumption that lower salt intake would in the long run lower blood pressure, to our knowledge, has not yet been confirmed in longitudinal population-based studies. We addressed these issues in randomly selected European population samples. We studied the incidence of mortality and morbidity and the incidence of hypertension in relation to 24-hour urinary sodium excretion at baseline. We examined cross-sectionally and longitudinally the association between blood pressure and 24-hour urinary sodium.

## METHODS

### Study Population

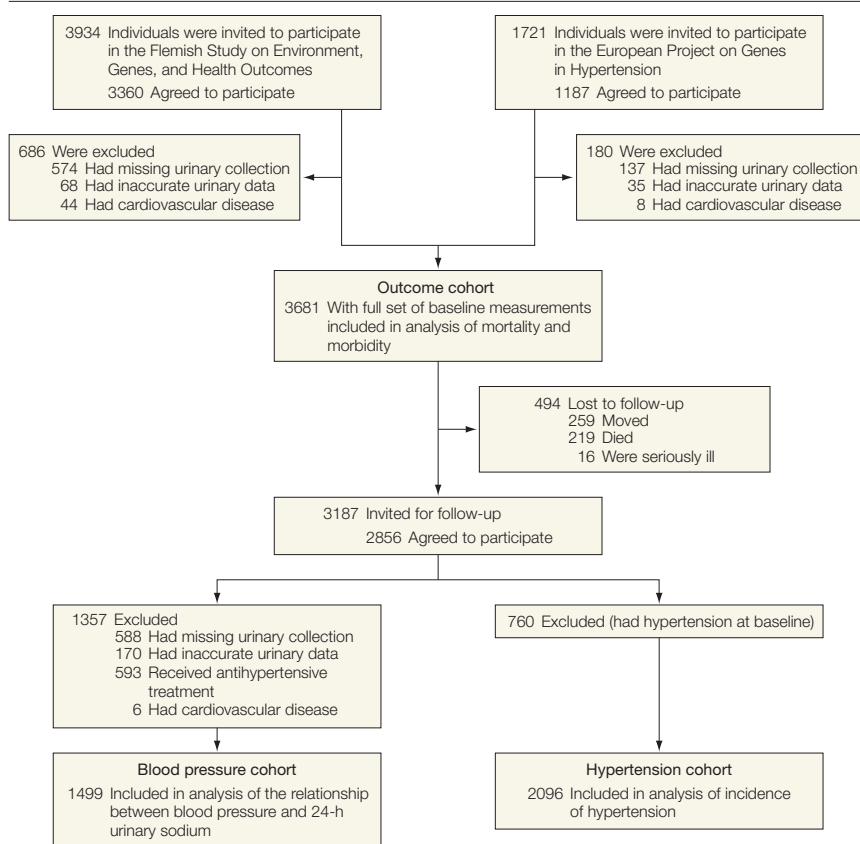
Recruitment for the Flemish Study on Environment, Genes, and Health Out-

comes (FLEMENGHO) started in 1985.<sup>14</sup> From August 1985 to November 1990, a random sample of the households living in a geographically defined area of Northern Belgium was investigated with the goal to recruit an equal number of participants in each of 6 subgroups by sex and age (20-39, 40-59, and  $\geq 60$  years). All household members aged 20 years or older were invited, provided that the quota of their sex-age group had not yet been satisfied. From June 1996 until January 2004 recruitment of families continued using the former participants (1985-1990) as index persons and also including teenagers.<sup>14</sup> The participants were repeatedly followed up. In all study phases, we used the same standardized methods to measure clinical and biochemical variables, administer questionnaires, and determine incidence of fatal and nonfatal outcomes.<sup>15</sup> The European Project on Genes in Hypertension (EPOGH) recruited participants from 1999 to 2001.<sup>16</sup> The EPOGH investigators were trained at the Studies Coordinating Centre in Leuven, Belgium, and applied the same protocol, questionnaires, and follow-up procedures, as used in FLEMENGHO.<sup>16</sup> Questionnaires were translated from Dutch into Czech, Italian, Polish, and Russian and back translated into Dutch to ensure that all questions had the same meaning in all languages. At baseline the participants collected a 24-hour urine sample. The last follow-up examination, which also included a 24-hour urine sampling, took place from 2005 to 2008 in FLEMENGHO and from 2006 to 2008 in EPOGH, both of which studies were conducted according to the principles outlined in the Helsinki Declaration for Investigation of Human Participants.<sup>17</sup> Each local institutional review board approved the study protocol. Participants provided written informed consent.

