

Incidence of hypertension in individuals with different blood pressure salt-sensitivity: results of a 15-year follow-up study

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Objective To evaluate the incidence of hypertension and the rate of decline in renal function in a sample of 47 Olivetti Heart Study (OHS) participants whose blood pressure (BP) salt-sensitivity and renal tubular sodium handling had been assessed in 1987–88.

Methods During the 2002–04 OHS follow-up examination, medical history, physical examination and blood and urine sampling were performed in 36 of the 47 participants to the baseline study (age 60 ± 6 years; average follow-up = 15.1 ± 0.6 years). The renal length was measured in 23 participants by kidney ultrasonography. Based on the baseline salt-sensitivity evaluation, the subjects were classified into a lower salt-sensitivity (LSS, $n = 20$) and a higher salt-sensitivity group (HSS, $n = 16$).

Results In comparison with the LSS group, HSS participants had a significantly higher incidence of hypertension (87.5 versus 50.0%, $P = 0.02$), a higher glomerular filtration rate (median, first to fourth quartile: 81.9, 72.3–95.2 versus 72.3, 59.9–81.2 ml/min; $P = 0.03$) and greater kidney length (median, first to fourth quartile: 68.2, 63.3–72.1 versus 61.9, 58.7–62.7 mm/m of height; $P = 0.003$). The incidence of hypertension remained significantly higher in HSS individuals after adjustment for

age, intercurrent changes in body mass index and baseline blood pressure on low sodium diet ($P = 0.04$).

Conclusion Our findings indicate that individuals with higher BP salt-sensitivity have a higher rate of incident hypertension and suggest an altered renal tubular sodium handling involving a trend to increased glomerular filtration rate and blood pressure over time as a possible mechanism. *J Hypertens* 25:1465–1471 © 2007 Lippincott Williams & Wilkins.

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Keywords: blood pressure, glomerular filtration rate, prospective study, renal function, sodium dependent hypertension

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Introduction

A heterogeneous blood pressure (BP) response to changes in dietary sodium chloride intake, a phenomenon generally referred to as BP salt-sensitivity, is observed in both hypertensive patients and normotensive individuals [1–3]. On the basis of the feature characteristics of well described forms of monogenic hypertension [4–6], it is conceivable that a different ability of the kidney to excrete sodium and water is involved in this phenomenon [7].

We have previously reported on BP, renal function and tubular sodium handling in a sample of healthy normotensive male volunteers drawn from a middle-aged male working population in 1987–88 [3]. Our results showed that those with higher salt-sensitivity, estimated by their BP response to low salt diet, had increased BP, greater

proximal tubular sodium reabsorption and higher glomerular filtration rate (GFR) when on habitual high sodium diet compared to those with a lower degree of salt-sensitivity. These alterations were no longer apparent when the subjects were placed on a low sodium diet (40 mmol Na/day for 3 days). We speculated that the trend to greater tubular sodium reabsorption detected in the more salt-sensitive subjects elicited humoral adaptive responses to overcome the difficulty in sodium excretion at the cost of an increase in BP and GFR.

Other studies have reported increased GFR and/or intraglomerular pressure in salt-sensitive hypertension [8–13]. In turn, hyperfiltration could heighten susceptibility to renal function deterioration and actually it has been found to be associated with early organ damage in hypertensive patients [14].

The aim of the present study was to evaluate BP and renal function in the same individuals studied in 1987–88 [3] during the 2002–04 follow-up examination of the Olivetti Heart Study (OHS), an average of 15 years after the original observation.

Patients and methods

Baseline evaluation (1987–88)

Forty-seven healthy normotensive male employees of the Olivetti Factory in Pozzuoli (Naples) volunteered to participate in the above-mentioned study of the association between salt-sensitivity, BP and renal function carried out in 1987–88 [3]. They were seen at the medical centre located within the factory premises; the examinations were performed in the morning. Participants were asked to refrain from smoking and from engaging in strenuous physical exercise in the hours preceding the examination. At the time of the visit, they were following their habitual diet and were fasted for at least 13 h. They underwent a physical examination, complete anthropometric measures and a blood test. Body weight and height were measured on a standard beam balance scale with an attached ruler. Body weight was measured to the nearest 0.1 kg and height was measured to the nearest cm with subjects wearing only light indoor clothing without shoes. Body mass index (BMI) was calculated as weight (kg) divided by the square of the height (m²). BP was measured in a quiet and comfortable room using a standard mercury sphygmomanometer by a well trained operator. After the subject had remained seated for at least 10 min, three consecutive measures were taken of systolic (SBP) and diastolic (DBP) blood pressure at 2-min intervals and the last two measurements were used for the analysis. Mean BP (MBP) was calculated as $DBP + \frac{1}{3}SBP$. A fasting venous blood sample was taken in the seated position without stasis after the BP measurements. The blood specimens were immediately centrifuged and stored at -70°C until analysed.

