SODIUM, POTASSIUM, AND BLOOD PRESSURE

STUDIES IN THE YOUNG AND THE OLD

Cover design: Robbert den Bleker.

Printing:  Haveka B.V., Alblasserdam.

ISBN 90-9009108-4.

SODIUM, POTASSIUM, AND BLOOD PRESSURE

STUDIES IN THE YOUNG AND THE OLD

NATRIUM, KALIUM EN BLOEDDRUK

ONDERZOEK BIJ KINDEREN EN OUDEREN

PROEFSCHRIFT

ter verkrijging van de graad van doctor
aan de Erasmus Universiteit Rotterdam
op gezag van de rector magnificus
Prof. dr P.W.C. Akkermans M.A.
en volgens besluit van het College voor Promoties.

De openbare verdediging zal plaatsvinden op
woensdag 22 mei 1996 om 15.45 uur

door

Johanna Marianna Geleijnse

geboren te 's-Gravenhage.

Promotiecommissie

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	Prof. dr M.A.D.H. Schalekamp

It is too bad that we cannot cut the patient in half in order to compare two regiments of treatment.

Béla Schick (1877-1967), Austrian pediatrician

Acknowledgements

Financial support by the Netherlands Heart Foundation and the Rotterdam Medical Research Foundation (ROMERES) for the publication of this thesis is gratefully acknowledged.

Additional financial support has been obtained from the Netherlands Institute for Health Sciences (NIHES).

Financial support for the mineral salt intervention study was obtained from Akzo Nobel Salt Europe, The Netherlands, who also provided the mineral salt. The author gratefully acknowledges the contribution of Friesland Frico Domo, Meneba Meel B.V., Nestlé Nederland B.V., Nistria Dieetvleeswaren B.V., Quality Bakers Nederland B.V., and U.V.G. Nederland B.V.

The study of sodium intake in newborns was supported by the Netherlands Heart Foundation and Nutricia B.V.

The EPOZ study was supported by grants from the Netherlands Prevention Fund.

The Rotterdam Study is supported by the NESTOR stimulation program for geriatric research in the Netherlands (Ministry of Health and Ministry of Education), the Municipality of Rotterdam, the Netherlands Organization for Scientific Research (NWO), the Netherlands Prevention Fund, the Netherlands Heart Foundation, and the Rotterdam Medical Research Foundation (ROMERES).

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Geleijnse JM, Grobbee DE, Hofman A. Sodium and potassium intake and blood pressure change in childhood. BMJ 1990;300:899-902.

Grobbee DE, Geleijnse JM, Hofman A. Sodium and potassium intake and blood pressure change in childhood. *Re.* BMJ 1990;300:1397.

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Chee D, Geleijnse JM, Elliott P, Hofman A, Nichols R, Grobbee DE. Does urinary sodium and potassium excretion in childhood predict blood pressure change in early adulthood? Submitted.

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Geleijnse JM, Witteman JCM, den Breeijen JH, Hofman A, de Jong PTVM, Pols HAP, Grobbee DE. Dietary electrolyte intake and blood pressure in older subjects. The Rotterdam Study. J Hypertens, in press.

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Geleijnse JM, Witteman JCM, Bak AAA, den Breeijen JH, Grobbee DE. Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension. BMJ 1994;309:436-40.

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Chapter 4.4
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CHAPTER 1

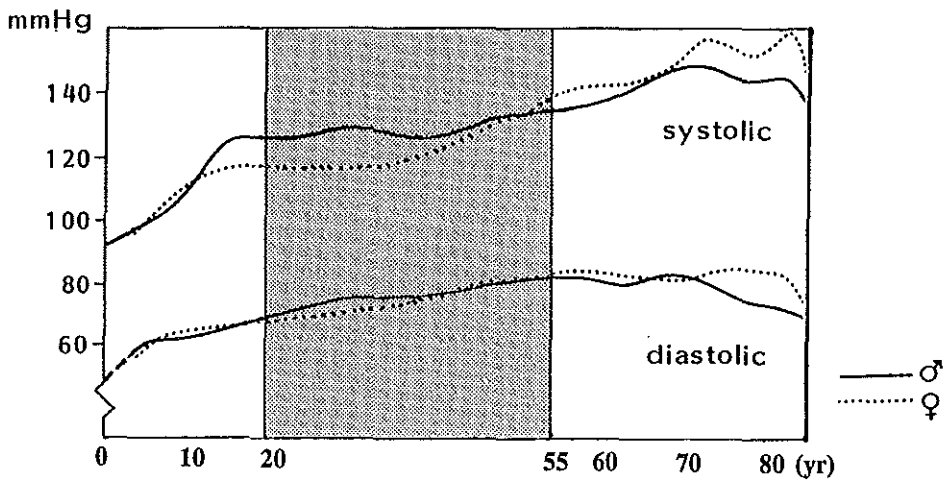
RATIONALE

1
Rationale

Blood pressure rises sharply from infancy through adolescence. About two thirds of the total lifetime increase in systolic blood occurs in childhood. Throughout adult life, the rise in blood pressure with age continues slowly but steadily. Whereas the mean diastolic blood pressure level seems to decline after the age of 55, systolic blood pressure increases even further at older age (fig. 1.1).

The age-related rise in blood pressure has hardly been observed in populations with a low sodium and high potassium intake, which gave rise to the hypothesis that these electrolytes could be implicated in the aetiology of hypertension. However, most observational studies within single populations could not confirm the relationship between dietary sodium and potassium intake and blood pressure. The lack of an association has often been attributed to inaccurate assessment of electrolyte intakes or blood pressure, or to the restricted ranges of intakes within a single population. An alternative explanation, however, could be that a population consists of a heterogeneous group of individuals, whose blood pressures may react quite differently to dietary influences. Evidence is now

Figure 1.1 Mean level of systolic and diastolic blood pressure at young and old age.*



* Data have been obtained from a study among 476 Dutch neonates (Hofman A, *et al.*, JAMA 1983;250:370-3) and from a cross sectional study among 10,355 subjects in the Netherlands (Valkenburg HA, *et al.* Ned Tijdschr Geneeskd 1980;124:183-9). Used with permission of the authors and publishers.

accumulating that there are subgroups that are susceptible to the intake of electrolytes, and others that are not. The sensitivity of blood pressure to electrolytes, in particular to sodium, may vary during life. During infancy, a high sodium intake could harmfully affect the immature kidney tissue, thereby having an influence on the natriuresis setpoint and the development of blood pressure in the years thereafter. At older age, the ability of the kidney to excrete sodium is reduced and the renin-angiotensin system becomes less responsive, which may increase the susceptibility of blood pressure to a higher intake of salt.

This thesis focuses on the relation between electrolyte intake and blood pressure during two phases in life that seem of particular importance in view of the sodium-blood pressure association, namely childhood and old age. Because the renal handling of sodium and potassium is closely related, the associations of these electrolytes with blood pressure were concomitantly considered in most of the studies described in this thesis. The role of neonatal sodium intake in determining blood pressure 15 years later in life is reported in Chapter 2. Chapter 3 describes the role of dietary sodium, potassium, and sodium/ potassium ratio in determining the rise in blood pressure from childhood into adulthood, using long-term follow-up data of a young subcohort drawn from a large Dutch population study (EPOZ). In Chapters 4.1 and 4.2 the association between electrolyte intake and blood pressure at old age was investigated cross sectionally within the cohort of the Rotterdam Study, a population based study among men and women aged 55 and over. Subsequently, a double blind, randomised, multifactorial intervention trial was conducted to see whether moderate dietary sodium restriction, combined with potassium and magnesium supplementation, would reduce blood pressure in older people with mild to moderate hypertension (Chapter 4.3). Some studies have pointed towards a potential unfavourable effect of sodium restriction on the blood lipid profile. In Chapter 4.4 we investigated whether this was also the case in our study. The findings of the presented studies are discussed and new research areas are delineated in Chapter 5.

CHAPTER 2

LONG-TERM EFFECTS OF NEONATAL SODIUM RESTRICTION ON BLOOD PRESSURE

2

Long-term effects of neonatal sodium restriction on blood pressure

Introduction

Despite extensive research, the causes of the epidemic of high blood pressure in westernised societies remain largely unknown. Population studies indicate that primary hypertension has its roots in childhood.[1,2,3] It has been shown that blood pressure levels in infancy and childhood are moderately predictive for blood pressure later in life.[4,5,6] Consequently, determinants of blood pressure in early life could be important in relation to future hypertension.

In a randomised, double blind trial among 476 newborn Dutch infants conducted in 1980, sodium intake was positively related to blood pressure during the first six months of life.[7] In the present analysis we investigated whether contrasting levels of sodium intake in infancy are still associated with blood pressure differences later in life. For this purpose, blood pressure in 167 youngsters who had participated in the original trial was measured again after 15 years of follow-up. In addition, possible modification of the effect of sodium on blood pressure by sex, body mass index and resting heart rate was investigated.

Methods

Sodium-blood pressure trial

A group of 476 newborn infants participated in a randomised double blind trial of the effect of sodium intake on blood pressure. All infants were born in 1980 to healthy women living in Zoetermeer, The Netherlands. Two hundred and thirty-one infants were randomly assigned to a low sodium diet and 245 infants to a normal sodium diet during the first six months of life. Systolic blood pressure was measured in the first week of life and every 4 weeks thereafter using a Doppler ultrasound device connected to a random-zero sphygmomanometer. Diastolic blood pressure could not be recorded accurately by this procedure. A detailed description of the study protocol has been given previously.[7]

The average daily amount of sodium ($\pm$ SD) consumed during the trial amounted to 0.89 $\pm$ 0.26 moles in the low sodium group and 2.50 $\pm$ 0.95 moles in the normal sodium group. After 25 weeks of intervention, systolic blood pressure in the low sodium group was 2.1 mmHg lower (90% CI 0.5 to 3.7, p_1=0.01) than in the normal sodium group after adjustment for weight and length at birth, systolic blood pressure in the first week, and blood pressure observers.

Subjects for the follow-up study

A total of 466 infants (98%) completed the trial and were eligible for the present follow-up study. The current addresses of 185 children could not be traced. Seventy-one children had moved out of Zoetermeer and they were not invited for logistic reasons. Eleven children could not be contacted by telephone. A total of 199 children was contacted (45% of those eligible). Twelve children refused participation. Twenty children could not participate because of illness, holiday, or other activities. A total of 167 children (84% of those contacted) agreed to participate and they visited the study centre for blood pressure measurements. Of those, 71 children had initially been assigned to the low sodium group, and 96 children to the normal sodium group.

Follow-up measurements

Blood pressure and heart rate were measured on the right arm by two investigators, using an automatic device (Dinamap model 8100, Critikon Inc, Florida) while the participant was seated. After at least five minutes rest, four measurements were performed of which the last three were averaged. Body weight and height were measured without heavy clothing and shoes. The body mass index was computed as weight divided by height squared. During the visit at the study centre, information was obtained by means of a questionnaire on current use of medication, smoking, consumption of alcohol, physical activity (sports, biking and walking), education, presence of treated hypertension in parents (yes/no), and age at menarche. The educational level of the participants was rated on a 5-point scale and subsequently recoded to three levels (low, average or high education). The educational level of the parents, which had been assessed on a 9-point scale at the start of the trial, was also reduced to three levels. The participants collected an overnight urine specimen after visiting the study centre. The time of collection and urinary volume were recorded. Urinary sodium, potassium and creatinine were analysed by standard laboratory methods. The overnight urinary excretions of sodium and potassium were standardised to 24 hour values.

Data analysis

The present study population was regarded as a cohort with two different levels of (experimentally manipulated) sodium intake early in life. The exposure was based on the initial randomization code, irrespective of subsequent protocol deviations or compliance. The difference in blood pressure between the study groups after 15 years of follow-up was computed and tested for statistical significance by means of a two-tailed unpaired *t*

test. The loss to follow-up of subjects for the present study, although for reasons unrelated to the object of research, introduced unequal distributions of baseline and current characteristics between the study groups. Therefore, an additional analysis was performed to adjust for potential confounders. A multiple linear regression model was used with systolic and diastolic blood pressure as the outcome variables. Adjustments were made for sex, length and weight at birth, maternal educational level, maternal systolic blood pressure at baseline, educational level of the participant, presence of treated hypertension in parents and blood pressure observers. An indicator for the sodium group (0=low, 1=normal) was entered as an independent variable. The regression coefficient

Table 2.1 Baseline characteristics of the follow-up cohort according to study group (n=167).

	Normal sodium (n=96)	Low sodium (n=71)
Sex ratio (% M/F)	50/50	54/46
Length at birth (cm)	50.9 (2.0)	51.5 (1.7) *
Weight at birth (g)	3406 (422)	3583 (405) †
Systolic blood pressure (mmHg)	86.4 (21.4)	88.2 (20.1)
Heart rate (beats/min)	69.1 (9.7)	69.8 (10.0)
Duration of pregnancy (weeks)	39.7 (1.2)	40.0 (1.2)
Blood pressure father (mmHg):		
Systolic	125.1 (10.4)	126.7 (13.7)
Diastolic	79.8 (11.6)	80.7 (14.7)
Blood pressure mother (mmHg):		
Systolic	111.6 (10.7)	114.7 (10.0) ‡
Diastolic	70.4 (11.5)	73.2 (10.1)
Educational level father (%):		
Low	25	38
Average	25	21
High	50	41
Educational level mother (%):		
Low	22	48
Average	45	27
High	33	25 §

Values are means with standard deviation in parentheses, or percentages.
* $t=1.94$, $p_2=0.05$; † $t=2.74$, $p_2=0.007$; ‡ $t=1.91$, $p_2=0.06$; § $X^2_{trend}=19.1$, $p_2=0.015$.

for the sodium group yielded by this model estimates the adjusted blood pressure difference between the sodium groups. The analyses were repeated for boys and girls separately and in strata of body mass index and resting heart rate. Stratification for body mass index and heart rate was performed by dividing the persons into two groups according to the sex-specific medians of the distributions. The differences in blood pressure are given with a 95% confidence interval and a two-sided p-value.

Results

Baseline characteristics of the follow-up cohort are given in table 2.1. A larger proportion of boys was observed in the low sodium group than in the normal sodium group, but the difference was not statistically significant. Length and weight at birth were significantly higher in the low sodium group than in the normal sodium group. Furthermore, mothers were significantly lower educated and maternal systolic blood pressure tended to be higher in the low sodium group. Other baseline characteristics were similar in the two groups.

Characteristics of the participants after 15 years of follow-up are given in table 2.2. No significant differences in height, body weight, body mass index and physical activity were observed between the study groups. Frequencies of smoking and consumption of alcohol were similarly distributed in both groups. Significantly more participants in the low sodium group than in the normal sodium group reported to have one parent currently treated for hypertension. None of the participants had both parents currently treated for hypertension. Participants in the low sodium group were significantly lower educated than those in the normal sodium group. Among girls, the age at menarche was not significantly different between the groups.