### Definition of Cohorts

As shown in the flow chart (FIGURE 1), 4547 participants took part in the study, 3360 in FLEMENGHO and 1187 in

**Figure 1.** Flowchart for Participants in the Study



Outcome cohort, hypertension cohort, and blood pressure cohort refer to participants used to study the incidence of mortality and morbidity, the incidence of hypertension, and the changes in blood pressure over follow-up, respectively. See "Methods" section for the definition of inaccurate urine collections.<sup>8</sup>

EPOGH. We excluded, respectively, 642 and 172 because their baseline 24-hour urine collection was either missing or unreliable. Inaccurate urine collections were defined as a volume less than 300 mL per 24 hours, a 24-hour creatinine excretion of less than 4 mmol or higher than 25 mmol in women and less than 6 mmol or more than 30 mmol in men.<sup>8</sup> To study the incidence of mortality and morbidity in relation to sodium excretion, we excluded an additional 44 FLEMENGHO and 8 EPOGH participants because they had a history of cardiovascular disease. The outcome cohort, therefore, included 3681 participants. During follow-up, 219 participants died, 16 became seriously ill, and 259 moved out of the study areas, potentially leaving 3187 participants, 2856 (89.6%) of whom agreed to take part in the follow-up examinations. After exclusion of 760 patients with hypertension at baseline, the hypertension cohort consisted of 2096 participants (Figure 1). To study the relation between blood pressure and 24-hour urinary sodium, both cross-sectionally and longitudinally over time, we excluded 588 and 170 participants whose 24-hour urine collection at follow-up was either missing or unreliable, 593 participants taking antihypertensive drug treatment at baseline, or at follow-up, and 6 untreated participants who at follow-up had developed cardiovascular disease. The blood pressure cohort comprised 1499 untreated participants without CVD at baseline and follow-up (Figure 1).

### Measurements

Experienced observers measured each participant's blood pressure at baseline and follow-up by auscultation of the Korotkoff sounds. After the participants had rested for 5 minutes in the sitting position, they obtained 5 consecutive blood pressure readings (phase V diastolic pressure) to the nearest 2 mm Hg, using mercury sphygmomanometers. Standard cuffs had a 12 × 24 cm inflatable portion, but if upper arm girth exceeded 31 cm, larger cuffs with 15 × 35 cm bladders were used. For

analysis, the 5 blood pressure readings obtained at baseline or at follow-up were averaged. Digit preference was checked at 6-month intervals.<sup>16</sup> Hypertension was defined as untreated blood pressure equal to or exceeding 140 mm Hg systolic or 90 mm Hg diastolic or the use of antihypertensive drugs.

On average, 1 week after blood pressure measurement (median, 5; range, 0-17 days at baseline; median, 3 days; range, 0-15 days at follow-up), participants collected an exactly timed 24-hour urine sample in a 2500 mL wide-neck plastic container (Sarstedt article number 77.576, Nümbrecht, Germany). Sodium and potassium in urine were determined by flame photometry and creatinine by an automated enzymatic method at certified laboratories.

Overweight was considered a body mass index, calculated as weight in kilograms divided by height in meters squared, of 25 to less than 30; obesity, 30 or higher. The observers administered the same questionnaire at baseline and follow-up to collect each participant's medical history; smoking status; drinking habits; medication use, including contraceptive and hormone replacement therapy; and educational attainment. Venous blood samples were drawn for blood glucose and serum total cholesterol measurement. Diabetes mellitus was determined by self-reported diagnosis, fasting glucose level of at least 126 mg/dL or random blood glucose level of 200 mg/dL, or use of antidiabetic agents.<sup>18</sup> (To convert glucose from mg/dL to mmol/L, multiply by 0.0555; sodium from mmol/d to g/d multiply by 0.02299.)

### Assessment of Outcome

In each country, outcomes were adjudicated against source documents, as described in previous publications.<sup>15,19</sup> The adjudication process was the same for both cohorts. We ascertained vital status of FLEMENGHO participants through December 31, 2009, and of EPOGH participants through August 15, 2008. We obtained the *International Classification of Disease* codes for the immediate and underlying

causes of death.<sup>19</sup> For 2856 participants, we also collected information on the incidence of nonfatal events via follow-up visits with repeat administration of the same standardized questionnaire used at baseline. Follow-up data were available for 329 FLEMENGHO participants from 1; 639 from 2; and 1229 from 3 or more follow-up visits and for 659 EPOGH participants from 1 follow-up visit. Physicians ascertained the diseases reported on the death certificates or by the questionnaires against the medical records of general practitioners or hospitals. Fatal and nonfatal stroke did not include transient ischemic attacks. Coronary events included fatal and nonfatal myocardial infarction and coronary revascularization. Fatal and nonfatal cardiovascular events comprised coronary end points, stroke, fatal and nonfatal left ventricular heart failure, aortic aneurysm, cor pulmonale, and pulmonary or arterial embolism. Hospitalizations for unstable angina were coded as ischemic heart disease. Heart failure was either a clinical diagnosis or the diagnosis on the death certificate but was in all cases validated against hospital files or the records held by family physicians. For all end points, we censored participants from analysis after the occurrence of a first event.

### Statistical Analysis

For database management and statistical analysis, we used SAS software, version 9.1.3 with the JMP add-on, version 8 (SAS Institute Inc, Cary, North Carolina). Departure from normality was evaluated by Shapiro-Wilk statistic and skewness by the computation of the coefficient of skewness, namely the third moment about the mean divided by the cube of the standard deviation. We computed 95% confidence intervals (CIs) of rates as  $R \pm \sqrt{(R/T)}$ , where  $R$  and  $T$  are the rate and the denominator used to calculate the rate. We compared means and proportions by the standard normal  $z$  test and the  $\chi^2$  statistic, respectively. Statistical significance was a 2-sided significance level of .05.