Evaluation of salt-sensitivity and renal tubular sodium handling at the 1987–88 (baseline) examination

The evaluation of salt-sensitivity was performed at baseline (1987–88 examination) and was based on the individual MBP change upon shifting from the NaCl-rich habitual diet (averaging 184 ± 9 mmol/24 h) to a 3-day salt restricted diet (averaging 69 ± 5 mmol/24 h). Based on the median value of MBP change in the whole study population, we identified a group of individuals with a lower level of salt-sensitivity (LSS, $n = 24$; MBP decrease less than 5.7%) and a group with higher salt-sensitivity (HSS, $n = 23$; MBP decrease greater than 5.7%).

An evaluation of segmental renal tubular sodium handling was also made at baseline both on high and low NaCl diet. To this purpose, on the evening before the visit, the participants took a 300 mg lithium carbonate capsule (Carbolithium; IFI, Milan, Italy) delivering 8.1 mmol of

elemental lithium. On the following morning, a timed fasting urine collection was performed and a blood sample was obtained at the mid-point of the collection for the measurement of serum and urinary lithium and creatinine concentration. Standard formulae were used to calculate the rates of fractional proximal and distal sodium reabsorption [3].

Follow-up (2002–04 examination)

Thirty-six of the 47 participants in the baseline (1987–88) observation (LSS = 16, HSS = 20) were re-examined during the 2002–04 OHS follow-up examination (mean follow-up length = 15.1 ± 0.6 years). Of the 11 subjects lost to follow-up, four had changed their residence and could not be located, three refused to participate, one was unable to attend because of a serious invalidating condition and three patients had died before the follow-up visit (one due to coronary heart disease and two due to neoplastic diseases).

The follow-up visits were performed at the Outpatient Clinic of the Department of Clinical and Experimental Medicine, Federico II University of Naples Medical School between November 2002 and June 2004. Anthropometric indices and BP were measured adopting the same procedures used at baseline observation. The diagnosis of hypertension was based on the finding of values of ≥ 140 mmHg systolic and/or ≥ 90 mmHg diastolic BP or on the current assumption of antihypertensive medications prescribed by the participants' family doctors.

Segmental tubular sodium handling was not evaluated at the follow-up examination. However, a 24-h urine collection was obtained from each participant for the measurement of sodium excretion, taken as an estimate of daily dietary sodium intake, and of urinary albumin excretion rate (AER). Urinary sodium concentration was measured by flame photometry and urinary albumin concentration by an immunoturbidimetric assay (Horiba ABX Diagnostics, Rome, Italy) using a Cobas-Mira analyser (Roche Instrument Center, Rotkreuz, Switzerland).

Kidney ultrasonography was carried out only at the 2002–2004 follow-up examination in a subsample of 23 participants by a duplex–Doppler apparatus (Esaote-Hitachi 570 AU; Hitachi Medical Corporation, Japan) with convex 3.5-MHz transducer. Patients' position always included supine or lateral decubitus. Usually, a combination of intercostal and sub-costal approaches were necessary to obtain, in the coronal plane, the outcome measurements [i.e. the maximal bipolar and the kidney parenchymal (cortex plus medullary pyramids) thickness diameters].

To allow for the comparison of renal function at baseline and at 15-year follow-up, GFR was assessed in both occasions by the calculation of creatinine clearance

according to the Cockcroft–Gault formula [15]:

$$\left(\frac{[(140 - \text{age (years)}) \times \text{weight (kg)}]}{72 \times \text{serum creatinine (mg/dl)}} \right)$$

At baseline, serum creatinine was measured both on habitual and on low NaCl diet.

Statistical analysis

Data were expressed as median and first to fourth quartile, or as otherwise indicated. The relationships between BP salt-sensitivity determined at baseline and long-term outcomes (i.e. rate of hypertension, decline in renal function and kidney morphology) were evaluated by non-parametric Spearman correlation analysis. Because kidney length was strictly dependent on body size, its values were adjusted for height. Between-group comparisons were performed by Mann–Whitney test for unpaired data. Comparison between frequencies of specified conditions was performed by the chi-squared test. The predictive value of BP salt-sensitivity on the rate of hypertension was evaluated by logistic regression analysis adjusting for possible confounders (age, family history of hypertension, BMI changes over the follow-up period, baseline BP). Because AER distribution disclosed significantly from normality, log-transformed AER values were used for statistical analysis. $P < 0.05$ was considered statistically significant.