Table 2.3 shows the differences in blood pressure between the study groups after 15 years of follow-up. Systolic and diastolic blood pressure levels were slightly higher in the normal sodium group than in the low sodium group, but the differences were not statistically significant. After adjustment for potential confounders (indicated in table 2.3), systolic blood pressure was 3.6 mmHg higher (95% CI 0.5 to 6.6 mmHg, p_2=0.02) and diastolic blood pressure was 2.2 mmHg higher (95% CI -0.2 to 4.5 mmHg, p_2=0.08) in the normal sodium group than in the low sodium group. The change in regression coefficients after adjustment was attributable to the inclusion of length and weight at birth, maternal educational level, maternal systolic blood pressure, and presence of treated hypertension in parents, in the multivariate model. A small additional change was observed after further adjustment for educational level of the participant, sex, and blood

Table 2.2 Current characteristics of the follow-up cohort according to study group (n=167).

	Normal sodium (n=96)		Low sodium (n=71)	
Height (cm)	170.9	(8.5)	171.9	(8.4)
Body weight (kg)	59.0	(11.0)	59.8	(9.9)
Body mass index (kg/m^2)	20.1	(2.7)	20.2	(2.8)
Systolic blood pressure (mmHg)	117.5	(10.6)	116.1	(10.5)
Diastolic blood pressure (mmHg)	56.4	(7.8)	55.8	(7.7)
Heart rate (beats/min)	77.0	(10.9)	81.2	(11.6) *
Physical activity (hrs/week)	7.8	(4.8)	6.7	(3.8)
Age at menarche (yrs)	12.8	(1.2)	12.5	(1.1)
Smoking (%)	9		9	
Alcohol consumption (%)	13		11	
Hypertension in father or mother (%)	8		18	†
Educational level:				
Low	17		30	
Average	36		41	
High	47		29	‡
Urinary excretion (mmol/24h):				
Sodium	85	(46)	75	(31)
Potassium	29	(16)	25	(10)
Sodium/potassium ratio	3.4	(1.7)	3.3	(1.5)
Creatinine	11.2	(4.3)	11.4	(3.4)

Values are means with standard deviation in parentheses, or percentages.
* $t=2.4$, $p_2=0.017$; † $X^2=3.7$, $p_2=0.05$; ‡ $X^2_{trend}=12.1$, $p_2=0.016$.

pressure observers, whereas no change in regression coefficients was observed after adjustment for baseline systolic blood pressure. Differences in sodium and potassium excretion between the study groups were small and inclusion of these variables in the model (with or without correction for creatinine excretion) did not change the results.

The effect of sodium on blood pressure did not differ significantly between boys and

Table 2.3 Differences in blood pressure (BP) level between the normal sodium and low sodium group after 15 years of follow-up.

	Systolic BP (mmHg)	Diastolic BP (mmHg)
Difference	1.5 (-1.8, 4.7) *p=0.38*	0.6 (-1.8, 3.0) *p=0.61*
Adjusted difference*	3.6 (0.5, 6.6) *p=0.02*	2.2 (-0.2, 4.5) *p=0.08*

Values are mean differences (normal minus low sodium group) with 95% confidence interval in parentheses and two-sided p-value.
* Adjusted for sex, length and weight at birth, education, hypertension in parents, maternal education, maternal systolic blood pressure, and blood pressure observers.

girls, or between subjects with a body mass index below and above the median of the distribution. When the analysis was restricted to persons with a resting heart rate above the median, the adjusted differences in blood pressure between the sodium groups were 6.0 mmHg (95% CI 1.5 to 10.5 mmHg, $p_2=0.01$) for systolic blood pressure, and 4.8 mmHg (95% CI 0.9 to 8.7 mmHg, $p_2=0.02$) for diastolic pressure. In persons with a resting heart rate below the median, differences in blood pressure were small (-0.8 mmHg and -1.7 mmHg for systolic and diastolic blood pressure, respectively) and not statistically significant.

Discussion

This paper presents the results of a long-term follow-up of a cohort of children who had been exposed to contrasting levels of sodium intake during the first six months of life. The findings show that sodium intake in infancy is associated with systolic and diastolic blood pressure 15 years later in life, after adjustment for confounders. The blood pressure effect of sodium appears to be modified by resting heart rate.

The children remeasured for the present analysis forms a subgroup of the original population that participated in a double-blind randomised trial of low *vs.* normal sodium intake.[7] As such, the study is a cohort study in which the contrast in baseline exposure, *i.e.* neonatal sodium intake, has been experimentally achieved. Forty percent of the subjects initially assigned to the normal sodium group, and 31% of the subjects in the low sodium group, participated in the follow-up study. Whereas the study groups in the original trial were similar with regard to length and weight at birth, maternal systolic

blood pressure and maternal educational level, these variables differed between the sodium groups in the follow-up study. Furthermore, in the present study, subjects in the low sodium group were lower educated and reported more often current treatment for hypertension in one of the parents. These observed differences could be related to the change in blood pressure during childhood. Systolic blood pressure of the mother at the start of the study, for example, appeared to be positively associated with the blood pressure of the child 15 years later. Because maternal blood pressure at baseline was higher in the low sodium group than in the normal sodium group, the intervention-related difference in blood pressure levels at follow-up was reduced. In order to reliably estimate the true effect of neonatal sodium intake on future blood pressure, the analyses were repeated using a multivariate model that included all potential confounders. The conclusions of the present study are based on the adjusted blood pressure differences.

We cannot infer from our findings which mechanism has led to higher blood pressures in the normal sodium group. Possibly, the preference for a certain level of salt intake is determined early in life. Subjects in the present study who had been exposed to lower sodium intakes during infancy may have maintained a reduced salt intake after the trial, eventually resulting in lower blood pressure levels. The overnight excretion of sodium in the low sodium group indeed tended to be reduced compared to the normal sodium group. However, urinary potassium, which is inversely related to blood pressure and probably a stronger predictor of blood pressure change in childhood than sodium,[8] was also lower in these children. As only a single overnight urine specimen for the assessment of sodium was collected at the time of the follow-up measurements, we cannot make a firm statement about salt intake during the preceding period. Several alternative explanations for the blood pressure difference can be given. Sympathetic nervous system overactivity may be related to essential hypertension through a sustained increase in peripheral vascular resistance.[9] A possible interaction between salt intake and the sympathetic nervous system in determining blood pressure level has been suggested.[10,11] In the present study, the blood pressure effect appeared to be restricted to those with higher resting heart rates. Staessen *et al.*, in a population study, similarly found a significant positive association between 24 hour urinary sodium and blood pressure in subjects with high heart rates, whereas an opposite tendency was observed in persons with lower heart rates.[10] An interaction between a high dietary sodium intake, environmental stress, and sympathetic neural control of renal function as part of the early hypertensive process has also been reported.[12] Furthermore, exposure to high sodium levels in infancy may cause damage of the immature kidney tissue and adversely affect the development of blood

pressure during growth and maturation.[13] An alternative explanation for the higher blood pressure levels in the normal sodium group could be an alteration in renal sodium handling, resulting from early changes in renal haemodynamics. In line with this hypothesis, an increased renal vasoconstriction and a decreased renin and aldosterone secretion has been observed in young offspring of hypertensive parents.[14]

Environmental exposures *in utero* and in infancy may be more important in relation to cardiovascular disease than exposures in adulthood, as 'programming' of different systems and organs in the body may take place very early in life.[15] Evidence is accumulating that birth weight is inversely related to the risk of hypertension later in life.[16,17,18,19] The present study suggests that neonatal sodium intake could be related to blood pressure level in adolescence. Data on the effect of nutrient intake in infancy on future blood pressure are scarce. Studies in this field may provide clues for the prevention of hypertension in westernised societies, and a further understanding of its causes.

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CHAPTER 3

ELECTROLYTES AND BLOOD PRESSURE AT YOUNG AGE

THE EPOZ STUDY

3.1

Sodium and potassium intake and blood pressure change in childhood

Introduction

Primary hypertension is one of the most important risk factors for cardiovascular disease and probably has its onset in the first decades of life. Study of blood pressure in childhood may shed light on the aetiology of hypertension and indicate opportunities for measures to prevent hypertension in adult life.[1] Blood pressure in children is determined by genetic and environmental factors. Race, sex, and anthropometric characteristics such as height and body weight have been identified as determinants of blood pressure and the rise in childhood.[2,3,4] Although the effect of biological maturation is still a subject of debate, alterations in growth and sex hormones may also be related to changes in blood pressure.[5]

The part played by dietary factors has been thoroughly studied. Sodium intake has been the main topic, but most studies have been concerned with adults. Findings in some but not all interpopulation studies suggest that the prevalence of hypertension is lower in areas with a low sodium intake, although considerable doubt remains about the nature and significance of this.[6] In children and young adults findings are even less consistent.[7] Moreover, the rise in blood pressure with age might to some extent be dependent on the average level of sodium intake in a population. Recently the INTERSALT Co-operative Research Group found an additional rise in systolic blood pressure of 0.003 mmHg with a sodium intake that was on average 1 mmol/24h higher in adults.[8] If such an effect of the diet was already acting in childhood and persisted over a lifetime the consequences for the incidence of hypertension in a population might be substantial.[9] An inverse association of blood pressure with potassium has been noted occasionally, although this finding remains controversial.[10] Moreover, there may be an interaction among various dietary electrolytes. In particular, the sodium/potassium ratio could be important.

Because advice on diet may well play a part in intervention, studies on the effect of dietary components on blood pressure remain important. In this study children with high intakes of sodium and potassium were compared with those having low intakes with regard to their individual changes in blood pressure over time. Change in blood pressure rather than actual blood pressure in children may be a predictor of adult blood pressure and of hypertension.[11,12]

Methods

Population

Between 1975 and 1978 the total population aged 5 years and over in two districts of Zoetermeer, a suburban town in the western part of the Netherlands, was invited to take part in a study of risk factors for cardiovascular disease.[3,4] Of 5,670 eligible subjects aged 5-19 years, 4,649 (82%) were examined. From this group a random sample of 596 children was selected for annual follow-up in a study of blood pressure tracking and its determinants.[3,4] They were examined four weeks after the initial examination and subsequently at yearly intervals. Children with established secondary hypertension were excluded. For the present analysis we selected children aged up to 17 at entry into the study and whose follow-up included at least six yearly examinations. Of the 233 subjects in the cohort, 108 were boys and 125 girls. The mean follow-up period was seven years.

Measurements

Blood pressure measurements were performed with a random zero sphygmomanometer as described in detail elsewhere.[3] Paramedical workers were trained to measure systolic and diastolic blood pressure according to a standardised protocol. Cuffs 23 cm by 10 or 14 cm were used, depending on the arm circumference. In children aged over 10 generally the largest cuff was used. Blood pressure was measured in the left arm after 15 minutes' sitting. Diastolic blood pressure was recorded at the fifth Korotkoff phase. Two blood pressure readings were taken and the average was used for analysis. Height and body weight were measured with the participant wearing light indoor clothing without shoes. Urine samples were analysed for sodium and potassium by flame photometry. Urine was

Table 3.1.1 Characteristics of the total study group at entry into study.

	Mean (SD)	Range
Age (yrs)	13.2 (2.7)	5.9 - 17.0
Height (cm)	159.3 (16.2)	115.0 - 193.0
Body weight (kg)	48.8 (14.6)	20.0 - 80.0
Systolic blood pressure (mmHg)	112.4 (12.9)	81.0 - 153.0
Diastolic blood pressure (mmHg)	68.4 (8.7)	44.0 - 97.0

collected as six timed overnight samples.[13,14] The collection began at supper and ended with the first urine voided the next morning. Labelled containers were provided, on which the subjects noted the times of starting and finishing each collection. From these the mean 24 hour sodium and potassium intakes were calculated. Electrolyte excretion measured in timed overnight urine samples correlates reasonably well with true mean 24 hour excretion rates in young subjects.[13,14] The main difference between the two measurements is a somewhat higher within person variability in the overnight samples. Both methods require multiple samples, and plainly these are more easily collected overnight.

Data analysis

Six complete annual records of each subject were used in the analysis. To quantify the change in blood pressure during the follow-up period individual slopes of blood pressure against time were calculated by using linear regression analysis. The association of urinary sodium, potassium, and sodium/potassium ratio, with blood pressure slope was analysed by multiple linear regression analysis. To adjust for differences in sex, initial age, and change in height and body weight during follow-up, these variables were included in the model. When analysing the effect of high sodium intake, adjustments were made for potassium intake, and vice versa. Furthermore, to assess the effect of electrolyte intake on the change in blood pressure, the study group was divided into subgroups based on thirds of the distributions of mean sodium and potassium intake and mean sodium/potassium ratio over the follow-up period. In all analyses lower and upper thirds were compared. Data are presented as mean changes per year and 95% confidence intervals. Equality of group means was tested for both high and low sodium, potassium, and sodium/potassium ratio groups by using analysis of variance. Significance of differences was assessed by two tailed tests throughout. To see whether the relation between electrolyte intake and change in blood pressure was different in boys and girls or in different age groups, the data were analysed by sex and age at the initial survey. The median of the initial age distribution was used in stratifying the children for age. In the younger group the age range was 5.9-13.7 years and in the older group 13.8-17.0 years.

Results

Table 3.1.1 gives the characteristics of the subjects at the start of the study. Changes in height, body weight, systolic blood pressure, and diastolic blood pressure during the follow-up period are given in table 3.1.2. Table 3.1.3 shows the mean values and ranges

Table 3.1.2 Yearly rate of change in height, body weight, systolic blood pressure, and diastolic blood pressure during follow-up.

	Rate of change*	95% confidence interval
Height (cm/year)	2.61	(2.31, 2.91)
Body weight (kg/year)	2.85	(2.60, 3.10)
Systolic blood pressure (mmHg/year)	1.95	(1.65, 2.25)
Diastolic blood pressure (mmHg/year)	0.58	(0.39, 0.77)

* Coefficient of linear regression.

Table 3.1.3 Average excretion of sodium, potassium, and sodium/potassium ratio, and ranges according to thirds of distributions of electrolyte excretion in study groups during follow-up.

		Range	
	Mean	Lower third	Upper third
Sodium excretion (mmol/24h):			
Total study group	135.6	61.5 - 117.7	147.5 - 251.5
Boys	140.8	61.5 - 127.2	158.2 - 251.5
Girls	131.1	68.5 - 115.0	139.8 - 215.3
Younger group	138.4	68.5 - 119.8	147.5 - 251.5
Older group	132.8	61.5 - 113.5	147.5 - 215.3
Potassium excretion (mmol/24h):			
Total study group	43.7	15.8 - 37.7	47.8 - 77.3
Boys	47.0	20.2 - 41.5	51.2 - 77.3
Girls	40.9	15.8 - 35.3	43.5 - 71.0
Younger group	43.3	15.8 - 37.2	47.3 - 77.3
Older group	44.1	20.2 - 38.5	47.8 - 75.8
Sodium/potassium ratio:			
Total study group	3.3	1.1 - 2.8	3.6 - 7.4
Boys	3.1	1.1 - 2.6	3.4 - 7.4
Girls	3.3	1.6 - 2.8	3.7 - 5.8
Younger group	3.3	1.6 - 2.8	3.6 - 5.8
Older group	3.2	1.1 - 2.6	3.6 - 7.4

of average sodium and potassium excretion, and sodium/potassium ratio, in the lower and upper thirds of the study groups during the follow-up. In boys the mean 24 hour sodium excretion ranged between 61.5 and 251.5 mmol, which reflects a daily salt intake of 3.6-14.7 g. In girls the mean 24 hour sodium excretion ranges between 68.5 and 215.3 mmol, corresponding to a salt intake of 4.0-12.6 g/day. Potassium intake was higher in boys than in girls and therefore the sodium/potassium ratio was higher in girls. During the study period age showed no independent association with electrolyte intake.