To explore the plausibility of the Cox model in the outcome cohort, we plotted incidence rates by tertiles of the 24-hour urinary sodium excretion at baseline, while standardizing for study population, sex, and age by the direct method. In line with other studies,<sup>20-24</sup> the assumption of a log-linear association between outcome and the 24-hour urinary sodium excretion at baseline was not fulfilled. We therefore compared the risk in each tertile with the overall risk in the whole study population using multiple Cox regression and deviation from mean coding.<sup>25</sup> This

approach allows computation of CIs for the hazard ratio (HR) in each tertile without definition of an arbitrary reference group. We used Cox proportional hazard regression as implemented in the PROC SURVIVAL procedure of the SUDAAN software (Research Triangle Institute, Research Triangle Park, North Carolina), version 10.01, to calculate HRs in the outcome and hypertension cohorts, while allowing for covariables and accounting for family clusters. The baseline characteristics considered as covariables in Cox regression were study popula-

tion, sex, age, blood pressure level, body mass index, alcohol intake, use of anti-hypertensive drugs, urinary potassium excretion, educational attainment, and additionally smoking status, total cholesterol level, and diabetes for analyses involving the outcome cohort.

For the blood pressure cohort, we used the *t* test and the McNemar test to evaluate changes from baseline to follow-up in continuous and categorical variables, respectively. Our statistical methods also included single and multiple linear regressions. We included in our model covariables with known physiological relevance for blood pressure. We applied a generalization of the standard linear model, as implemented in the PROC MIXED procedure of the SAS package, to investigate the associations between blood pressure and explanatory variables, while accounting for family clusters and adjusting for covariables. We defined absolute change as a difference between follow-up and baseline values, and relative (percentage) change as the absolute change divided by baseline value multiplied by 100.

**Table 1.** Baseline Characteristics of Study Participants by Cohort<sup>a</sup>

Characteristics	Cohort		
	Outcome (n = 3681)	Hypertension (n = 2096)	Blood Pressure (n = 1499)
Follow-up, median (IQR), y	7.93 (6.35-17.20)	6.48 (5.13-9.19)	6.14 (5.14-7.93)
Participant characteristics, No. (%)			
FLEMENGHO	2674 (72.6)	1644 (78.4)	1109 (74.0)
EPOGH	1007 (27.4)	452 (21.6)	390 (26.0)
Women	1941 (52.7)	1133 (54.1)	786 (52.4)
Hypertension	949 (25.8)		148 (9.9)
Diabetes mellitus	152 (4.1)	40 (1.9)	29 (1.9)
Antihypertensive treatment	443 (12.0)		
Use of female sex hormones	381 (10.4)	250 (11.9)	165 (11.0)
Use of NSAIDs	502 (13.6)	283 (13.5)	185 (12.3)
Educational attainment, No. (%)			
≤Elementary school	1210 (32.9)	679 (32.4)	437 (29.1)
Secondary school	1896 (51.5)	1118 (53.3)	854 (57.0)
Higher education	575 (15.6)	299 (14.3)	208 (13.9)
Smokers, No. (%)	1044 (28.4)	653 (31.2)	455 (30.4)
Alcohol intake ≥5 g/d, No. (%)	886 (24.1)	465 (22.2)	345 (23.0)
Characteristic, mean (SD)			
Age, y	40.9 (16.3)	38.6 (14.6)	38.3 (14.2)
Blood pressure, mm Hg <sup>b</sup>			
Systolic	124.7 (17.1)	118.7 (10.4)	120.9 (12.8)
Diastolic	76.3 (10.6)	73.3 (8.0)	74.6 (8.9)
BMI	25.2 (4.6)	24.5 (4.0)	24.6 (4.0)
Total cholesterol, mg/dL	209 (46)	207 (46)	207 (42)
24-h urinary measurements, mean (SD)			
Duration, h:m	23:52 (00:59)	23:51 (01:02)	23:48 (01:08)
Volume, L	1.52 (0.64)	1.52 (0.65)	1.54 (0.65)
Sodium, mmol	178.0 (74.8)	174.2 (74.1)	172.7 (62.5)
Potassium, mmol	66.2 (26.3)	66.8 (25.5)	66.3 (22.4)
Sodium-to-potassium ratio	2.93 (1.56)	2.81 (1.27)	2.78 (1.12)
Creatinine, mmol	11.6 (3.9)	11.7 (3.8)	11.9 (3.7)

Abbreviations: BMI, body mass index, which is calculated as weight in kilograms divided by height in meters squared; EPOGH, the European Project on Genes in Hypertension; FLEMENGHO, the Flemish Study on Environment, Genes, and Health Outcomes; IQR, interquartile range; NSAID, nonsteroid antiinflammatory drug.

SI conversion factors: To convert sodium from mmol to g, multiply by 0.02299; potassium from mmol to g, multiply by 0.039098; creatinine from mmol to g, multiply by 0.11312; cholesterol from mg/dL to mmol/L, multiply by 0.0259.

<sup>a</sup>Outcome cohort, hypertension cohort, and blood pressure cohort refer to participants used to study the incidence of mortality and morbidity, the incidence of hypertension, and the changes in blood pressure over follow-up, respectively (see Figure 1). See "Methods" section for details of each study.