The study protocol was approved by the local ethics committee and all participants gave their informed consent to participate in both occasions.

Results

Table 1 shows the baseline characteristics of the LSS and HSS subjects undergoing the follow-up study. The HSS group had a trend to greater BMI compared with the LSS group. On high-salt diet, a significantly higher BP and a trend to greater GFR were observed in HSS compared

with LSS participants. These differences were not apparent when the subjects were on a low-sodium diet.

The duration of follow-up was similar for the two groups. At follow-up examination, only slight changes were observed in BMI [HSS = +1.6 (0.7–3.1), LSS = +0.9 (–0.7–2.1) kg/m², $P = 0.26$]. Urinary 24-h sodium excretion was similar in the two groups [HSS = 129 (103–148), LSS = 141 (108–193) mmol/24 h, $P = 0.22$]. Likewise, no difference was detected in family history of hypertension (at least one relative affected, HSS = 37.5, LSS = 62.5%, $P = 0.10$).

Blood pressure

There were 24 (68.6%) incident cases of hypertension in the entire sample, 14 in the HSS (87.5%) and ten in the LSS group (50.0%), chi-squared = 5.625; $P = 0.018$ (Fig. 1a). The percentage of subjects aware of being hypertensive and taking regular antihypertensive drug therapy at follow-up visit was five-fold greater in the HSS than in the LSS group [8/16 (50%) versus 2/20 (10.0%), Fisher's exact test: $P = 0.01$].

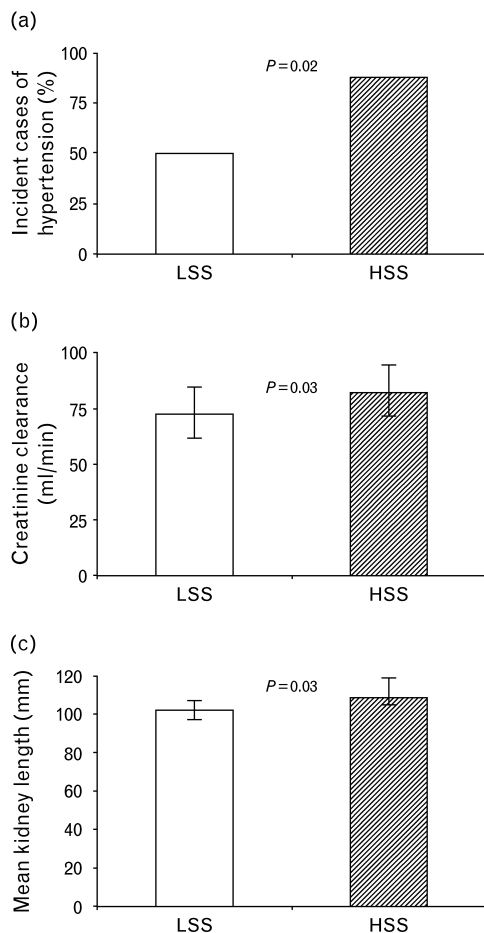
To rule out the influence of confounders in the association between the degree of salt-sensitivity and incidence of hypertension, a logistic regression model was used with incident hypertension (yes/no) as dependent variable, salt-sensitivity degree category (LSS/HSS) as independent variable and the following covariates: family history of hypertension (at least one relative affected, yes/no), age (years), BMI changes (%) during the follow-up period and BP (mmHg) on low NaCl diet at baseline. According to this model (Table 2, Model 1), salt-sensitivity assessed at baseline was a significant independent predictor of the incidence of hypertension. Statistical significance was lost when in the same model the baseline BP on low NaCl diet was replaced by the baseline BP recorded on high NaCl intake (Table 2, model 2). Baseline diastolic BP, both on low and high NaCl diet was also a significant predictor of hypertension.