Table 3.1.4 shows the association between the yearly rate of change in systolic blood pressure and urinary electrolyte excretion. No significant relation between sodium excretion and change in systolic blood pressure could be detected. Urinary potassium excretion, however, was strongly and inversely associated with systolic blood pressure in this cohort (coefficient of linear regression -0.45 mmHg/year/mmol; p=0.0004) whereas the systolic blood pressure slope was higher when the sodium/potassium ratio was higher

Table 3.1.4 Association of yearly rate of change in systolic blood pressure with urinary excretion of sodium, potassium, and sodium/potassium ratio.*

	Sodium	Potassium	Sodium/potassium ratio
Regression coefficient†	0.003 (-0.006, 0.012)	-0.045 (-0.069, -0.020)	0.356 (0.069, 0.642)
Mean slope:‡			
Lower third	2.04 (1.56, 2.52)	2.44 (1.99, 2.89)	1.43 (0.97, 1.88)
Middle third	1.64 (1.19, 2.09)	1.87 (1.42, 2.32)	1.91 (1.46, 2.36)
Upper third	2.12 (1.65, 2.59)	1.43 (0.98, 1.88)	2.24 (1.79, 2.69)

* Adjusted for differences in sex, initial age and change in height and body weight. Findings for sodium are adjusted for potassium excretion, and *vice versa*; 95% confidence intervals in parentheses.
† Regression coefficients (mmHg/yr/mmol, or mmHg/yr/unit for sodium/potassium ratio) for the group as a whole.
‡ Mean systolic blood pressure slopes (mmHg/yr) in subgroups based on tertiles of the electrolyte excretion distributions.

(0.356 mmHg/year/unit; p=0.02). The effects of these associations were reflected in the levels of annual increase in systolic blood pressure in children in the lower, middle, and upper thirds of the distribution of electrolyte excretion (table 3.1.4).

Figure 3.1.1 shows the differences in rise in systolic blood pressure during follow-up between subjects with high and low potassium intakes for the group as a whole and for subgroups based on sex and age. Mean yearly change in systolic blood pressure was 1.4 mmHg in the group with a high potassium intake and 2.4 mmHg in the group with a low potassium intake (p=0.007). The difference (1.0 mmHg) amounted to half the average yearly change in systolic blood pressure recorded in the group as a whole (table 3.1.2). This finding seemed to be most pronounced for boys: 2.1 mmHg/year in those with a high intake and 3.1 mmHg/year in those with a low intake (p=0.04). The stratified analysis disclosed no clear difference in effect in different age groups.

Figure 3.1.2 shows the differences in rise in systolic blood pressure between groups with high and low urinary sodium/potassium ratios. In children with a high sodium/potassium ratio a slope of 2.2 mmHg/year was recorded, compared with 1.4 mmHg/year in children with a low sodium/potassium ratio (p=0.02). The difference in blood pressure slope between the groups with high and low ratios was present in both boys and girls. The effect of sodium/potassium ratio on change in systolic blood pressure seemed to be stronger in older children. In the group initially aged 13.8-17.0 years the difference between the groups with high and low sodium/potassium ratios was 1.0 mmHg/year (p=0.03).

Neither sodium, nor potassium, nor the sodium/potassium ratio was significantly related to the change in diastolic blood pressure. When the data were reanalysed taking initial blood pressure readings into account, results were unaffected.

Discussion

The main findings in this longitudinal study were that both potassium intake and the ratio of sodium to potassium intake were related to the change in systolic blood pressure in childhood. Children with a high dietary intake of potassium had a smaller annual increase in systolic blood pressure than children with a low intake. The sodium/potassium ratio showed a positive relation with blood pressure. Interestingly, in this age group there was no clear effect of sodium intake alone. These findings corroborate the report by Lever *et al.*, who hypothesised that in the early stages of hypertension blood pressure is raised by a process more related to potassium than to sodium.[15] Moreover, findings in experimental studies suggest that an effect of sodium intake on blood pressure may be

Figure 3.1.1 Differences in yearly systolic blood pressure change (mmHg/year) during follow-up between children with high and low potassium excretions (mean slope in upper tertile of the potassium excretion distribution minus slope in lower tertile). Adjusted for sex, initial age, change in height and body weight, and sodium intake; with 95% confidence intervals.

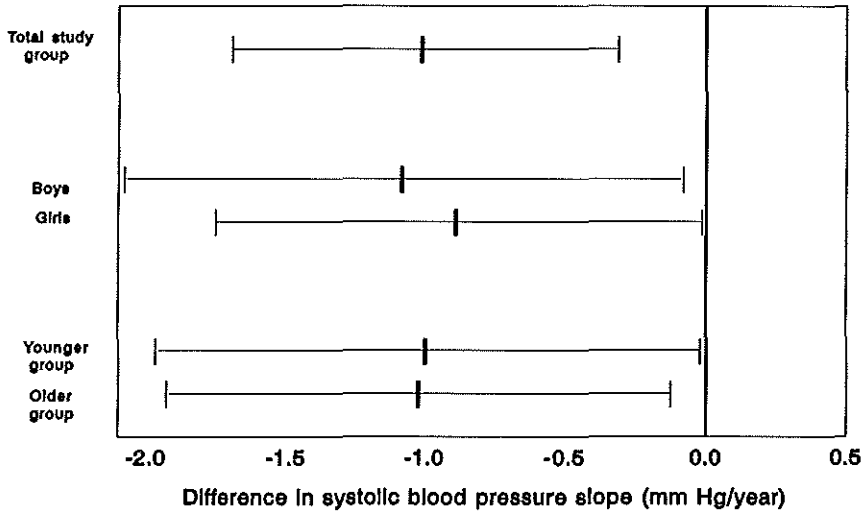
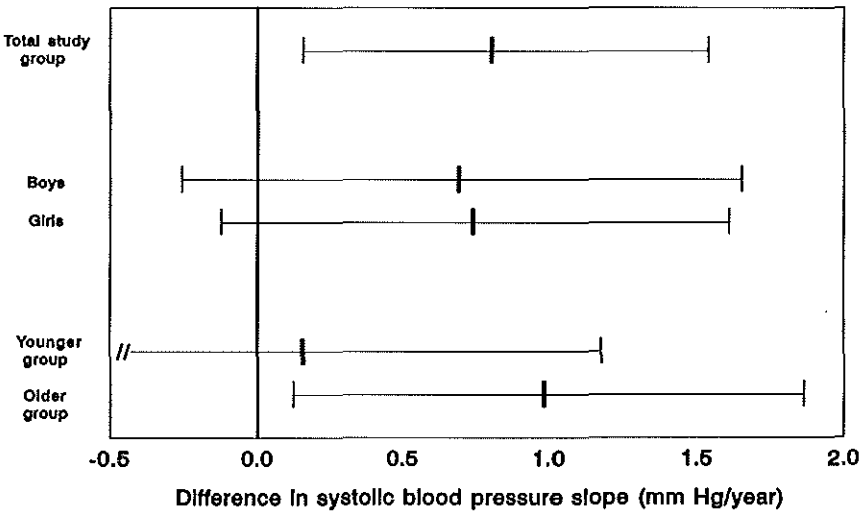


Figure 3.1.2 Differences in yearly systolic blood pressure change (mmHg/year) during follow-up between children with high and low sodium/potassium excretions (mean slope in upper tertile of the sodium/potassium excretion distribution minus slope in lower tertile). Adjusted for sex, initial age, and change in height and body weight; with 95% confidence intervals.



present only in older age groups.[16] One trial conducted in newborn infants, however, found a small but significant effect of sodium intake on the blood pressure slope during the first months of life.[17]

The inverse association between potassium intake and the rise in systolic blood pressure was similar in the two age groups. By contrast, the relation between the sodium/potassium ratio and the blood pressure slope was stronger with age. As this age related phenomenon could not be ascribed to either sodium or potassium it was probably related to an age dependent interaction between the two. Khaw and Barrett-Connor found an increased sensitivity of blood pressure to the dietary sodium/potassium ratio with ageing in men.[18]

Some studies have failed to detect a relation between potassium or the sodium/potassium ratio and blood pressure in children or adults.[7,19,20] This may be explained in several ways. Firstly, in some studies only one urine sample was used to estimate the daily sodium and potassium intake. The large intraindividual variability of urinary cation excretion, notably sodium, may obscure results.[21] This calls for repeated measurements of electrolyte excretion.[14] Sodium and potassium intakes in our study were assessed by calculating the mean daily sodium and potassium excretion from six timed overnight urine samples. By averaging multiple measurements, the effect of intraindividual day to day variability is reduced and sodium and potassium intakes are estimated more precisely. Secondly, if the relation between potassium and blood pressure exists only in childhood or in the early stages of hypertension, no observable effect might be present in study populations that are older.[15] Thirdly, in some surveys on potassium the study period was quite short. If the effect of potassium becomes evident only after a sufficient time of exposure it might be too weak to be detected in these studies.

There are several ways by which potassium intake might affect the rise in blood pressure.[22] Potassium may reduce blood pressure by vasodilatation, thereby causing a decrease in total peripheral resistance and an increase in cardiac output. Some studies suggest that potassium might lower blood pressure by acting as a diuretic or by altering the activity of the renin-angiotensin system. Others give evidence that potassium might modify peripheral and central neural regulation of blood pressure. We can draw no conclusions from our study about the way that potassium acts. Nor is there a ready explanation for a possible mechanism of sodium-potassium interaction. Finally, there remains a possibility that potassium intake and the urinary sodium/potassium ratio are indicators of another, as yet unknown, determinant of blood pressure change in childhood rather than being direct causal factors in blood pressure regulation.

In conclusion, this study supports the view that dietary potassium and the dietary sodium/potassium ratio may be important in the early pathogenesis of hypertension. Possibly a sufficient intake of potassium or a reduction of the dietary sodium/potassium ratio in youth may prove to be beneficial in the early prevention of hypertension.

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3.2

Does urinary sodium and potassium excretion in childhood predict blood pressure change in early adulthood?*

Introduction

There is accumulating evidence that the origins of primary hypertension may be found in childhood.[1,2,3] Blood pressure in childhood or early adult life rises progressively through to middle age, and predicts both the blood pressure level and presence of hypertension in later life.[4,5,6,7,8,9,10,11,12]

Among a population of children first examined in the 1970s, we reported previously a significant inverse association between change in systolic blood pressure with age and urinary potassium excretion, and a direct association with the urinary sodium/potassium ratio, with follow-up to the end of 1985.[1] To further explore the long-term importance of electrolyte excretion in blood pressure development, we present here findings from this cohort on change of blood pressure with age over the subsequent six year period (1985-1991) in relation to earlier values of urinary excretion of sodium, potassium, and sodium/potassium ratio obtained between 1978 and 1985. Previous studies have shown a fall in blood pressure in girls (but not boys) starting around the age of puberty.[13] The analyses were therefore performed separately in subgroups by sex and median age.

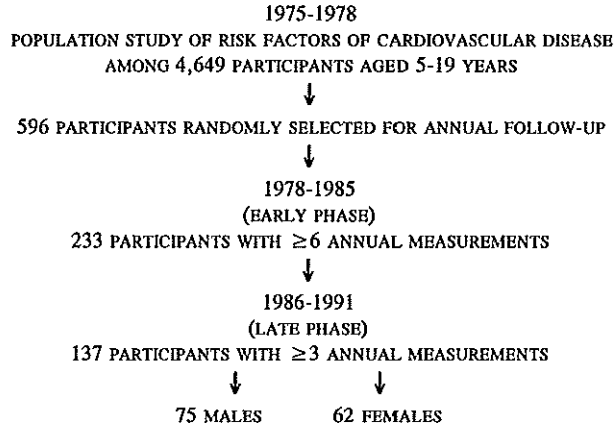
Methods

Population

Between 1975 and 1978 the total population aged 5 years and over in two districts of Zoetermeer, a suburban town in the western part of the Netherlands, was invited to participate in a study of risk factors for cardiovascular disease.[14,15] Of 5,670 eligible persons aged 5-19 years, 4,649 (82%) were examined. A random sample of 596 participants was selected for annual follow-up in a study of blood pressure tracking and its determinants.[14,15] Participants with established secondary hypertension were excluded. We reported previously on 233 of these children, aged up to 17 years at entry, whose follow-up included at least six annual examinations in the early phase of the study, *i.e.*, up to the end of 1985.[1] Among this subsample, 137 individuals (58%, 75 males and 62 females) had at least three annual examinations in the late phase of the study, *i.e.* from 1986 to 1991, and are included in the present report. The average period of follow-up for these individuals was 13 years from entry. The selection of subjects for the present analysis is summarised in Figure 3.2.1.

* *In collaboration with Chee D et al., London School of Hygiene and Tropical Medicine, UK*

Figure 3.2.1 Selection of the study population



Measurements

Blood pressure was measured in the left arm after 15 minutes' sitting by trained paramedical workers using a random zero sphygmomanometer according to a standard protocol. Cuffs measuring either 23x10 or 23x14 cm were used depending on the arm circumference. Two blood pressure readings were taken at each examination and then averaged. Height and body weight were measured with the participant wearing light indoor clothes without shoes. Overnight urine samples were collected annually. Labelled containers were provided on which the participants noted the starting and finishing times of each urine collection. Collections began at supper and ended with the first urine voided the next morning. Urinary volume was measured, and the urine was analysed for sodium and potassium concentrations using flame photometry. Electrolyte excretions were standardized to 24 hour values.

Data analysis

Urinary excretion of sodium, potassium, and sodium/potassium ratio for each individual was taken as the mean of the six (or more) annual measurements obtained in the early phase of the study.

Change in systolic and diastolic blood pressure with age (mmHg/year) in the late phase of the study was estimated for each individual by simple linear regression of blood

Table 3.2.1 Characteristics of the participants in the early phase of the study.