<sup>b</sup>For the blood pressure determination and the diagnoses of hypertension and diabetes mellitus, see the "Methods" section.

## RESULTS

### Characteristics at Baseline by Cohort

TABLE 1 lists the baseline characteristics of the whole study population by cohort. Baseline characteristics are provided in eTables 1 and 2 for the outcome cohort and in eTables 3 and 4 for the hypertension cohort (available at <http://www.jama.com>) by tertiles of the urinary sodium excretion and by sex. eTable 5 describes the baseline and follow-up characteristics of the blood pressure cohort by country. All participants were white Europeans. From 72.6% to 78.4% of participants were recruited in Flanders. The 3 cohorts included just more than 50% of women.

### Analysis of Outcome

In the outcome cohort, median follow-up was 7.9 years. During 39 780 person-years of follow-up, 219 participants died (5.51 deaths per 1000 person-years), and 232 experienced a fatal or

nonfatal cardiovascular complication (5.83 events per 1000 person-years). Mortality included 84 cardiovascular and 135 noncardiovascular deaths. eTable 6 lists the cause-specific mortality and morbidity for the entire outcome cohort and in the FLEMENGHO and EPOGH study populations, separately.

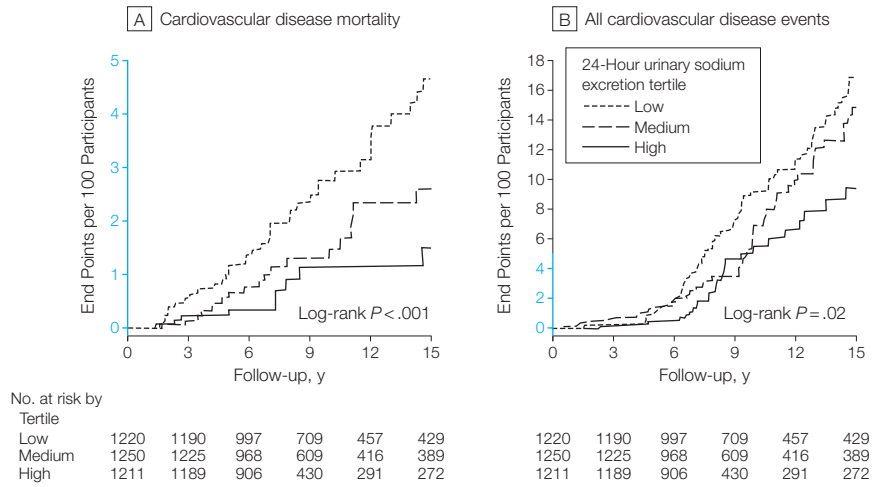
FIGURE 2 shows Kaplan-Meier survival function estimates for cardiovascular mortality and the composite cardiovascular end points in tertiles of the 24-hour urinary sodium excretion. Cardiovascular deaths decreased across increasing tertiles of 24-hour urinary sodium: from 50 in the low (death rate, 4.1%; 95% CI, 3.5%-4.7%), 24 in the medium, (death rate, 1.9%; 95% CI, 1.5%-2.3%); and 10 in the high tertile (death rate, 0.8%, 95% CI, 0.5%-1.1%;  $P < .001$ ). The mean 24-hour urinary sodium excretion for each tertile was defined as 106 mmol for the low, 165 mmol for the medium; and 250 mmol for the high tertile.

Figure 1 (available at <http://www.jama.com>) shows standardized rates of mortality and combined fatal and nonfatal outcomes across tertiles. TABLE 2

shows the multivariable-adjusted HRs expressing the risk in each tertile of the sex-specific distribution of the 24-hour urinary sodium excretion compared with the overall risk in the whole

outcome cohort. The risk of cardiovascular mortality was significantly elevated in the low tertile (HR, 1.56; 95% CI, 1.02-2.36;  $P = .04$ ) with a significant inverse association between

**Figure 2.** Kaplan-Meier Survival Function Estimates for Cardiovascular Mortality and All Cardiovascular Events



Tertiles of 24-hour urinary sodium excretion are sex-specific based on baseline measures (see Table 2). This analysis includes the outcome cohort (see Figure 1 and Table 1). Regions of y-axis scales drawn in blue indicate range from 0 to 5.