Table 1 Baseline (1987/88 follow-up) characteristics of the salt-sensitive and the salt-resistant group

	LSS ($n = 20$)		HSS ($n = 16$)	
	Median	1st to 4th quartile	Median	1st to 4th quartile
Age (years)	46.0	42.2–51.5	42.0	40.2–45.0
Height (m)	1.71	1.64–1.76	1.66	1.64–1.70
Body weight (kg)	74.5	65.5–81.5	74.0	68.5–83.2
BMI (kg/m ²)	25.5	22.6–26.7	26.3	25.4–28.2
BP on high NaCl diet (mmHg)	117/81	110–123/76–86	128/87*	115–133/82–89
BP on low NaCl diet (mmHg)	118/79	112–123/77–82	111/75*	109–119/71–81
Δ Mean BP from high-to-low NaCl diet (%)	–2.3	–5.0, 3.0	–10.8	–16.1, –8.7
GFR on high NaCl diet (ml/min)	86.1	77.9–94.1	92.1	82.1–113.2
GFR on low NaCl diet (ml/min)	86.4	79.1–93.7	90.3	81.8–102.5
FPRNa on high NaCl diet (%)	75.8	73.8–79.9	75.9	71.8–78.3
FPRNa on low NaCl diet (%)	81.8	79.1–84.2	80.5	75.8–83.5
FDRNa on high NaCl diet (%)	94.4	93.5–96.7	96.4	95.9–97.0
FDRNa on low NaCl diet (%)	98.5	97.9–99.9	98.7	98.3–99.1

* $P < 0.05$. BP, Blood pressure; BMI, body mass index; GFR, glomerular filtration rate; FPRNa, fractional proximal reabsorption of sodium; FDRNa, fractional distal reabsorption of sodium; HSS, higher salt-sensitivity; LSS, lower salt-sensitivity.

Fig. 1



(a) Incidence of hypertension, (b) glomerular filtration rate and (c) kidney length (expressed as the average of the longitudinal diameter of the left and the right kidney), estimated during the 2002–04 follow-up of the Olivetti Heart Study in individuals, normotensive at baseline, with different blood pressure salt-sensitivity assessed at baseline examination (1987–88). Incidence of hypertension: Pearson chi squared = 5.625; $P = 0.018$. Glomerular filtration rate: Mann–Whitney, $P = 0.03$. Kidney length: $n = 23$ (LSS = 11; HSS = 12); Mann–Whitney, $P = 0.03$; Data are expressed as median and first to fourth quartile. LSS, Lower salt-sensitivity; HSS, higher salt-sensitivity.

Kidney function and morphology

The GFR was greater in the HSS group compared to the LSS group (Fig. 1b) at follow-up examination. When comparing GFR at baseline and after 15-year follow-up, however, a similar decrease was observed in the two groups [LSS: -1.0 ($-1.8, -0.5$); HSS: -0.9 ($-1.2, -0.6$)% of baseline value per year, $P = 0.46$].

AER, taken as an index of renal damage, was higher in the HSS than in the LSS group, but the difference was not statistically significant [HSS: 8.9 (3.9–17.7); LSS: 6.9 (3.8–17.4) mg albumin/24 h; $P = 0.38$].

Kidney ultrasound scan was performed in 23 participants (LSS = 11; HSS = 12). HSS participants had significantly

Table 2 Logistic regression model of predictors of incidence of hypertension during 15-year follow-up in individuals with different salt sensitivity of blood pressure

	Beta \pm SE	P
Model 1		
Salt sensitivity (LSS/HSS)	5.188 \pm 2.208	0.02
Age (years)	-0.320 ± 0.179	0.07
FH+ (yes/no)	1.764 \pm 1.370	0.20
BMI change (1987/88 to 2002/04) (%)	0.044 \pm 0.303	0.88
Systolic BP on low NaCl diet (mmHg)	0.013 \pm 0.084	0.87
Diastolic BP on low NaCl diet (mmHg)	0.433 \pm 0.215	0.04
Model 2		
Salt-sensitivity (LSS/HSS)	1.213 \pm 1.232	0.32
Age (years)	-0.215 ± 0.121	0.07
FH+ (yes/no)	1.076 \pm 1.299	0.41
BMI change (1987/88–2002/04) (%)	0.262 \pm 0.292	0.37
Systolic BP on high NaCl diet (mm Hg)	0.001 \pm 0.071	0.90
Diastolic BP on high NaCl diet (mm Hg)	0.303 \pm 0.144	0.03

FH+, positive family history of hypertension (at least one relative affected); BMI, body mass index; BP, blood pressure; HSS, higher salt-sensitivity; LSS, lower salt-sensitivity.

higher mean longitudinal kidney diameter (expressed as the average of the longitudinal diameter of the left and the right kidneys) as either absolute (Fig. 1c) or height-adjusted values [HSS: 68.2 (63.3–72.1); LSS: 61.9 (58.7–62.7) mm/m of height; Mann–Whitney, $P = 0.003$].