	Mean (SD)	
	Males (n=75)	Females (n=62)
Age (yrs)	14.1 (3.3)	13.6 (3.1)
Systolic blood pressure (mmHg)	118.2 (15.9)	110.5 (10.6)*
Diastolic blood pressure (mmHg)	72.2 (9.5)	70.6 (8.4)
Body mass index (kg/m^2)	19.7 (12.9)	19.3 (12.2)
Urinary excretion:		
Sodium (mmol/24h)	138.0 (56.7)	139.9 (59.4)
Potassium (mmol/24h)	42.1 (20.1)	43.5 (21.6)
Sodium/potassium ratio	4.1 (1.8)	3.9 (2.2)

* $p<0.001$, males vs. females.

pressure against age. Changes of height and weight in the late phase were obtained in similar fashion. The relationship of the mean urinary variables of the early phase to blood pressure change during the late phase was analysed using multiple linear regression, with adjustment for sex, mean age and body mass index in the early phase, and change in height and weight in the late phase. In addition, when analysing relationships with urinary sodium excretion, adjustment was made for urinary potassium excretion and *vice versa*. The number of blood pressure observations in the late phase for each individual was used to weight the regression analyses.[16] The analyses were performed separately in subgroups by sex and age. Age strata were formed by dividing the study group into 'younger' and 'older' groups according to the median of the age distribution in the early phase of the study (14.3 years for males, 13.7 years for females).

Results

Characteristics for males and females obtained in the early phase of the study are shown in Table 3.2.1. Values were similar in both sexes, except for mean systolic pressure that was significantly higher in males (118.2 mmHg, *vs.* 110.5 mmHg in females, $p<0.001$). Mean urinary excretion during the early phase of the study was around 139 mmol/24 hour for sodium, around 43 mmol/24 hour for potassium, and around 4 for sodium/potassium

Table 3.2.2 Regression coefficients for average yearly change of systolic and diastolic blood pressure (BP), height, and weight in the late phase of the study, divided by median age into younger and older age groups (n=137).

	b (SE)*			
	Males (n=75)		Females (n=62)	
	Younger group	Older group	Younger group	Older group
Change of:				
Systolic BP (mmHg/yr)	0.22 (0.15)	0.64 (0.16)	0.04 (0.16)	-0.15 (0.18)
Diastolic BP (mmHg/yr)	0.03 (0.15)	0.06 (0.16)	0.22 (0.14)	-0.30 (0.14)
Height (cm/yr)	2.32 (0.15)	1.37 (0.12)	1.86 (0.12)	0.63 (0.16)
Weight (kg/yr)	1.62 (0.13)	0.84 (0.15)	1.56 (0.13)	0.65 (0.17)

* Linear regression coefficient (unadjusted) with standard error in parentheses.

ratio. Yearly changes in systolic and diastolic blood pressure, height, and weight during the late phase of the study are shown in Table 3.2.2. The data are presented separately for males and females, and are further divided by median age into younger and older age groups. For males, there was an increase in blood pressure with age which was more marked at older ages. For females, blood pressure increased in the younger group (<13.7 years) but decreased at older ages (≥ 13.7 years).

Table 3.2.3 shows the regression coefficients in males and females for the yearly change in systolic and diastolic blood pressures in the late phase of the study in relation to urinary sodium, potassium, and sodium/potassium ratio obtained in the early phase. Sodium and the sodium/potassium ratio were positively related to change in systolic and diastolic blood pressure in males and females. In females, the association of sodium with change in diastolic pressure and the association of sodium/potassium ratio with change in systolic blood pressure reached statistical significance. For potassium, significant inverse associations were observed both with changes in systolic and diastolic blood pressure in males and females.

Discussion

The study found that among a cohort of children aged 5-17, changes in blood pressure with age observed between 1986 and 1991 were positively related to earlier urinary

excretion of sodium and sodium/potassium ratio measured between 1978 and 1985. Change in systolic and diastolic blood pressure in the late phase was significantly inversely associated with earlier urinary potassium excretion. To our knowledge, this is the first time that findings on electrolyte excretion in relation to future change in blood pressure in the same individuals have been reported, potentially with important implications for the primary prevention of high blood pressure and frank hypertension in later life.

The participants reported on here were a subsample of a larger cohort. By definition, they had high compliance with the annual study measurements, and therefore may not have been fully representative of the base population. However, it seems improbable that the key findings of a relationship of change of blood pressure with age to earlier electrolyte excretion, based on individual data, could have been created by any resultant bias. The findings were independent of changes over time in height and weight, or body mass index, and again it seems unlikely that they could be explained by unmeasured or residual confounding. Blood pressures were based on annual readings using a random-zero sphygmomanometer according to a standardized protocol.

Data on change of blood pressure with age were similar to those obtained in other cohorts of children, including the fall in blood pressure observed in girls around puberty.[16] Estimates of urinary electrolyte excretion were based on overnight urine

Table 3.2.3 Multiple regression analysis of yearly change in systolic and diastolic blood pressure in males and females in the late phase of the study in relation to urinary electrolyte excretions in the early phase.

	Sodium	Potassium	Sodium/potassium ratio
Systolic BP slope*			
Males	0.03 (-0.13, 0.19)	-0.31 (-0.09, -0.52)†	0.094 (-0.045, 0.233)
Females	0.06 (-0.02, 0.14)	-0.25 (-0.11, -0.39)†	0.193 (0.043, 0.343)†
Diastolic BP slope*			
Males	0.02 (-0.14, 0.18)	-0.38 (-0.16, -0.59)†	0.108 (-0.033, 0.249)
Females	0.54 (0.11, 0.97)†	-0.25 (-0.11, -0.39)†	0.086 (-0.033, 0.205)

* Mean blood pressure slope (mmHg/yr/10 mmol electrolyte excretion, or mmHg/yr/unit sodium/potassium ratio); adjusted for mean age, body mass index, sodium (potassium model) or potassium (sodium model) in early phase, and change of height and weight in late phase; with 95% confidence interval in parentheses.
† $p<0.05$.

collections, which in young people tend to correlate reasonably well with those obtained from 24 hour urine ollections.[17,18] By basing estimates of electrolyte excretion on at least six annual urine collections, well-known problems of regression dilution caused by the unreliability of a single measure of sodium or potassium excretion were minimized.[19,20]

Many studies pointed to a positive association of sodium,[21,22,23,24,25,26,27,28] and an inverse association of potassium[23,29,30,31] with blood pressure, but most of the human evidence has been obtained in adults rather than children. While the few trials of sodium reduction in children have yielded inconsistent results,[32,33,34] a trial among newborn babies reported systolic blood pressures at 6 months lower by an average of 2.1 mmHg among the group randomised to a reduced sodium diet, in comparison with a 'usual sodium' group.[3]

The regression coefficients in the present study indicate that a one standard deviation change in urinary excretion of sodium, *i.e.*, around -60 mmol (1.4 g) sodium per day, or potassium, *i.e.*, around +20 mmol (0.8 g) potassium per day, could have major impact on the future change of blood pressure with age. For example, a lower sodium intake or higher potassium intake as indicated above was associated with an average systolic blood pressure that was lower by up to 3.6 mmHg and 1.2 mmHg respectively over a 10-year period. These figures are of similar magnitude to changes predicted from the INTERSALT study, among adults aged 20 to 59 years, of around a 2 mmHg lower systolic pressure over a 10-year period for a 60 mmol lower sodium excretion.[21] Differences in average blood pressure of that order are associated with large differences in adult risks of coronary heart disease and stroke.[26,35]

As amply demonstrated by the high mean sodium/potassium ratio in this study (in excess of four), the diets of children and young people tend to be dominated by processed foods high in sodium, and are low in potassium-rich foods such as fruits and vegetables. It would seem prudent to move towards a lower sodium/higher potassium diet for children, as already advocated for adults,[35] for the primary prevention of high blood pressure and hypertension in later life.

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CHAPTER 4

ELECTROLYTES AND BLOOD PRESSURE AT OLD AGE

THE ROTTERDAM STUDY

4.1
Urinary sodium and potassium excretion and blood pressure in older subjects

Introduction

A large number of studies have examined the relationship between salt intake of populations and the occurrence of hypertension. It has been shown that in primitive populations with a low intake of salt, and a concurrently high intake of potassium, hypertension is less prevalent than in Western societies. Epidemiologic studies within single populations, on the other hand, often fail to demonstrate a relation between electrolyte intake and blood pressure. This could be due to the fact that a population consists of a heterogeneous group of individuals, whose blood pressures may react quite differently to dietary influences. Intervention studies indeed have shown a large variability in blood pressure responses upon changes in sodium and/or potassium intake, with some people experiencing a blood pressure decrease, others an increase, and others no blood pressure change at all.[1,2,3] From the viewpoint of prevention, it is worth identifying subgroups of people that are expected to respond favourably to specific dietary interventions. Age-associated changes in the cardiovascular system and renal function may increase the sensitivity of blood pressure to inadequate intake of nutrients in the elderly.[4,5,6] Studies on the effect of electrolytes on blood pressure at older age, however, are still scarce. We investigated whether blood pressure was related to sodium and potassium excretion in older participants of the Rotterdam Study.

Methods

The Rotterdam Study

The Rotterdam Study is a population-based study which aims to investigate the occurrence and determinants of chronic disabling diseases at older age.[7] All residents of a suburb of Rotterdam over 55 years of age were invited to take part in the study. A total of 7,983 men and women (78%) agreed to participate. During a home interview, information was obtained on current health status, medical history, family history of diseases, education, and income by means of a computerised questionnaire. The participants subsequently visited the study centre for clinical examination. For the present analysis cross-sectional data of the baseline study were used.

Measurements

Two blood pressure readings were taken at the study centre and the average is used in the present analysis. Systolic and diastolic blood pressure measurements were performed on the right arm using a random-zero sphygmomanometer with a 38 x 14 cm cuff, after the participant had been seated for at least five minutes. Data on history of hypertension and use of cardiovascular medication were obtained during the home interview by means of a questionnaire. A physician checked all packages of medication at the study centre.

Participants collected an overnight urine specimen before the centre visit. Time of collection and urinary volume were recorded. Urinary sodium and potassium were analysed by flame photometry. The overnight urinary excretions were standardised to 24 hour values.

Population for analysis

A total of 7,129 subjects (89% of the cohort) visited the study centre. Urinary electrolytes were analysed for a random group of 2,564 participants. Time of collection and urinary volume were adequately recorded for 1,926 subjects. Blood pressure readings were available for 1,876 of those with complete urinary data. Subjects treated with antihypertensive drugs (n=590) were excluded from the analyses. Subjects who were not treated, but reported a diagnosis of hypertension in the past (n=267), were also excluded because they could intentionally have changed their diets. Thirteen subjects were not included because of incomplete data on potential confounders. A total of 1,006 participants was thus left for the present analysis.

Data analysis

Linear regression analyses were performed with systolic and diastolic blood pressure as the dependent variables. Urinary sodium and potassium were studied separately and combined in a multivariate model with adjustment for age, sex, and body mass index. Subgroup analyses were performed in men and women. Regression coefficients (b) are reported with 95% confidence intervals (95% CI) and two-tailed p-values (p).

Results

Characteristics of the study population are shown in table 4.1.1. Thirty-three per cent (n=328) of the subjects had a systolic blood pressure above 140 mmHg or a diastolic pressure above 90 mmHg. Mean 24 hour sodium excretion was 119 mmol, which corresponds to a dietary sodium intake of 2.7 grams (7.0 grams of salt) per day. The

Table 4.1.1 Characteristics of the study population (n=1,006).

Variable	Mean (SD), or percentage
Males (%)	46
Age (yrs)	67.3 (8.4)
Systolic blood pressure (mmHg)	132.2 (20.0)
Diastolic blood pressure (mmHg)	70.5 (10.0)
Heart rate (beats/min)	75.6 (12.0)
Body mass index (kg/m^2)	25.8 (3.4)
Cigarette smokers (%)	26
Alcohol users (%)	66
Urinary sodium excretion (mmol/24h)	119 (61)
Urinary potassium excretion (mmol/24h)	44 (19)
Urinary sodium/potassium ratio	2.9 (1.3)

mean 24 hour potassium excretion was 44 mmol, which corresponds to an intake of 1.7 grams per day.

In table 4.1.2 the relations of electrolytes with systolic and diastolic blood pressure are presented. Findings are adjusted for age, sex, and body mass index. Urinary sodium showed no significant independent relation with blood pressure, but after inclusion of potassium in the multivariate model a 100 mmol increase in sodium was associated with a 2.2 mmHg increase in systolic (p=0.06), and a 0.8 mmHg increase in diastolic blood pressure (p=0.14). In men, these associations were 4.0 mmHg/100 mmol sodium (p=0.01) for systolic blood pressure, and 1.2 mmHg/100 mmol sodium (p=0.14) for diastolic pressure. In women there was no significant association of sodium with either systolic (-0.5 mmHg/100 mmol sodium, p=0.80) or diastolic pressure (0.2 mmHg/100 mmol sodium, p=0.81).

Urinary potassium was significantly inversely associated with blood pressure (table 4.1.2). After adjustment for sodium, a 100 mmol increase in potassium was associated with a 9.4 mmHg decrease in systolic (p=0.01) and a 4.9 mmHg decrease in diastolic blood pressure (p=0.01). For systolic blood pressure, the association was stronger in men

(-11.3 mmHg/100 mmol potassium, p=0.02) than in women (-6.3 mmHg/100 mmol, p=0.25). For diastolic blood pressure, the associations were of the same magnitude in men (-4.5 mmHg/100 mmol potassium, p=0.08) and in women (-5.2 mmHg/100 mmol potassium, p=0.07).

When the analyses were repeated with additional adjustment for heart rate (beats per minute), smoking (current, past or never), alcohol use (yes/no), education (7 categories) or income (13 categories), the results did not change.

Discussion

The present study shows that sodium was not independently related to blood pressure. However, when urinary potassium was included in the multivariate regression model a positive relation with systolic blood pressure emerged in men. An independent, inverse association of urinary potassium with systolic and diastolic blood pressure was observed after adjustment for age, sex, and body mass index. The association of potassium with blood pressure became stronger after additional adjustment for sodium excretion.

Table 4.1.2 Association of sodium and potassium excretion with blood pressure (BP) in 1,006 older men and women.

	Systolic BP (mmHg)			Diastolic BP (mmHg)		
	b (95% CI)*		p	b (95% CI)		p
Separately in model						
Sodium	0.7	(-1.3, 2.7)	*0.48*	0.0	(-1.0, 1.1)	*0.98*
Potassium	-5.9	(-12.1, 0.3)	*0.06*	-3.6	(-6.9, -0.4)	*0.03*
Sodium/potassium ratio	0.82	(-0.07, 1.71)	*0.07*	0.32	(-0.14, 0.79)	*0.18*
Together in model						
Sodium	2.2	(-0.1, 4.5)	*0.06*	0.8	(-0.4, 2.0)	*0.19*
Potassium	-9.4	(-16.5, -2.2)	*0.01*	-4.9	(-8.7, -1.1)	*0.01*

* Linear regression coefficient (mmHg per 100 mmol electrolyte excretion, or mmHg per unit sodium/potassium ratio) adjusted for age, sex, and body mass index; 95% confidence interval in parentheses.