**Table 2.** Mortality and Cardiovascular Events by Tertiles of the 24-Hour Urinary Sodium Excretion at Baseline

	24-Hour Urinary Sodium Excretion Tertiles at Baseline							P Value
	Low (n = 1220)	Medium (n = 1250)	High (n = 1211)					
No. of women	645	658	638					
Range, mmol	50-126	127-177	178-400					
Mean (SD), mmol	95.1 (22.0)	150.2 (15.0)	231.7 (50.9)					
No. of men	575	592	573					
Range, mmol	50-158	159-221	222-400					
Mean (SD), mmol	120.1 (28.4)	188.8 (17.6)	290.5 (56.2)					
	<b>Total No. of Events of Outcome Cohort</b>	<b>No. of Events</b>	<b>Adjusted HR (95% CI)<sup>a</sup></b>	<b>No. of Events</b>	<b>Adjusted HR (95% CI)<sup>a</sup></b>	<b>No. of Events</b>	<b>Adjusted HR (95% CI)<sup>a</sup></b>	
Mortality								
All causes	219	118	1.14 (0.87-1.50)	64	0.94 (0.75-1.18)	37	1.06 (0.84-1.33)	.10
Cardiovascular	84	50	1.56 (1.02-2.36) <sup>b</sup>	24	1.05 (0.72-1.53)	10	0.95 (0.66-1.38)	.02
Noncardiovascular	135	68	0.98 (0.71-1.36)	40	0.90 (0.68-1.20)	27	1.11 (0.83-1.47)	.64
Fatal and nonfatal events								
All cardiovascular	232	100	1.13 (0.90-1.42)	79	1.11 (0.90-1.36)	53	0.90 (0.73-1.11)	.55
Coronary	98	45	1.42 (0.99-2.04)	34	1.17 (0.89-1.54)	19	0.86 (0.65-1.13)	.10
Stroke	33	13	1.07 (0.57-2.00)	13	1.29 (0.75-2.20)	7	0.78 (0.45-1.33)	.64

Abbreviations: CI, confidence interval; HR, hazard ratio.

This analysis includes the outcome cohort (see Figure 1 and Table 1).

<sup>a</sup>Hazard ratios were computed by deviation from mean coding<sup>25</sup> and express the risk in each tertile of the distribution of 24-hour urinary sodium excretion at baseline compared with the overall risk in the whole outcome cohort. We applied Cox proportional hazard regression to derive HRs, while allowing for covariables and accounting for family clusters. All HRs were adjusted for study population, sex, and baseline variables: age, body mass index, systolic blood pressure, 24-hour urinary potassium excretion, antihypertensive drug treatment, smoking and drinking alcohol, diabetes, total cholesterol, and educational attainment. Adjustment for diastolic blood pressure or mean arterial pressure did not materially alter the findings.

<sup>b</sup>P values are for linear trend across the tertiles of 24-hour sodium excretion.

<sup>c</sup>P = .04.

cardiovascular mortality and tertile of sodium excretion ( $P = .02$ ).

In sensitivity analyses involving cardiovascular mortality in relation to sex-specific tertiles of 24-hour urinary sodium stratified for age ( $<60$  vs  $\geq 60$  years), there were 18 deaths (eTable 7; available at <http://www.jama.com>) in the younger age group and 66 deaths (eTable 8) in the older age group. The HRs in the low tertiles were 1.41 (95% CI, 0.70-2.83,  $P = .33$ ) for the younger group and 1.52 (95% CI, 0.94-2.47,  $P = .09$ ) for the older group. Models not including adjustment for systolic blood pressure at baseline (eTable 9) or using 24-hour urinary sodium-to-potassium ratio at baseline as the exposure variable (eTable 10) produced consistent results for cardiovascular mortality. By censoring the adjusted Cox models for cardiovascular mortality at 6, 9, 12, 15, 18, and 21 years, we furthermore explored whether the risk in the low tertile changed with longer follow-up (eTable 11). The HRs were 1.65 (95% CI, 0.85-3.22,  $P = .14$ ) at 6 years, 1.20 (95% CI, 0.54-2.63,  $P = .65$ ) at 9 years, 1.61 (95% CI, 0.77-3.35,  $P = .20$ ) at 12 years, 1.68 (95% CI, 0.88-3.20,  $P = .12$ ) at 15 years, 1.66 (95% CI, 1.00-2.75,  $P = .048$ ) at 18 years, and 1.56 (95% CI, 1.02-2.36,  $P = .039$ ) at 21 years. Excluding cardiovascular deaths that occurred within 3 years of enrollment did not remove significance from the HR in the low tertile (1.67; 95% CI, 1.05-2.68;  $P = .03$ ).

### Incidence of Hypertension

The median follow-up was 6.5 years in the hypertension cohort. There were 552 cases of incident hypertension. Unadjusted Kaplan-Meier survival function estimates (eFigure 2) and multivariable-adjusted HRs (eTable 12) showed that baseline 24-hour urinary sodium did not predict the incidence of hypertension. In the entire hypertension cohort, across increasing tertiles of urinary sodium, the number of incident cases amounted to 187 (27.0%; HR, 1.00; 95% CI, 0.87-1.16;  $P = .95$ ) in the low, 190 (26.6%; HR, 1.02; 95% CI, 0.89-1.16,  $P = .79$ ) in the medium, and

175 (25.4%; HR, 0.98; 0.86-1.12,  $P = .78$ ) in the high tertile.

### Cross-sectional Analysis of Blood Pressure

In minimally adjusted analyses, in which we accounted only for country, sex, age, and family clusters, most associations of systolic and diastolic blood pressures with 24-hour urinary sodium excretion were significant at baseline as well as at follow-up. In fully adjusted models (eTable 13), the cross-sectional associations of systolic blood pressure with the 24-hour urinary sodium remained significant for the entire blood pressure cohort at baseline and follow-up and for EPOGH participants at baseline and for FLEMENGHO participants at follow-up. For the entire blood pressure cohort, a 100-mmol increase in the 24-hour urinary sodium excretion was associated with increases in systolic pressure of 1.14 mm Hg at baseline and 1.46 mm Hg at follow-up. In fully adjusted models, the cross-sectional associations of diastolic blood pressure with 24-hour urinary sodium excretion lost significance at baseline as well as at follow-up (eTable 13).