Salt-sensitivity was inversely associated with kidney length as both absolute ($r = -0.476$, $P = 0.02$) and height-adjusted values ($r = -0.446$, $P = 0.03$). There was also a direct association between kidney length and GFR, either expressed as unadjusted ($r = 0.653$; $P = 0.001$) or height-adjusted kidney length ($r = 0.425$; $P = 0.04$). Renal parenchymal thickness was similar in the two groups [LSS: 14.3 (12.5–17.0); HSS: 17.5 (14.7–18.4) mm; $P = 0.10$], also after adjustment for kidney length.

Supplemental analysis with adoption of a different criteria for definition of salt-sensitivity

We carried out supplemental analyses using a second criteria for definition of salt-sensitivity (i.e. a 10 mmHg fall in MBP when shifting from high to low sodium diet), according to Weinberger *et al.* [16]. By so doing, two groups were identified, respectively, 14 salt-sensitive and 22 salt-resistant individuals. These two groups were comparable with each other with respect to age, BMI and length of follow-up. GFR was higher in salt-sensitive individuals at baseline [93.3 (82.4–114.3) versus 86.1 (76.3–93.5) ml/min; $P = 0.06$] and at the follow-up examination [82.0 (72.1–97.5) versus 73.6 (60.2–96.5) ml/min; $P = 0.04$]. Mean longitudinal kidney diameter was significantly higher in salt-sensitive than in salt-resistant subjects [111.0 (105.0–121.0) versus 102.2 (98.4–109.2) mm; $P = 0.03$]. The incidence of hypertension was 86% (12/14) versus 54% (12/22) ($P = 0.07$) and that of current antihypertensive treatment was 43% (6/14) versus 18% (4/22) ($P = 0.14$) in the salt-sensitive and the salt-resistant groups, respectively. At logistic regression analysis, salt-sensitivity defined by this criteria

was a significant predictor of the incidence of hypertension ($P=0.04$), controlling for age, BMI change, follow-up length, family history of hypertension and baseline BP on low sodium diet.

Discussion

The present study evaluated the incidence of arterial hypertension and renal function outcomes over 15 years in a group of originally normotensive and clinically healthy men with different BP salt-sensitivity. Our main finding was that the incidence of hypertension was significantly higher among individuals with a higher degree of salt-sensitivity at baseline compared to subjects with lower salt-sensitivity. Although previous studies analysed cardiovascular morbidity in hypertensive patients [17] and total mortality in both normotensive and hypertensive individuals [18] according to BP salt-sensitivity, to our knowledge, this is the first demonstration of an independent predictive value of salt-sensitivity with regard to the probability of normotensive individuals to develop high BP in the future. These results provide further support to the role of salt-sensitivity and indirectly of excess dietary salt intake in the pathogenesis of hypertension.

In general, the occurrence of hypertension was high in this study population. At the end of the follow-up period, almost all the subjects in the salt-sensitive group had become hypertensive and half of them were on regular antihypertensive treatment prescribed by their family doctor. On multivariate analysis, it was found that the degree of salt-sensitivity was a significant independent predictor of the incidence of hypertension during the 15-year follow-up period. The predictive ability of salt-sensitivity was not confounded by the baseline BP value obtained on low salt diet, a condition in which the blood pressures of the LSS and HSS group were similar. By contrast, this predictive ability was lost when the baseline BP values during high sodium diet were included as covariate in the regression model: this is not surprising because these values were significantly different in the two groups as they were the expression of the different salt-sensitivity.

Although it is known that overweight and obesity are associated with alterations in renal sodium handling [19] and with BP salt-sensitivity [20–22], the difference in the risk of hypertension between HSS and LSS individuals was independent of the relatively small changes in body weight that occurred during the follow-up period.

The criteria used to define salt-sensitivity in our study were arbitrary. Indeed, no universally recognized definition for salt-sensitivity has yet been delivered. Previous studies in normotensive individuals [23] adopted a 5% fall in BP shifting from high to low sodium diet to define salt-sensitivity, a value that is very similar to the median of MBP response to the change in sodium intake

(corresponding to a 5.7% BP difference) in our study. As, however, in several other published studies, mostly dealing with hypertensive patients, a 10 mmHg BP fall on a low- compared to a high-salt diet was adopted as a cut-off to define BP salt-sensitivity [16,18], supplemental analyses were produced using this second criteria. Even so, salt-sensitivity was a significant independent predictor of the incidence of hypertension on multivariate analysis. In addition, the group of 'salt-sensitive' individuals identified by this cut-off displayed significantly higher GFR, and significantly greater mean renal diameter at follow-up, in the same way as when using the median of BP response as a salt-sensitivity cut-off.