Before these findings can be accepted, some methodological issues need to be considered. Urinary excretions of sodium and potassium are considered to adequately reflect the dietary intakes of these electrolytes.[8] However, excretions are determined by recent intakes and a single urine collection cannot be regarded to adequately reflect long-term dietary exposure. Multiple 24 hour urine samples collected over a period of several months would yield a better estimate of habitual intake. In our large population study, however, this could not be realised and participants collected a single overnight urine sample. Although overnight urinary excretions of sodium and potassium correlate reasonably well with 24 hour excretions,[8,9] misclassification of subjects inevitably has occurred and the observed relations in the present study are likely to be diluted. Furthermore, the choice of our study population may have influenced the strength of the observed associations. Subjects who are expected to be most vulnerable to an inadequate electrolyte intake, or to an unhealthy lifestyle in general, may have died before reaching old age. In addition, subjects who used antihypertensive drugs or reported hypertension were excluded from the analyses.

Though a relationship between sodium and blood pressure has been observed in the worldwide INTERSALT study,[10] most studies within populations have not been able to reproduce this finding.[11,12] This could reflect inaccurate assessment of sodium intake or blood pressure, or could be due to the fact that the range of salt intake within a single population is too restricted to adequately study the effect of high and low intakes on blood pressure. An alternative explanation could be that most studies included a large number of people who are probably not sensitive to salt intake. It has been suggested that the elderly are more sensitive to sodium intake than younger subjects.[1,13,14] In our older study population a positive relation between sodium excretion and systolic blood pressure was observed, though only in males after adjustment for potassium excretion. The inaccurate assessment of sodium intake in our study has probably lead to misclassification and biased the regression coefficients towards zero. This may explain why we did not observe a relation between sodium excretion and blood pressure in females.

Studies on potassium intake and blood pressure in older people are scarce and reported results are inconsistent. The Scottish Heart Health Study reported a significant independent inverse association between 24 hour potassium excretion and blood pressure in 7,354 men and women aged 40 to 59.[12] A large Dutch study among middle-aged adults, however, could not confirm an association between dietary potassium intake, assessed by means of a questionnaire, and blood pressure.[15] Recently, a significant dose-response relationship between change in diastolic blood pressure and 24 hour urinary

potassium excretion has been reported in the Trials of Hypertension Prevention (TOHP), but the blood pressure effect was small (-1.5 mmHg for the highest *vs.* the lowest quartile of change in urinary potassium).[16] In our study, subjects with higher systolic and diastolic blood pressure levels had a significantly lower excretion of potassium. The regression coefficients suggest that a twofold increase in daily potassium intake could theoretically lower systolic blood pressure by 4 mmHg, and diastolic pressure by 2.5 mmHg. In men, the observed associations between potassium and blood pressure were even stronger. It is possible that blood pressure becomes increasingly sensitive to an inadequate intake of potassium at older age. The INTERSALT study reported stronger associations between potassium excretion and blood pressure with increasing age.[17]

The dietary sodium/potassium ratio has been related to blood pressure levels, and could be a better predictor of blood pressure than either of the nutrients alone.[13] A recent trial among older untreated hypertensive subjects demonstrated a substantial reduction in blood pressure when sodium intake was reduced and potassium intake increased by means of a mineral salt.[18] In the present analysis, however, the sodium/potassium ratio was only weakly positively related to systolic and diastolic blood pressure. This may in part be explained by inaccurate assessment of both sodium and potassium intake by the single overnight urine collection.

In conclusion, our findings suggest that a high sodium intake may adversely affect blood pressure, especially in older men. A high intake of potassium, on the other hand, could have a favourable effect on blood pressure level in older men and women. The effect of electrolyte intake on blood pressure and the potential for prevention and intervention in the elderly warrants further investigation in controlled intervention studies.

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4.2
Dietary electrolyte intake and blood pressure in older subjects

Introduction

Dietary electrolyte intake could be an important, modifiable determinant of blood pressure.[1,2] Therapeutic dietary modifications are particularly relevant at older age as more adverse effects of antihypertensive drugs are experienced and compliance to drug therapy often becomes poorer.[3,4] Furthermore, age-associated changes in the cardiovascular system could increase the sensitivity of blood pressure to inadequate intake of nutrients.[5,6,7] Studies on the influence of electrolytes on blood pressure at older age, however, are still scarce. We investigated whether blood pressure was related to the intake of potassium, magnesium, and calcium in older participants of the Rotterdam Study.

Methods

The Rotterdam Study

The Rotterdam Study is a population-based study which aims to investigate the occurrence and determinants of chronic disabling diseases at older age.[8] All residents of a suburb of Rotterdam over 55 years of age were invited to take part in the study. A total of 7,983 men and women (78%) agreed to participate. During a home interview, information was obtained on current health status, medical history, family history of diseases, education, and income by means of a computerised questionnaire. The participants subsequently visited the study centre for clinical examination and an interview with a dietician. For the present analysis cross-sectional data of the baseline survey were used.

Blood pressure measurements

Two blood pressure readings were taken at the study centre and the average is used in the present analysis. Systolic and diastolic blood pressure measurements were performed on the right arm using a random-zero sphygmomanometer with a 38 x 14 cm cuff, after the participant had been seated for at least five minutes. Data on history of hypertension and use of cardiovascular medication were obtained during the home interview by means of a questionnaire. A physician checked all packages of medication at the study centre.

Dietary assessment

Before visiting the study centre the participants received a checklist on which they

indicated all foods and drinks that they regularly consumed (*i.e.* once a month or more) during the preceding year. The completed checklist was subsequently used as the basis for a detailed interview by a trained dietician at the study centre who was not informed about the purpose of the present study and blinded with regard to the blood pressure levels of the participants. Seasonal variations in the diet were taken into account. The dietician registered quantities and frequencies of consumption on a semiquantitative food frequency questionnaire. The questionnaire comprised 170 food items in 13 food groups and was a modified version of a self-administered questionnaire that had been used and validated previously in a large prospective study in the Netherlands.[9] During the course of the study a computerised version of the questionnaire was introduced, which contained multiple checks on the data. The dietician used this computerised questionnaire in 59% of the interviews. Intakes of potassium, magnesium, calcium, alcohol, and total energy were calculated from the food data with the use of Dutch food composition tables.[10] Sodium intake could not adequately be assessed by the food frequency questionnaire.

Population for analysis

A total of 7,129 subjects (89% of the total cohort) visited the research centre. No dietary information was obtained from participants of the Rotterdam Study pilot phase (n=271) and from nursing homes residents (n=635). Participants that scored low on neuropsychological testing (n=122) were not interviewed because they were considered unable to adequately recall dietary intakes. For logistic reasons, no interview was carried out in a random group of 455 subjects. Diet was thus assessed in 5,646 participants. Two hundred and twelve subjects were excluded because they did not fully cooperate during the interview and the dietician considered their reported diets unreliable. Blood pressure readings were available for 5,153 of the remaining participants. Subjects treated with antihypertensive drugs (n=1,587) were excluded from the analyses. In addition, subjects with a salt-restricted diet (n=49), subjects who reported regular use of mineral supplements (n=257), and subjects with incomplete data on potential confounders (n=21) were excluded. A total of 3,239 participants was left for the present analysis.

Data analysis

Dietary potassium, magnesium and calcium were adjusted for energy intake by regressing the electrolyte intakes on total energy and adding the residuals to the mean intakes, as described by Willett *et al.*[11] Linear regression analyses were performed with systolic and diastolic blood pressure as the dependent variables. Energy-adjusted electrolyte intakes

were studied separately and in combination in the multivariate model with adjustment for age, sex, body mass index, and alcohol intake. The analyses were repeated in predefined subgroups, *i.e.* men and women, younger and older subjects (below or above the median of the age distribution), and normotensive and hypertensive subjects (blood pressure below or above 140/90 mmHg). Regression coefficients (b) are reported with standard errors (SE) and two-tailed p-values (p). P-values below the α-level of 0.05 were considered statistically significant.

Results

Characteristics of the study population are shown in table 4.2.1. Forty-two percent (n=1,360) of the subjects had a systolic blood pressure above 140 mmHg or a diastolic pressure above 90 mmHg, and 21% (n=670) reported a diagnosis of hypertension in the

Table 4.2.1 Characteristics of the study population (n=3,239).

Variable	Mean (SD), or percentage
Males (%)	43
Age (yrs)	66.8 (7.6)
Systolic blood pressure (mmHg)	136.3 (21.4)
Diastolic blood pressure (mmHg)	73.0 (11.0)
Body mass index (kg/m^2)	25.5 (3.4)
Cigarette smokers (%)	24
Alcohol users (%)	81
Dietary intake:	
Total energy (kcal/day)	2022 (512)
Alcohol (g/day)*	13.7 (16.7)
Potassium (mg/day)	3700 (824)
Magnesium (mg/day)	311 (75)
Calcium (mg/day)	1127 (398)

* Alcohol intake among alcohol users.

past. Age, body mass index, and alcohol intake were significantly associated both with systolic and diastolic blood pressure. Sex was significantly associated with diastolic blood pressure only (table 4.2.2). Total energy intake, smoking (number of cigarettes per day), education (7 categories), and income (13 categories) were not significantly associated with blood pressure (data not shown).

In table 4.2.3 the relations of energy-adjusted electrolyte intakes with systolic and diastolic blood pressure are presented. Findings were adjusted for age, sex, body mass index, and alcohol intake. Potassium intake was inversely associated with systolic (regression coefficient -0.9 mmHg/gram potassium, $p=0.11$) and diastolic blood pressure (-0.8 mmHg/gram potassium, $p=0.01$). The relation between potassium and diastolic blood pressure was more pronounced in men (-1.2 mmHg/gram potassium, $p=0.01$) than in women (-0.5 mmHg/gram potassium, $p=0.25$). For systolic blood pressure, the association was similar in men and women. Regression coefficients for potassium did not differ significantly between younger and older subjects, or between hypertensives and normotensives. After adjustment for magnesium and calcium, the associations of potassium with blood pressure for the group as a whole were weaker (-0.75 and -0.39 mmHg/gram potassium for systolic and diastolic pressure respectively) and no longer statistically significant.

An increase of 100 mg in magnesium intake was associated with a 1.2 mmHg decrease in systolic ($p=0.07$) and a 1.1 mmHg decrease in diastolic blood pressure ($p<0.01$). The association of magnesium with systolic blood pressure was more pronounced in men (-1.8 mmHg/100 mg magnesium, $p=0.06$) than in women (-0.9 mmHg/100 mg magnesium, $p=0.36$). This was also the case for diastolic blood pressure (-1.4 mmHg/100 mg magnesium ($p<0.01$) in men, compared to -0.8 mmHg/100 mg magnesium ($p=0.13$) in women). The associations of magnesium with blood pressure were similar in younger and older subjects, and in hypertensives and normotensives. After simultaneous inclusion of potassium and calcium intake in the regression model, the association of magnesium with systolic blood pressure for the group as a whole became stronger (-1.8 mmHg/100 mg magnesium, $p=0.09$), whereas the results for diastolic pressure remained unchanged.

Dietary calcium was not significantly independently associated with blood pressure, except for a subgroup of 1,360 hypertensive subjects in which a significant inverse association of calcium with diastolic blood pressure was observed (-2.2 mmHg/gram calcium, $p=0.01$). In other subgroups, associations of calcium with blood pressure did not differ from the results obtained in the group as a whole. After simultaneous inclusion of potassium and magnesium in the regression model, a significant positive association of

calcium intake with systolic blood pressure emerged (3.4 mmHg/gram calcium, p=0.01).

When the analyses were repeated with additional adjustment for smoking, education or income the results did not change. Similar results were also obtained when subjects who reported a diagnosis of hypertension in the past, but were not currently treated with antihypertensive drugs, were excluded from the analyses.

Discussion

Within the older population of the Rotterdam Study, dietary potassium and magnesium intake were inversely and independently related to systolic and diastolic blood pressure after adjustment for age, sex, body mass index, and alcohol intake. Calcium intake showed no independent relation with blood pressure, except within hypertensive subjects where a significant inverse association with diastolic blood pressure was observed. When all electrolytes were considered together in the regression model, potassium and magnesium retained their inverse associations with systolic and diastolic blood pressure. For calcium, however, a significant positive association with systolic blood pressure emerged.

Some limitations of the study need to be discussed. First, we could not study the effect of sodium, because salt use during cooking and dining could not adequately be assessed by the questionnaire that we used in our study. A fruit- and vegetable-rich diet, which is the main provider of potassium and magnesium, is generally a healthy diet that contains

Table 4.2.2 Association of age, sex, body mass index, and alcohol intake with blood pressure (BP) in 3,239 older men and women.

	Systolic BP (mmHg)		Diastolic BP (mmHg)	
	b (SE)*	p	b (SE)	p
Intercept	59.3		67.3	
Age (yrs)	0.77 (0.05)	*<0.0001*	-0.10 (0.03)	*<0.0001*
Sex (0=male, 1=female)	-0.56 (0.76)	*0.46*	-1.50 (0.41)	*<0.0001*
Body mass index (kg/m^2)	0.98 (0.10)	*<0.0001*	0.51 (0.06)	*<0.0001*
Alcohol intake (g/day)	0.07 (0.02)	*0.01*	0.03 (0.01)	*0.01*

* Linear regression coefficient with standard error in parentheses (all variables in model).

Table 4.2.3 Association of energy-adjusted electrolyte intakes with blood pressure in 3,239 older men and women.

	Systolic BP (mmHg)		Diastolic BP (mmHg)	
	b (SE)*	p	b (SE)	p
Separately in model				
Potassium (g/day)	-0.94 (0.59)	*0.11*	-0.84 (0.31)	*0.01*
Magnesium (mg/day)	-0.012 (0.007)	*0.07*	-0.011 (0.004)	*<0.01*
Calcium (g/day)	1.30 (1.03)	*0.21*	-0.33 (0.55)	*0.55*
Combined in model				
Potassium (g/day)	-0.75 (0.91)	*0.41*	-0.39 (0.66)	*0.42*
Magnesium (mg/day)	-0.018 (0.011)	*0.09*	-0.011 (0.006)	*0.06*
Calcium (g/day)	3.43 (1.24)	*0.01*	0.91 (0.66)	*0.17*

* Linear regression coefficient adjusted for age, sex, body mass index, and alcohol intake with standard error in parentheses.

fewer fatty and salty foods. The observed inverse associations of potassium and magnesium with blood pressure could therefore partially result from a low intake of sodium. Second, it should be noted that the choice of our study population may have influenced the strength of the observed associations. Subjects who are expected to be most vulnerable to an inadequate electrolyte intake, or to an unhealthy lifestyle in general, may have died before reaching old age or have been using antihypertensive drugs. These people were proportionately less well represented in our study. Finally, when nutrients are studied in relation to disease it is difficult to rule out completely confounding influences. Dietary patterns are closely related to other factors that may also influence blood pressure, such as age, alcohol consumption, body weight, education, and physical activity. We considered most of these variables in our analyses, but could not adjust for physical activity. This may have given rise to residual confounding, because a healthy lifestyle with regular physical activity is associated with a higher intake of potassium and magnesium through fruits and vegetables, and lower blood pressure levels. However, total

energy intake, which is correlated with physical activity,[12] was not associated with blood pressure in our older population.