### Longitudinal Analysis of Blood Pressure

During 6.1 years of follow-up, systolic and diastolic blood pressures increased significantly in all centers except for systolic blood pressure in Pilsen (eTable 5). The annual changes for the entire blood pressure cohort averaged (SE) 0.37 (0.051) mm Hg systolic and 0.47 (0.039) mm Hg diastolic ( $P < .001$  for both). Untreated hypertension was present in 148 participants (9.9%) at baseline and 298 (19.9%) at follow-up. Of 1351 initially normotensive participants, 204 (15.1%) became hypertensive during follow-up. Of 148 initially hypertensive participants, 54 (36.5%) were reclassified as normotensive at follow-up (McNemar statistic, 87.2;  $P < .001$ ).

The 24-hour urinary sodium excretion remained unchanged during follow-up ( $P = .15$ ). Only in Kraków did the 24-hour urinary sodium excretion

decrease by a mean (SE) of 6.27 mmol (1.04 mmol) per year ( $P < .001$ ). The absolute and relative changes in systolic and diastolic pressures and 24-hour urinary sodium were not normally distributed for the entire blood pressure cohort (Shapiro-Wilk statistic  $\geq 0.92$ ;  $P < .001$ ; eFigure 3).

Changes in systolic blood pressure during follow-up were positively related to the corresponding changes in 24-hour urinary sodium in the entire blood pressure cohort and FLEMENGHO participants (TABLE 3). In absolute terms, a 100-mmol increase in the 24-hour urinary sodium excretion over follow-up was associated with a 1.71 mm Hg increase in systolic blood pressure ( $P < .001$ ), while accounting for family cluster, and with adjustments applied for study population, sex, and baseline values of changes in age, body mass index, and alcohol intake (stopping, no change, and starting;  $-1,0,1$ ), 24-hour urinary potassium excretion, use of female sex steroids ( $-1,0,1$ ), and use of nonsteroidal anti-inflammatory drugs ( $-1,0,1$ ). In relative terms, a doubling of the 24-hour urinary sodium excretion was associated with 2.2% increase in systolic blood pressure ( $P < .001$ ; Table 3). In these multivariable-adjusted analyses, the associations between the changes in diastolic blood pressure and 24-hour urinary sodium did not reach significance in absolute or relative terms. EFigures 4 and 5 illustrate the aforementioned multivariable-adjusted changes in systolic and diastolic blood pressure by deciles of the changes in 24-hour urinary sodium.

### COMMENT

In multivariable-adjusted models systolic pressure, but not diastolic pressure, was positively and independently correlated with the 24-hour urinary sodium excretion. This correlation was present at baseline and follow-up in the whole study population but was not consistent among FLEMENGHO and EPOGH participants. A key finding was that in longitudinal analyses, systolic but not diastolic blood pressure changed in line with the change in urinary sodium excretion. However, this association did

not translate into a higher risk of hypertension or cardiovascular complications. In contrast, we found a weak but consistent inverse association between cardiovascular mortality and the 24-hour urinary sodium excretion at baseline.

In the blood pressure cohort, sodium excretion, on average, did not change in any country with the exception of Poland, where at baseline it was higher than in any other study site. This observation is in keeping with the lack of changes in urinary sodium excretion in 38 US studies conducted over 46 years (1957-2003)<sup>26</sup> and in 13 surveys carried out in the United Kingdom over 25 years (1984-2008).<sup>27</sup> These studies<sup>26,27</sup> along with our current results support the concept that sodium intake is difficult to manipulate and is regulated<sup>27</sup> to maintain the concentration of extracellular and serum sodium within a narrow range. Exchangeable sodium is increased in hypertensive patients and correlates positively with arterial pressure,<sup>28</sup> but patients with primary hypertension do not have a larger extracellular fluid volume, plasma volume, or blood volume compared with normotensive controls.<sup>29</sup>

In the longitudinal analysis of the blood pressure cohort, systolic pressure increased by 1.71 mm Hg for a 100-mmol per day increment in urinary sodium, whereas diastolic pressure remained unaffected. Two meta-analyses<sup>10,30</sup> reported blood pressure responses to salt restriction of similar magnitude in normotensive individuals. The effect sizes were 1.0 mm Hg systolic ( $P < .001$ ) and 0.1 mm Hg diastolic ( $P = .64$ ) per 100-mmol decrease in 24-hour urinary sodium<sup>30</sup> or 1.2 mm Hg systolic ( $P < .001$ ) and 0.26 mm Hg diastolic ( $P = .12$ ) per 160 mmol.<sup>10</sup> In a meta-regression analysis by He and MacGregor,<sup>31</sup> a reduction of salt intake by 3 g/d predicted a decrease in systolic/diastolic blood pressure by 3.6 to 5.6/1.9 to 3.2 mm Hg in hypertensive patients and by 1.8 to 3.5/0.8 to 1.8 mm Hg in normotensive participants. Systolic pressure increases with age at least until the eighth decade of life, whereas diastolic pressure increases until age 50