Another novel finding of the present study was that individuals with greater salt-sensitivity, who had an increased rate of proximal tubular sodium reabsorption and a greater GFR at baseline compared to the LSS group [3], maintained an increased GFR at the 15-year follow-up visit. On this occasion, it was found that their higher GFR was associated with greater kidney length. Unfortunately, measurements of renal tubular sodium handling were not available at this time.

These results, in accordance with the evidence provided by several forms of monogenic hypertension [4–6] and by studies in essential hypertensive patients [12–13], support the contention that BP salt-sensitivity is the expression of an alteration of renal sodium handling impairing the ability of the kidney to excrete a large dietary sodium load and leading to a progressive increase in BP [3,24]. The renal sodium handling abnormality and the increased GFR were apparent before hypertension developed [3].

Very few data are available in the literature on the relationships between salt-sensitivity, glomerular hyperfiltration and risk of hypertension. Former kidney donors, who feature renal compensatory hypertrophy and increased single-nephron GFR, were found to have an increased risk of hypertension in some but not all studies [25–27]. Nevertheless, in these subjects, a persistent relative increase in GFR was associated with increased kidney size [27]. Hyperfiltration and/or increased intraglomerular pressure have been reported in hypertensive blacks and in other forms of salt-sensitive hypertension [8]. According to Schmieder *et al.* [14], hyperfiltration *per se* is an early marker of target organ damage. Moreover, in a 6-year follow-up study in essential hypertensive patients with normal renal function, it was found that the higher the GFR at baseline, the greatest the increase in serum creatinine at follow-up [28]. However, our prospective data in normotensive individuals did not confirm this finding. In spite of the greater incidence of hypertension in HSS individuals, the decline in GFR was similar in HSS and LSS participants, with GFR remaining higher in the group of

subjects with higher degree of salt-sensitivity: this finding was corroborated by the absence of significant differences in renal parenchymal thickness and in the albumin excretion rate. This somewhat unexpected result might be explained by the relatively young age of our study population, by the absence of both hypertension and diabetes at baseline examination and by the protective effect exerted by antihypertensive treatment, as expected based on the results of studies carried out in sodium dependent forms of hypertension [29,30]. Moreover, there is evidence that renal deterioration following hyperfiltration is generally associated with a reduction of the total number of nephrons and with loss of renal mass [31–34]. Although our data must be interpreted with caution due to the small sample size and the absence of baseline measurement of morphological parameters, they are in accordance with studies in kidney donors and in patients with solitary kidneys due to nephrectomy or to unilateral renal agenesis, which do not show a higher incidence of renal insufficiency until a further renal mass loss occurs [31–32].

Limitations

The sample under study was composed of white men only; thus, our findings cannot be extrapolated to women, nor to other ethnic groups.

The assessment of salt-sensitivity was made only at baseline and was based on the BP response to a very short period of dietary salt restriction. Moreover, both at baseline and at follow-up, BP was measured very carefully according to a well standardized protocol; however, measurements could not be repeated on a second separate occasion. These limitations were dictated by the epidemiological nature of our study which did not allow the performance of a second examination at a short distance of time. We acknowledge that they can make the evaluation of both BP salt-sensitivity and incidence of hypertension less accurate than desirable. Nevertheless, we believe it is most unlikely that they would explain our main findings. It is expected that inaccuracies in the measurement of any given variable due to introducing a larger regression dilution bias should impair the detection of true biological associations. The same is also conceivable if we consider, as a further limitation of our study, the relatively small sample size.

Finally, kidney ultrasonography was performed only at follow-up examination in a limited number of subjects: therefore, we do not know whether differences in kidney dimensions preceded the occurrence of hypertension.

In conclusion, the present study provides long-term prospective data on the incidence of hypertension and renal function outcomes in normotensive individuals with normal renal function at baseline and different degree of BP salt-sensitivity. Salt-sensitivity was associ-

ated with a pattern characterized by an increased risk of hypertension, altered proximal tubular sodium handling, enhanced GFR and increased kidney size. Further follow-up of the study participants is warranted to establish whether these alterations will be followed by detectable renal function deterioration in the future.

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