Studies on potassium and blood pressure in older people are scarce. The potassium content of the diet has been related to blood pressure in a number of observational studies among middle-aged men and women, but findings are inconsistent.[13,14] Cappuccio and MacGregor summarized 19 published trials of the effect of potassium supplementation on blood pressure. Blood pressure reductions of 5.9 mmHg systolic and 3.4 mmHg diastolic were observed with an average, substantial increase in potassium intake of 86 mmol (3.4 grams) per day.[15] Recently, a significant dose-response relationship between change in diastolic blood pressure and 24-hour urinary potassium excretion has been reported in the Trials of Hypertension Prevention (TOHP), but the blood pressure effect was small (-1.5 mmHg for the highest *vs.* the lowest quartile of change in urinary potassium).[16] In a trial among hypertensive elderly, potassium supplementation resulted in a significant blood pressure reduction,[17] which is in agreement with the results of our study. We found that lower potassium intakes were observed in subjects with higher blood pressure levels. This suggests that blood pressure levels in the elderly adversely respond to an inadequate intake of potassium.

We observed an inverse relationship of magnesium with systolic and diastolic blood pressure. Some other large population studies have previously suggested a role for magnesium in determining blood pressure level.[18,19] A trial among middle-aged and older Dutch women showed a 3.4 mmHg decrease in diastolic blood pressure when daily magnesium intake was doubled.[20] The TOHP, on the contrary, could not achieve a blood pressure reduction after 3 or 6 months of intervention with magnesium supplements in middle-aged adults.[21] Possibly, the effect of magnesium on blood pressure becomes apparent only at older age, which could explain the inverse association between magnesium and blood pressure in our study. An alternative explanation for our findings could be the strong association of magnesium intake with intake of fibre, an agent that may also lower blood pressure.

Many observational studies have reported an inverse association between calcium intake and blood pressure,[2,22] though negative results have also been reported.[23] We observed an independent relation of calcium intake only with diastolic blood pressure in hypertensive subjects. Possibly, the sensitivity of calcium increases with blood pressure level. Drug-treated hypertensive subjects were removed from our analysis, which may explain why no relation was observed in the group as a whole. Furthermore, the majority of our subjects had an adequate intake of calcium, whereas other studies that showed an

inverse association with blood pressure reported lower calcium intakes. An unexpected positive relation of calcium intake with systolic blood pressure emerged after adjustment for potassium and magnesium intake. Because the association was not consistent and disagrees with findings in previous studies, this probably resulted from multicollinearity. This problem occurs when the variation in one variable is substantially reduced because of the inclusion of one or more other variables. Possibly, the relation estimated from the residual variation after removing the effect of potassium and magnesium is not attributable to calcium itself, but to other factors that are associated with calcium intake and not with potassium and magnesium intake. Intake of saturated fat, for example, is correlated with calcium intake through consumption of dairy products and may have given rise to the unexpected, positive relation with blood pressure. Nevertheless, we cannot rule out the possibility that the influence of calcium on blood pressure becomes different at advanced age as a result of age-related changes in biological mechanisms. A positive association between calcium and blood pressure in elderly Chinese subjects has previously been reported by Woo *et al.*[24]

The complexity of the human diet makes it difficult to separate the effect of any specific nutrient from possible effects of other nutrients. The intake of potassium is highly correlated with the intake of magnesium as both minerals are often ingested together through the same vegetables and fruits. The problem of multicollinearity cannot adequately be solved by statistical methods. The simultaneous inclusion of strongly correlated variables in a multivariate regression model may give rise to unanticipated, spurious results. In our study, this was probably the case when dietary potassium and magnesium were included in the multivariate model together with dietary calcium. Although our data are not incompatible with independent effects of potassium and magnesium intake, inference from observational studies can probably best focus of mixtures of nutrients rather than on individual factors. Our findings suggest that an increase in the intake of foods rich in potassium and magnesium could lower blood pressure at older age.

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4.3

Reduction in blood pressure with a low sodium, high potassium, high magnesium salt in older subjects with mild to moderate hypertension

Introduction

Results from many studies suggest a role for minerals in blood pressure regulation. Sodium may increase blood pressure[1], whereas the reverse has been reported for potassium and magnesium.[2,3] Several studies have shown a stronger relation of the sodium/potassium ratio with blood pressure than sodium or potassium alone.[4,5,6] Hence, dietary measures to reduce blood pressure might be more effective when the intake of several minerals is changed simultaneously. Older subjects with a high blood pressure may benefit most from salt restriction, as the strength of association between sodium and blood pressure increases with age and blood pressure in cross-sectional studies.[4,7] Results of intervention studies support this hypothesis, though most trials have focused on young and middle-aged subjects.[8,9] Intervention studies in elderly people addressing multiple modest changes in mineral intake are needed to assess the potential of this intervention for blood pressure lowering at advanced age.

We conducted a randomised, double blind, placebo controlled trial of the effect of a reduced sodium intake and increased potassium and magnesium intake on blood pressure by using a mineral salt (sodium:potassium:magnesium (mmol) 8:6:1)*, in older subjects with mild to moderate hypertension.

Methods

Subjects

Subjects were recruited from the population based cohort of the Rotterdam Study, which consists of non-hospitalised older inhabitants of a suburb of Rotterdam. Details of the study have been reported.[10,11] All subjects had their blood pressure measured between 1990 and 1992. Men and women, aged 55 to 75, with a blood pressure above 140 mmHg systolic or 85 mmHg diastolic without antihypertensive treatment (n=419), were invited by letter and telephone for remeasurement of blood pressure. To be eligible for the trial, subjects' systolic blood pressure had to be between 140 and 200 mmHg or diastolic blood pressure between 85 and 110 mmHg at two measurements one week apart. In addition, systolic blood pressure had to be not below 130 mmHg and diastolic pressure not below 70 mmHg.

* *SagaSalt®*
Dutch product name 'Jozo Vitaal', distributed by Akzo Nobel Salt Europe

Table 4.3.1 Baseline characteristics of subjects in the control group and mineral salt group.

	Controls (n=51)	Mineral salt group (n=49)
Male/female	25/26	26/23
Age (years)	67.1 (4.5)	65.7 (4.6)
Blood pressure (mmHg):		
Systolic	157.5 (12.8)	158.0 (15.0)
Diastolic	90.8 (8.9)	89.8 (9.6)
Pulse rate (beats/min)	80.6 (12.6)	77.7 (12.6)
Height (cm)	167.0 (9.1)	169.2 (9.4)
Body weight (kg)	76.0 (11.3)	77.5 (10.1)
Body mass index (kg/m^2)	27.2 (3.2)	27.1 (3.4)
No (%) of cigarette smokers	12 (23.5)	9 (18.4)
Serum:		
Sodium (mmol/l)	137.1 (2.4)	137.0 (3.1)
Potassium (mmol/l)	4.2 (0.4)	4.3 (0.3)
Magnesium (mmol/l)	0.86 (0.06)	0.86 (0.06)
Calcium (mmol/l)	2.4 (0.1)	2.4 (0.1)
Ionised calcium (mmol/l)	1.24 (0.04)	1.24 (0.04)
Urine:		
Sodium (mmol/day)	138 (50)	139 (52)
Potassium (mmol/day)	81 (25)	86 (22)
Sodium/potassium ratio	1.8 (0.6)	1.6 (0.4)
Magnesium (mmol/day)	5.2 (1.7)	5.4 (1.9)
Calcium (mmol/day)	4.8 (2.2)	4.7 (1.9)
Creatinine (mmol/day)	10.2 (2.8)	10.0 (2.7)

Values are means with standard deviations in parentheses, except where stated otherwise.

Subjects with a history of myocardial infarction, angina pectoris, diabetes mellitus, or impaired renal function (serum creatinine >200 μmol/l) or eating a salt restricted diet on medical advice were excluded. Thirty subjects could not be contacted. A total of 125 subjects were excluded after being contacted by telephone because they showed no interest (n=56) or because they met one of the exclusion criteria (n=69). Of the 264 subjects who eventually had their blood pressure remeasured (63% of those initially invited), 17 did not fulfil blood pressure criteria, 40 had started antihypertensive treatment, 55 met other exclusion criteria, and 52 refused the trial. This left 100 subjects who were randomised.

Protocol

Randomisation was carried out within eight strata defined by sex and baseline blood pressure by using a computerised randomisation table. During 24 weeks, the intervention group received a mineral salt (sodium:potassium:magnesium (mmol) 8:6:1) for use in cooking and at the table, and foods prepared with the mineral salt. The control group received common salt (sodium chloride) and foods prepared with common salt. The mineral salt is extracted from natural sources in Iceland and consists of 41% sodium chloride, 41% potassium chloride, 17% magnesium salts, partly as potassium-magnesium double salts (carnallite and kainite), and 1% trace minerals.[12]

Trial foods included bread, cheese, luncheon meats, canned and instant soups, and smoked sausage. Together these foods provide around 57% of the salt intake of the Dutch elderly population.[13] The sodium/potassium ratio (mmol/mmol) ranged from 1.3 (cheese) to 1.8 (canned soups) in mineral salt foods and from 6.7 (smoked sausage) to 22.7 (instant soups) in control foods. Salt and foods for both groups looked identical and were provided free of charge by means of a double blind coding system based on the randomisation numbers. Participants were asked to avoid changes in dietary habits and lifestyle, to adhere as much as possible to the trial salt and foods, and to register deviations from the protocol in a diary. For each subjects we recorded the amount of foods provided. We contacted subjects monthly to check and encourage compliance.

The protocol was approved by the medical ethics committee of Erasmus University. All participants gave written informed consent. During the study, participants were not told the results of blood pressure measurements.

Measurements

Blood pressure, pulse rate, and body weight were assessed at baseline and after 8, 16 and

24 weeks of intervention. To obtain stable estimates blood pressure and pulse rate were measured at two visits with a week's interval (baseline, week 8 and week 16) or at three visits with weekly intervals (week 24) and the average taken as the estimate. Baseline blood pressure was the average of the last blood pressure screening and baseline measurements. Blood pressure was measured on the right arm by two investigators, using an automatic device (Dinamap model 8100; Critikon Inc, Florida) and a 51 cm by 15 cm cuff while the participant was seated. After at least five minutes' rest four measurements were taken, of which the last three were averaged. Body weight and height were measured without heavy clothing and shoes. Body mass index was computed as weight (kg) divided by height (m) squared. Subjects collected two successive 24 hour urine samples at baseline and at 8, 16 and 24 weeks.

Every eight weeks the subjects answered a questionnaire on health complaints, smoking, alcohol intake, physical activity, and drug use during the preceding period. At eight weeks subjects evaluated the appearance, saltiness, and palatability of the trial foods by filling in a questionnaire with five point rating scales. During intervention a dietician visited the subjects at home and used a sensitive balance to weigh the amount of trial salt added during cooking (PM 300 balance; Mettler-Toledo AG, Switzerland). Information on salt use was obtained by means of a questionnaire.

We sampled blood at baseline and at 24 weeks. Serum ionised calcium concentration was analysed with an ion selective electrode (ICA2 Ionized Calcium Analyzer, Radiometer, Copenhagen) and reported values are pH adjusted. Analyses of other electrolytes in blood and urine were performed by standard methods. Four to nine months after the study all subjects were invited again for blood pressure measurement. On this occasion we asked which salt the subject thought he or she had received during the study.

Data analysis

Changes in blood pressure and electrolyte excretion from baseline were compared between the control group and the mineral salt group. In addition, preplanned subgroup analyses were performed according to sex and age. The hypothesis of no difference between the groups was tested by a two sided *t* test. Results are expressed as means and 95% confidence intervals of the differences between groups. Adjustment of change in blood pressure for potential confounders was performed by analysis of covariance. Data analysis was carried out on an intention to treat basis. The study sample was large enough to detect a difference in blood pressure of 5 mmHg systolic and 4 mmHg diastolic with a power of 0.90 and a two sided p value of 0.05.

Table 4.3.2 Changes in blood pressure (BP) from baseline (51 controls, 49 subjects in mineral salt group), adjusted for change in body weight.

	Week 0	Week 8	Week 16†	Week 24‡	Intervention§
Systolic BP (mmHg):					
Controls	157.6 (2.0)	161.0 (2.1)	160.0 (2.2)	156.0 (1.9)	158.5 (1.8)
Mineral salt group	157.9 (2.0)	151.8 (2.1)	152.6 (2.2)	150.9 (1.9)	151.7 (1.8)
Difference (95% confidence interval)*		-9.7 (-13.6, -5.7) p<0.001	-8.7 (-13.0, -4.5) p<0.001	-7.7 (-12.3, -3.1) p=0.001	-8.7 (-12.2, -5.2) p<0.001
Diastolic BP (mmHg):					
Controls	91.0 (1.3)	92.7 (1.4)	92.3 (1.4)	90.9 (1.2)	92.1 (1.2)
Mineral salt group	89.7 (1.3)	87.0 (1.4)	86.7 (1.4)	86.8 (1.2)	86.9 (1.2)
Difference (95% confidence interval)		-4.2 (-7.0, -1.4) p=0.004	-4.0 (-7.1, -0.9) p=0.01	-2.8 (-5.8, 0.2) p=0.06	-3.6 (-6.0, -1.1) p=0.005

Values are means with standard error in parentheses.

* Difference in change from baseline between study groups.

† Values for week 16 missing for one control and one subject in the mineral salt group.

§ Mean of measurements at weeks 8, 16, and 24.

‡ Values for week 24 missing for two controls and one subject in the mineral salt group.

Results

Complete follow up was achieved by 97 of the 100 randomised subjects. Two of the controls withdrew after eight and 16 weeks because of admission to hospital for complaints not related to intervention. One person withdrew in the mineral salt group after six weeks because of dislike of the foods.

Randomisation established comparable study groups (table 4.3.1). Figure 4.3.1 presents blood pressure at baseline and during intervention. A difference in blood pressure change between the groups was present at eight weeks and persisted throughout. Systolic blood pressure (mean of measurements at weeks 8, 16 and 24) fell by 7.6 mmHg (95% confidence interval 4.0 to 11.2; $p<0.001$) and diastolic blood pressure by 3.3 mmHg (0.8 to 5.8; $p=0.009$) in the mineral salt group compared with the controls. After adjustment for change in body weight, values were 8.7 mmHg en 3.6 mmHg (table 4.3.2). The decrease in blood pressure was of the same magnitude in men and women and not modified by age (data not shown).