**Table 3.** Multivariable Adjusted Longitudinal Associations Between Changes in Blood Pressure and 24-Hour Urinary Sodium by Study Population<sup>a</sup>

Study Population	Absolute		Relative	
	Estimates (95% CI) <sup>b</sup>	P Value	Estimates (95% CI) <sup>b</sup>	P Value
Change in systolic pressure				
FLEMENGHO	2.373 (1.154 to 3.392)	<.001	2.740 (1.410 to 4.069)	<.001
EPOGH	0.196 (-1.409 to 1.801)	.81	0.085 (-2.181 to 2.351)	.94
All	1.711 (0.786 to 2.637)	<.001	2.211 (1.059 to 3.364)	<.001
Change in diastolic pressure				
FLEMENGHO	0.576 (-0.246 to 1.398)	.17	1.476 (-0.113 to 3.065)	.07
EPOGH	-0.052 (-1.317 to 1.212)	.94	-0.175 (-3.064 to 2.714)	.90
All	0.379 (-0.313 to 1.070)	.28	1.107 (-0.279 to 2.492)	.12

Abbreviations: CI, confidence interval; EPOGH, the European Project on Genes in Hypertension; FLEMENGHO, Flemish Study on Environment, Genes, and Health Outcomes.

<sup>a</sup>Reasons for exclusion from analysis are explained in the "Methods" section.

<sup>b</sup>Estimates and 95% CIs express the change in systolic blood pressure per 100-millimole increase in 24-hour urinary sodium excretion or the percentage change in systolic pressure for a doubling of 24-hour urine sodium. Parameter adjustment definitions are in the "Results" section. Estimates for all participants were adjusted for study population.

years and thereafter either levels off or slightly decreases.<sup>32</sup> In long-term studies such as ours, these divergent age-related systolic and diastolic trends in blood pressure associated with changes in 24-hour urinary sodium.

Several prospective studies dealt with the effects of salt intake on the incidence of hypertension or cardiovascular complications, but few<sup>21,33-36</sup> based their assessments on 24-hour urinary sodium excretion, the most accurate approach to assess salt intake. None described the longitudinal association between changes in blood pressure on a continuous scale in relation to changes in 24-hour urinary sodium excretion. He and colleagues<sup>34</sup> examined the effects of reducing salt intake on the incidence of hypertension for 128 participants. During the randomized intervention of 18 months the between-group gradient in 24-hour urinary sodium excretion averaged 33 mmol. After an average of 7 years of follow-up without any intervention, the multivariable adjusted odds of hypertension for active intervention vs control was 0.65 but in line with our findings, it did not reach significance (95% CI, 0.25-1.69;  $P = .37$ ).<sup>34</sup> In a 7-year study involving 233 randomly selected children, no association was found between the changes in blood pressure and salt intake that was extrapolated from overnight urine samples that were

repeatedly collected during follow-up, with sodium excretion rates averaged for analysis.<sup>37</sup>

In our current study, cardiovascular mortality was significantly elevated in the low tertile of 24-hour urinary sodium excretion with a significant inverse association with sodium excretion across tertiles. It is unlikely that these findings were due to reverse causality because we excluded patients with a history of CVD. Moreover, these observations were consistent when we censored cardiovascular deaths over a time span ranging from 6 to 21 years, or excluded cardiovascular deaths occurring within 3 years of enrollment. Similarly, models including or excluding systolic pressure as covariable produced consistent results. Our current observations on cardiovascular mortality are consistent with several other reports.<sup>33,38-40</sup> The National Health and Nutrition Examination Surveys (NHANES) I<sup>38</sup> and II<sup>39</sup> demonstrated an inverse association of cardiovascular and total mortality with salt intake as assessed from dietary recall with a similar trend in NHANES III.<sup>40</sup> Alderman and colleagues<sup>33</sup> followed up for 3.5 years 2937 patients with mild to moderate hypertension. There was an inverse association between the incidence of myocardial infarction and 24-hour urinary sodium excretion at baseline for the total population and for men, but not women. For men, the race- and age-adjusted HR expressing the risk in the lowest vs the

highest quartile of 24-hour urinary sodium was 4.3 (95% CI, 1.7-10.6). Other investigators criticized Alderman's findings, because he instructed his patients to avoid high-salt foods 4 to 5 days before sodium excretion measurements were taken, which might have led to distorted levels. In our epidemiological study, which was conducted outside a medical environment, participants did not receive any recommendations from the research team about moderating their salt consumption. The underlying mechanisms explaining the inverse association between cardiovascular mortality and 24-hour urinary sodium excretion might be that a salt intake low enough to decrease blood pressure also increases sympathetic nerve activity, decreases insulin sensitivity, activates the renin-angiotensin system, and stimulates aldosterone secretion.<sup>10</sup>