Table 4.3.3 shows the changes in body weight and electrolyte excretion from baseline. The 24 hour sodium excretion decreased on average by 28% (that is, by 38.4 mmol; 95% confidence interval 24.0 to 52.8); $p<0.001$) and potassium excretion increased by 22% (17.5 mmol (7.9 to 27.0); $p<0.001$) in the mineral salt group compared with the controls (fig 4.3.2). Urinary calcium and magnesium excretion did not change. Results were similar after adjustment for urinary creatinine excretion. Urinary volumes in both groups remained stable during intervention (data not shown). Change in body weight was on average 0.50 kg (95% confidence interval -0.03 to 1.03; $p=0.06$) more in the mineral salt group than in the controls. Serum electrolyte concentrations (table 4.3.4) were unchanged in both groups. Change in pulse rate during intervention was not significantly different between the groups (data not shown).

Appearance, saltiness, and palatability of the trial foods were rated equally by the two groups except for the bread and table salt, which were considered less salty by significantly more people in the mineral salt group than in the control group. None of the participants reported the flavour of the trial salt and foods as unpleasant. Seven per cent of the controls (3/44) reported a higher discretionary salt use during the trial as compared with 40% (16/40) of the mineral salt group. Salt use as assessed by weighing was similar in both groups - namely, 4.9 g (SD 4.8; range nil to 24.1 g) in the control group and 5.2 g (4.9; nil to 26.2 g) in the mineral salt group ($p=0.74$).

Reports of side effects and lifestyle changes during intervention were minimal and equally distributed among the study groups. The records of salt and foods provided and

the diaries on compliance indicated good adherence to the protocol in both groups.

Twenty five weeks (SD 4; range 16-37) after the study all 51 controls and 46 subjects from the mineral salt group (94%) visited the study centre. Differences in blood pressure change from baseline between the groups were 0.8 mmHg (95% confidence interval -4.5 to 6.0; p=0.77) systolic and -1.0 mmHg (-4.5 to 2.5; p=0.57) diastolic in untreated subjects. Sixteen of the controls (31%) compared with 33 (72%) subjects from the mineral salt group believed they had received mineral salt when asked after the trial.

Table 4.3.3 Body weight and electrolyte excretion at baseline and during intervention.†

	Week 0	Week 8	Week 16	Week 24
Body weight (kg):				
Controls	76.0 (1.6)	76.1 (1.6)	76.7 (1.6)	76.0 (1.7)
Mineral salt group	77.5 (1.4)	78.4 (1.4)	78.9 (1.5)	78.9 (1.4)
Sodium (mmol/24h):				
Controls	138 (7)	147 (7)	147 (7)	148 (7)
Mineral salt group	139 (8)	113 (5)	107 (5)	116 (4)
Potassium (mmol/24h):				
Controls	81 (4)	77 (3)	77 (4)	75 (3)
Mineral salt group	86 (3)	102 (4)	101 (5)	97 (4)
Sodium/potassium ratio:				
Controls	1.8 (0.1)	2.0 (0.1)	1.9 (0.1)	2.1 (0.1)
Mineral salt group	1.6 (0.1)	1.1 (0.1)	1.1 (0.1)	1.3 (0.1)
Magnesium (mmol/24h):				
Controls	5.2 (0.2)	5.8 (0.2)	5.5 (0.3)	5.4 (0.3)
Mineral salt group	5.4 (0.3)	6.1 (0.3)	5.8 (0.3)	5.7 (0.3)
Calcium (mmol/24h):				
Controls	4.8 (0.3)	4.8 (0.3)	4.6 (0.3)	4.9 (0.2)
Mineral salt group	4.7 (0.3)	4.4 (0.3)	4.1 (0.2)	4.3 (0.3)

Values are means with standard error in parentheses.
† On each occasion values for body weight and electrolyte excretion were obtained for at least 47 controls and 45 subjects in the mineral salt group.

Within the study groups, observed blood pressure changes during intervention did not differ between those who thought they had been given mineral salt and those who thought they had been given common salt or did not know.

Discussion

We observed a decrease in systolic and diastolic blood pressure in older hypertensive subjects when sodium intake was lowered and potassium and magnesium intake was increased by means of a mineral salt. However, before these results can be accepted some aspects of the trial need to be discussed.

We provided salt and foods which were palatable and eaten regularly by the participants in both groups. This was reflected in a persistent difference in sodium and potassium excretion between the study groups. From Dutch food tables[14] the daily magnesium intake was estimated to be 7 mmol higher in our mineral salt group than in the controls though this was not reflected in the urinary excretion values. The intervention effect on blood pressure in the mineral salt group seemed to be fully achieved after eight weeks and persisted throughout the study. After the trial the participants switched back to sodium salt and foods were no longer provided. The difference in blood pressure was no longer detectable 25 weeks after the study. No data on urinary electrolyte values were obtained at that time.

Cutler *et al.* reviewed 23 randomised trials and concluded that a 50 to 100 mmol reduction in sodium excretion per 24 hours was associated with a blood pressure fall of 4.9 mmHg systolic and 2.6 mmHg diastolic in hypertensive subjects.[9] A mean reduction of 38 mmol/24h in sodium excretion was achieved in our study. In a meta-analysis of 19 trials Cappuccio and MacGregor reported a fall in supine blood pressure of 5.9 mmHg systolic and 3.4 mmHg diastolic with a threefold to fourfold higher increase in potassium excretion than in this study.[15] Cross-sectional data from the INTERSALT study predicted smaller decreases of 1.9 and 1.2 mmHg respectively with a similar change in urinary potassium excretion.[7]

A 20 mmol increase in daily magnesium intake resulted in a diastolic blood pressure fall of 3.4 mmHg in a recent trial among Dutch women.[16] The mean reduction in blood pressure of 7.6 mmHg systolic and 3.3 mmHg diastolic observed in our study, in which sodium was lowered by 38 mmol, potassium intake raised by 18 mmol, and magnesium intake was estimated to be raised by 7 mmol, was larger than we would expect based on these previous estimates. The 95% confidence interval allows for a fall in systolic blood pressure as large as 11 mmHg.

Figure 4.3.1 Systolic and diastolic blood pressure (BP) at baseline and during intervention in controls and subjects in the mineral salt group.*

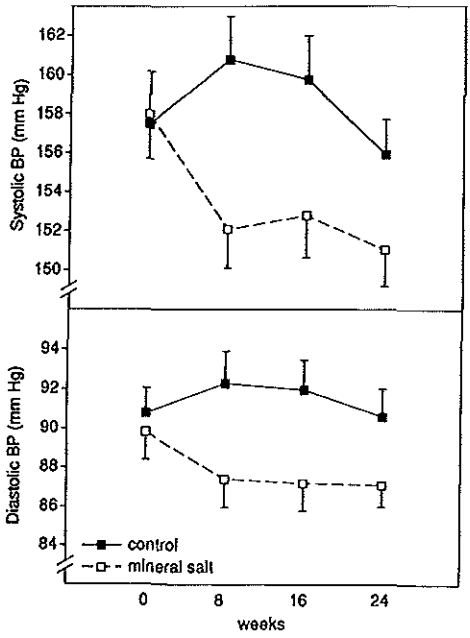
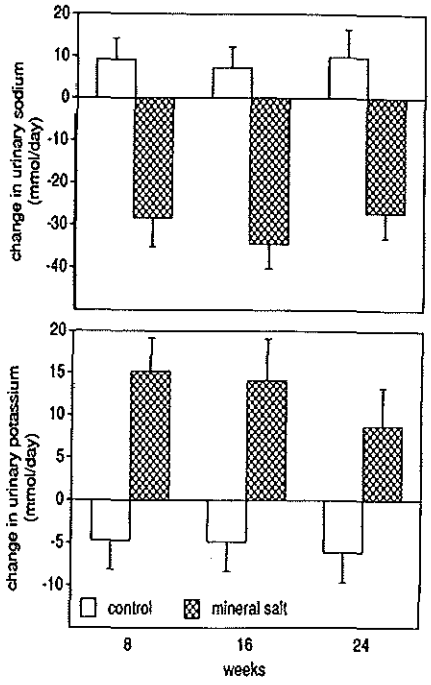


Figure 4.3.2 Mean changes in 24 hour excretion of sodium and potassium from baseline in controls and subjects in the mineral salt group.*



* Bars are standard errors of measurement.

Several factors could have contributed to the comparatively large blood pressure effect in our study. Firstly, the simultaneous alteration of sodium, potassium, and magnesium intake may more strongly affect blood pressure than a change of one mineral alone. To our knowledge no double blind, placebo controlled intervention trial on the combined effect of these minerals on blood pressure has been reported in humans. However, some data on the interaction of sodium and potassium are available. In an observational study Khaw and Barrett-Connor showed a stronger correlation of age adjusted blood pressure with the sodium/potassium ratio than with the individual minerals.[4] This was confirmed in mildly hypertensive young people.[5] The increased magnesium intake in our trial could have contributed to the reduction in blood pressure, possibly through interaction with sodium and potassium.[17,18] Moreover, possibly the unique nature of the mineral salt,

characterised by its source and double salt structures, also had a beneficial effect.

Secondly, the magnitude of the blood pressure fall could be related to the age of our study population. There is substantial evidence that elderly people benefit more from a reduction in sodium intake than young people.[7,19] We could not show a modification of the intervention effects with age, but the age range in our study was restricted.

There are many deaths from cardiovascular disease in elderly people. Thus a reduction in blood pressure as observed in our study potentially has important implications for morbidity and mortality in the older population.[20,21] We could effectively study the combined effect of sodium, potassium, and magnesium on blood pressure with a salt substitute, leaving the diet unchanged. Replacing common salt with the mineral salt

Table 4.3.4 Serum electrolyte concentrations at baseline and after 24 weeks of intervention.

	Week 0†	Week 24‡
Sodium (mmol/l):		
Controls	137.1 (0.4)	135.4 (0.5)
Mineral salt group	137.0 (0.5)	135.5 (0.4)
Potassium (mmol/l):		
Controls	4.17 (0.06)	4.23 (0.05)
Mineral salt group	4.27 (0.04)	4.35 (0.04)
Magnesium (mmol/l):		
Controls	0.86 (0.01)	0.82 (0.01)
Mineral salt group	0.86 (0.01)	0.83 (0.01)
Calcium (mmol/l):		
Controls	2.44 (0.02)	2.32 (0.01)
Mineral salt group	2.41 (0.02)	2.35 (0.01)
Ionised calcium (mmol/l):		
Controls	1.24 (0.01)	1.19 (0.02)
Mineral salt group	1.24 (0.01)	1.23 (0.02)

Values are means with standard error in parentheses.
† Values were missing for seven controls and four subjects in the mineral salt group.
‡ Values were missing for eight controls and four subjects in the mineral salt group.

resulted in a modest change in the mineral composition of the diet and was well accepted. This provides a practicable and more convenient dietary intervention than trying to get patients to restrict salt intake or to take a pure potassium chloride salt substitute.[22]

In conclusion our findings indicate that replacing sodium salt with a low sodium, high potassium, high magnesium salt could offer a valuable nonpharmacological approach to lowering blood pressure in mild to moderate hypertension, especially in older people.

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4.4

Long-term moderate sodium restriction does not adversely affect the serum HDL/total cholesterol ratio

Introduction

In severe hypertensive subjects, a clear benefit of sodium restriction on blood pressure has repeatedly been shown.[1] A number of short-term studies, however, have observed an adverse effect of salt restriction on the blood lipid profile of normotensive and hypertensive subjects.[2,3,4,5,6,7,8] In hypertensive subjects, the reduction of blood pressure will substantially improve the cardiovascular risk profile and outweigh any small, lipid-raising effect of salt restriction. The question, however, remains whether sodium restriction could be advocated as a safe health measure to reduce cardiovascular risk in the general population. In this respect, attention should primarily be focused on the ratio of HDL-cholesterol to total cholesterol as this is considered a better predictor of cardiovascular risk than total cholesterol or cholesterol subfractions separately.[9]

In a randomised, double blind trial we observed a substantial blood pressure reduction of 7.6 mmHg systolic and 3.3 mmHg diastolic when older untreated hypertensive subjects moderately reduced their sodium intake and increased their potassium and magnesium intake by means of a mineral salt during 24 weeks.[10] In this study, we investigated whether moderate sodium restriction affected the serum HDL/total cholesterol ratio.

Methods

One hundred men and women age 55 to 70 years with untreated hypertension (systolic blood pressure 140-200 mmHg and/or diastolic blood pressure 85-110 mmHg) participated in a randomised, double blind trial of the effect of mineral salt on blood pressure. During 24 weeks, 49 participants received a mineral salt (sodium:potassium: magnesium (mmol)= 8:6:1)* for use at cooking and at the table, and foods prepared with the mineral salt. Fifty-one controls received common salt and foods. Participants collected two consecutive 24 hour urine samples at baseline and after 8, 16 and 24 weeks of intervention for the assessment of sodium and potassium excretion. Blood sampling took place at baseline and after 24 weeks of intervention. A detailed description of the study has been presented elsewhere.[10]

* *SagaSalt®*
Dutch product name 'Jozo Vitaal', distributed by Akzo Nobel Salt Europe

Population for analysis

Blood serum for measurement of serum total cholesterol and HDL-cholesterol was available for 90 of 100 subjects. One control was excluded from the analyses because cholesterol lowering medication was started during the trial. This resulted in a total of 46 subjects in the mineral salt group (94%) and 43 controls (84%) for the present analysis.

Laboratory measurements

Blood serum had been stored for approximately two years at -20° Celsius. Analysis of serum total cholesterol was performed using an automated enzymatic procedure.[11] Serum HDL-cholesterol was measured similarly, after precipitation. No data on haematocrit were available to adjust findings for changes in plasma volume. Serum total protein is not expected to be influenced by the intervention and for this reason, change in plasma protein concentration was considered to be a marker of change in plasma volume. For the analysis of serum total protein a colorimetric method was used (Hitachi 747 Böhringer). Urinary sodium and potassium were measured by flame photometry.

Data analysis

Changes in serum total cholesterol, HDL-cholesterol and HDL/total cholesterol ratio from baseline were compared between the mineral salt group and controls and tested for statistical significance by Student's *t* test. Adjustment of change in lipids for change in serum total protein and potential confounders was performed by analysis of covariance. Means and 95% confidence intervals (95% CI) of the differences between groups are given. P-values below the α-level of 0.05 were considered statistically significant.

Results

Baseline characteristics of the study groups are shown in table 4.4.1. No significant differences were observed between the groups. After 24 weeks of intervention, 24 hour sodium excretion was significantly decreased by 41 mmol (95% CI 23 to 60 mmol, $p<0.001$) and potassium excretion significantly increased by 16 mmol (95% CI 4 to 28 mmol, $p=0.01$) in the mineral salt group compared with the controls. The changes in urinary magnesium and serum total protein during intervention were not significantly different between the study groups. In the mineral salt group, mean change in body weight during intervention was 0.4 kg more than in controls ($p=0.20$). This difference, though not statistically significant, was still present after 24 weeks.

Table 4.4.1 Baseline characteristics of the participants according to study group.