At variance with our current findings, other prospective studies suggested that a high-salt intake may lead to a worse outcome. In the Scottish Heart Health Study,<sup>21</sup> 24-hour urinary sodium predicted coronary heart disease in women but not men. The HRs for the lowest quintile vs the 4 other quintiles of sodium excretion combined were 1.16 (95% CI, 1.00-1.33) and 1.05 (95% CI, 0.96-1.14), respectively. The analyses were only adjusted for age. Cook and colleagues<sup>36</sup> analyzed the long-term results of dietary sodium restriction on cardiovascular outcomes by combining 10 to 15 years of follow-up of 744 and 2382 participants randomized in the Trials of Hypertension Prevention, phases 1 and 2. Net sodium reductions during the intervention period (from 18 to 48 months) were 44 mmol and 33 mmol per day, respectively. The follow-up for mortality was 100%, but only 77% for morbidity. With adjustments applied for trial, clinical site, race, sex, and age, the HRs for intervention vs control were 0.80 (95% CI, 0.51-1.26;  $P=.34$ ) for total mortality and 0.75 (95% CI, 0.57-0.99) for cardiovascular events ( $P=.04$ ).<sup>36</sup> In a 19-year follow-up study of 3126 Fins,<sup>35</sup> the multivariable-adjusted HRs associated with a 100-mmol increase in 24-hour urinary so-

dium were 1.26 (95% CI, 1.06-1.50) for total mortality, 1.45 (95% CI, 1.14-1.84) for CVD, and 1.51 (95% CI, 1.14-2.00) for coronary heart disease. When analyses were done separately for each sex, the HRs were significant in men only.<sup>35</sup>

In a meta-analysis including some of the aforementioned studies, Strazzullo and colleagues<sup>41</sup> reported that the risk of stroke increased by 6% (95% CI, 3%-10%;  $P=.04$ ) for an increase in sodium intake by 50 mmol per day. A similar trend for CVD was not significant (19%; 95% CI, -31%-107%;  $P=.53$ ).<sup>41</sup> Across the reports included in Strazzullo's meta-analysis,<sup>41</sup> the methods for assessing salt intake were not standardized. Studies with exclusively fatal outcomes were pooled with those including both fatal and nonfatal events. Moreover, the HRs used in the variance-weighted meta-regression analysis were not standardized to the same amount of sodium.<sup>41</sup>

Our current study has to be interpreted within the context of its potential limitations. First, one 24-hour urine collection might be insufficient to characterize an individual's habitual salt intake, but it does accurately reflect the average salt consumption of groups of subjects.<sup>42</sup> Thus, our analyses based on tertiles of 24-hour urinary sodium should be less vulnerable to the high intraindividual variability of sodium excretion. Second, our study population was relatively young, so that the number of events was relatively small, leading to a potential underestimation of the risk of excessive sodium intake. In particular, EPOGH participants were younger than those participating in the FLEMENGHO study and were only followed up for a median of 6.5 years compared with 10.6 years. Third, our study included only white Europeans and its findings therefore cannot be extrapolated to Asian or in particular black individuals, who might be more salt sensitive than white people.<sup>43,44</sup> Fourth, we did not assess sodium sensitivity. Blood pressure responses to changes in dietary salt intake are heterogeneous,<sup>45</sup> but there is no practical clinical test to

assess sodium sensitivity in individual subjects.

In conclusion, we observed significant cross-sectional and longitudinal associations between systolic pressure and sodium excretion in the whole study population. However, these associations were not consistent among FLEMENGHO and EPOGH participants. Diastolic pressure was not correlated with sodium excretion. Baseline sodium excretion did not predict the incidence of hypertension. The associations between systolic pressure and sodium excretion did not translate into less morbidity or improved survival. On the contrary, low sodium excretion predicted higher cardiovascular mortality. Taken together, our current findings refute the estimates of computer models of lives saved and health care costs reduced with lower salt intake.<sup>5-7</sup> They do also not support the current recommendations of a generalized and indiscriminate reduction of salt intake at the population level. However, they do not negate the blood pressure-lowering effects of a dietary salt reduction in hypertensive patients.<sup>10,30</sup>

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**Conflict of Interest Disclosures:** All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest and none were reported.

**Funding/Support:** The European Union grants IC15-CT98-0329-EPOGH, LSHM-CT-2006-037093. InGenious HyperCare, and HEALTH-F4-2007-201550 HyperGenes supported the Studies Coordinating Centre (Leuven, Belgium) and the studies in Pilsen (Czech Republic), Padova (Italy), Kraków (Poland), and Novosibirsk (Russian Federation). The Studies Coordinating Centre also received grants G.0575.06 and G.0734.09 from the Fonds voor Wetenschappelijk Onderzoek Vlaanderen, Ministry of the Flemish Community, Brussels, Belgium, and the grants OT/00/25 and OT/05/49 from the Katholieke Universiteit Leuven, Belgium. The Polish Ministry for Science and Higher Education supported the fellowship of Dr Stolarz-Skrzypek in Leuven. The Czech Society of Hypertension provided additional funding to Dr Seidlerová.

**Role of the Sponsor:** The funding source had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript.

**Online-Only Material:** eTables 1 through 13 and eFigures 1 through 5 are available at <http://www.jama.com>.

**Additional Contribution:** The authors gratefully acknowledge the expert assistance of Ms Sandra Covens and Ms Ya Zhu, who are employees of the Studies Coordinating Centre, Leuven, Belgium, and did not receive any compensation for their contribution to this study. The FLEMENGHO and EPOGH investigators at the time of the studies are listed at <http://www.jama.com>.

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