	Controls (n=43)	Mineral salt group (n=46)
Males (%)	22 (51)	27 (59)
Age (yrs)	67.0 (4.5)	65.9 (4.8)
Blood pressure (mmHg):		
Systolic	157.6 (12.1)	157.4 (15.2)
Diastolic	91.3 (9.2)	89.6 (9.9)
Height (cm)	167.4 (8.8)	169.5 (9.7)
Body weight (kg)	75.2 (10.3)	77.3 (6.9)
Body mass index (kg/m^2)	26.8 (2.8)	26.9 (3.0)
Serum:		
Total cholesterol (mmol/l)	7.0 (1.5)	6.9 (1.1)
HDL-cholesterol (mmol/l)	1.11 (0.37)	1.00 (0.20)
HDL/total cholesterol ratio	0.16 (0.06)	0.15 (0.03)
Total protein (g/l)	70.1 (8.2)	70.3 (5.1)
Urine:		
Sodium (mmol/24h)	136 (48)	143 (51)
Potassium (mmol/24h)	82 (25)	87 (20)
Sodium/potassium ratio	1.7 (0.6)	1.7 (0.4)

Values are means with standard deviation in parentheses, or numbers with percentages in parentheses

Urinary volumes in both groups were not significantly different and remained stable throughout the intervention period.

Serum total cholesterol at 24 weeks was significantly decreased in both groups, but 0.37 mmol/l (95% CI 0.02 to 0.71, p=0.04) more in the controls than in the mineral salt group after adjustment for age and sex. Serum HDL-cholesterol was decreased by 0.06 mmol/l in the controls, and increased by 0.05 mmol/l in the mineral salt group, yielding a statistically significant difference of 0.11 mmol/l (95% CI 0.02 to 0.20, p=0.02). The

HDL/total cholesterol ratio was increased 0.007 units (95% CI -0.006 to 0.020, p=0.25) more in the mineral salt group than in the controls (table 4.4.2).

After further adjustment for changes in potassium excretion, serum total protein and body weight during intervention, differences in change of lipids between the mineral salt group and the controls were more pronounced (table 4.4.2). Serum total cholesterol at 24 weeks was decreased 0.45 mmol/l (95% CI 0.12 to 0.77 mmol/l, p=0.009) in the controls compared with the mineral salt group. Serum HDL-cholesterol was increased 0.14 mmol/l (95% CI 0.05 to 0.22 mmol/l, p=0.002), and the HDL/total cholesterol ratio 0.010 units (95% CI -0.003 to 0.023, p=0.14) in the mineral salt group compared with the controls after adjustment for changes during intervention.

Discussion

Recently, concerns have been raised with regard to the health effects of sodium restriction. An increased activity of the sympathetic nervous system and elevated levels of plasma catecholamines and renin have been observed with sodium restriction. These effects are similar to those observed with diuretic therapy, and it has been postulated that sodium restriction, like diuretics, could adversely affect blood lipids and thereby the cardiovascular risk profile.[12,13,14,15]

In our study, we observed a decrease in total cholesterol level in both the controls and the mineral salt group. This could possibly be explained by the change of season, as the study started in autumn and ended in spring. A seasonal fluctuation of cholesterol level in humans has been reported by others.[16] The decrease in cholesterol may also be a concomitant effect of the intervention. Participants in both groups possibly adopted a healthier lifestyle or diet during the study period. However, serum total cholesterol decreased more in the controls than in subjects who reduced their sodium intake by the mineral salt. HDL-cholesterol, on the other hand, increased during moderate sodium restriction and this partially explains the lower decrease in total cholesterol in the mineral salt group. The HDL/total cholesterol ratio slightly increased following sodium restriction. Therefore, the net effect was an improvement in the cardiovascular risk profile for subjects in the mineral salt group.

The mineral salt group gained less weight during intervention than the controls, which may be due to extracellular fluid loss. However, urinary volumes remained stable during intervention and were similar in both groups. Furthermore, an increased loss of extracellular fluid is likely to be an acute effect of severe sodium restriction and probably is no longer present after 24 weeks of moderate sodium restriction. The present study was

Table 4.4.2 Change in serum total cholesterol, HDL-cholesterol and HDL/total cholesterol ratio from baseline in controls (n=43) and subjects in the mineral salt group (n=46).

	Week 0	Week 24	Change		Adjusted change*	
Total cholesterol (mmol/l)						
Controls	6.9 (0.20)	6.4 (0.16)	-0.60 (0.12)		-0.63 (0.12)	
Mineral salt group	6.9 (0.19)	6.6 (0.15)	-0.22 (0.12)		-0.18 (0.11)	
Difference†			0.37		0.45	
			[0.02 - 0.71]	*p=0.04*	[0.12 - 0.77]	*p=0.009*
HDL-cholesterol (mmol/l)						
Controls	1.11 (0.04)	1.04 (0.04)	-0.06 (0.03)		-0.07 (0.03)	
Mineral salt group	1.01 (0.04)	1.06 (0.04)	0.05 (0.03)		0.06 (0.03)	
Difference			0.11		0.14	
			[0.02 - 0.20]	*p=0.02*	[0.05 - 0.22]	*p=0.002*
HDL/total cholesterol ratio						
Controls	0.16 (0.008)	0.17 (0.007)	0.005 (0.005)		0.004 (0.005)	
Mineral salt group	0.15 (0.007)	0.16 (0.007)	0.013 (0.004)		0.014 (0.005)	
Difference			0.007		0.010	
			[-0.006 - 0.020]	*p=0.25*	[-0.003 - 0.023]	*p=0.14*

Values are adjusted for age and sex and presented as means with standard errors in parentheses.
* Additionally adjusted for changes in body weight, serum total protein and potassium excretion during intervention.
† Difference in change from baseline: mineral salt group compared with controls; with 95% confidence interval and two-tailed p-value.

not *a priori* designed to study the effect of sodium restriction on the plasma lipid profile. Consequently, we had no data on haematocrit, and we used change in serum total protein to adjust for changes in plasma volume. As this is only an indirect measure of change in plasma volume, residual confounding cannot be excluded. We therefore do not rule out the possibility that the mineral salt group experienced some volume depletion, which could explain the higher serum cholesterol and HDL-fraction levels in this group. The results on change in HDL/total cholesterol ratio, however, are not affected by differences in plasma volume between the groups. Comparing changes in HDL/total cholesterol ratio between the groups is therefore more valid than comparisons in total cholesterol and HDL-cholesterol separately. Because the HDL/total cholesterol ratio is a better predictor of cardiovascular risk than total cholesterol or cholesterol subfractions separately, we also consider this comparison most relevant to practice.

Because the salt that we used for intervention contains 41% potassium chloride and 17% magnesium salts, subjects in the mineral salt group increased their potassium and magnesium intake as well. Data on the effect of potassium on serum lipid concentrations are scarce. In rats, serum cholesterol was not significantly affected by a high potassium diet.[17] Kjeldsen *et al.* studied 50-year-old men on a low sodium diet combined with potassium supplementation and did not observe significant changes in serum total cholesterol and HDL-cholesterol.[18] Until now, there is no evidence that the moderate increase in daily potassium intake of 16 mmol could have accounted for the changes in HDL-cholesterol and total cholesterol in our study. With regard to magnesium, Singh *et al.* in a single-blind, randomised study, reported significant decreases in serum total cholesterol and LDL-cholesterol, and a marginal increase in HDL-cholesterol, when 214 subjects received a magnesium-rich diet containing approximately 800 mg more magnesium than a control diet.[19] Marken *et al.*, on the other hand, in a controlled study, did not observe significant changes in the blood lipid profile when 50 healthy volunteers were given 800 mg supplemental magnesium for 60 days.[20] Similarly, no effect was observed in 17 subjects with hypercholesterolaemia and/or hypertriglyceridaemia who received 1,785 mg magnesium for 6 weeks.[21] Magnesium intake in our study was increased by approximately only 170 mg per day in those who used the mineral salt. We think that this slight increase in magnesium intake could not have affected serum HDL- and total cholesterol levels in our study.

Several studies examined the effect of a reduced sodium intake on serum total cholesterol and cholesterol subfractions. Ruppert *et al.* demonstrated significantly higher levels of serum total cholesterol and LDL-cholesterol during one week of severe sodium

restriction to 20 mmol per day in normotensive adults.[2] Similar findings were reported in a small study among normotensive and untreated hypertensive men. Again, sodium intake was strongly reduced to 20 mmol per day.[3] These findings were confirmed by Sharma *et al.* who showed an increase in total cholesterol and LDL-cholesterol during a low sodium regimen of 20 mmol per day in 15 young, normotensive men.[4] In all studies, change in plasma volume was taken into account and the reported increases in lipids were not regarded to reflect haemoconcentration. Regrettably, none of the studies reported data on change in HDL/total cholesterol ratio, thereby making a true comparison with our study impossible.

The majority of studies on sodium restriction and serum cholesterol levels focused on short-term effects of a low-salt diet. However, long-term rather than short-term effects are relevant to practice. In our study, participants reduced their sodium intake for 24 weeks. No adverse effect on the HDL/total cholesterol ratio was observed. Our findings are confirmed by a 6-month study by Oberman *et al.* who showed no effect of a mild reduction in sodium intake, combined with a small increase in dietary potassium, on total cholesterol in untreated hypertensive patients.[22] Analogously, diuretic therapy does not seem to adversely affect serum lipids in the long-term. The Hypertension Detection and Follow-up Program observed an initial increase in total cholesterol with diuretic use during the first year, but during subsequent annual follow-up total cholesterol decreased below baseline levels.[23] The Framingham Study neither showed an increase in total cholesterol after a few years of diuretic use.[24]

Substitution of common sodium salt by a low sodium mineral salt appeared to be a feasible means for lowering blood pressure in older, untreated hypertensive subjects. A long-term moderate reduction in sodium intake was easily achieved by the mineral salt.[10] From our findings we conclude that long-term moderate sodium restriction does not adversely affect the cardiovascular risk status of the older hypertensive patient.

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CHAPTER 5

GENERAL DISCUSSION

5
General discussion

Introduction

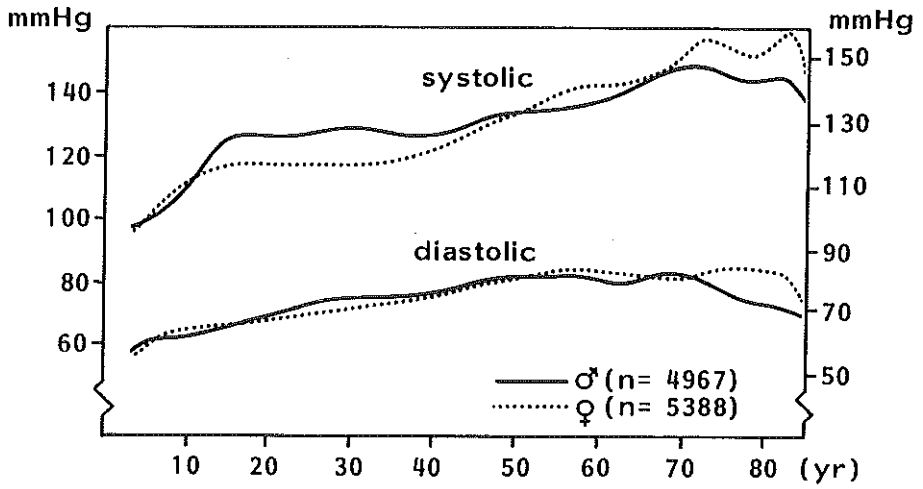
The limitations and merits of the individual studies described in this thesis have already been discussed extensively in the previous chapters. In this chapter, first a general overview will be given on blood pressure development during life. Subsequently, the role of sodium and potassium intake in determining blood pressure level and change will be discussed, implementing the findings of the studies described in this thesis. In the second part of the discussion, methodological aspects of the studies will be discussed. Finally, directions for further research will be delineated.

Blood pressure development during life

Hypertension is an important risk factor for heart disease and stroke. In Western societies, blood pressure levels increase consistently during the course of life.[1] Judson and Nicholson, in 1914, were the first to report that the rise in blood pressure already starts in childhood.[2] This finding has repeatedly been confirmed by others in the years thereafter.[3] In Dutch youngsters, an average yearly change of 2 mmHg in systolic and 1 mmHg in diastolic blood pressure is observed from birth until the age of 20 (fig 5.1).[4] The rise in blood pressure is strongly related to growth and maturation.[5] During puberty systolic blood pressure rises more sharply in boys than in girls, due to the difference in age at which maturation is achieved. The rise in blood pressure becomes less pronounced after the age of 20. Throughout adult life, blood pressure increases slowly but steadily. At the age of 55, diastolic blood pressure achieves a plateau and tends to decrease with advancing age. Systolic blood pressure level keeps increasing at older age. There is reason to believe that the roots of hypertension are to be found in childhood, or even in infancy.[6] Growth-promoting processes, probably involving neuroendocrine mechanisms, may both elevate blood pressure and stimulate somatic growth and maturation in children.[5] Genetic and environmental factors may interact with these processes and influence the rise in blood pressure in childhood. A blood pressure level that is 'set' in adolescence may be carried forward in adult life by a self-perpetuating process.[7,8] In line with this hypothesis, it has been shown that subjects who experienced the largest rise in blood pressure at young age were most likely to develop hypertension later in life.[9]

Blood pressure, as most other physiological parameters, is normally distributed within a population. The dividing line between 'normotension' and 'hypertension' is arbitrary, and

Figure 5.1 Age- and sex-specific average levels of systolic and diastolic blood pressure.*



* Data have been obtained from a cross-sectional study among 10,355 subjects in the Netherlands (Valkenburg HA, *et al.* Ned Tijdschr Geneeskd 1980;124:183-9. Used with permission of the authors and publisher).

more or less reflects the level of blood pressure where, in general, the benefits of treatment with antihypertensive drugs exceed the costs and potential adverse effects of therapy.[10]

Electrolytes and blood pressure

Sodium

Ambard and Beaujard, in the beginning of this century, were the first researchers who related the intake of salt to blood pressure in hypertensive patients.[11] At the same time, a number of clinical and animal experiments were published by others who related salt intake to febrile illness, cardiac failure, edema and several other kind of illnesses. Kempner in the 1940s developed a rice-fruit diet, low in sodium and high in potassium, which appeared successful in lowering blood pressure in malignant hypertension.[12]

Epidemiologic research already began in 1927 with a study by Thomas, who related salt intake to the prevalence of hypertension in Greenland Eskimos.[13] From that time on, a large number of studies linking the salt intake of populations with the incidence or

prevalence of hypertension have been performed. It was noted that hypertension is virtually nonexistent in unacculturated societies with a low salt intake, and that blood pressure does not increase with age in these populations. Dahl, in 1960, presented a graph that indicated an almost perfect linear relationship between the prevalence of hypertension and salt intake among five separate populations around the world.[14] However, this study was hampered by severe methodological shortcomings: some populations were represented by only a small number of individuals, estimates of salt intake were not uniform, and no adjustments were made for differences in age and sex distributions. In the 1980s, a large international epidemiologic study (INTERSALT) was initiated to overcome these problems.[15] The INTERSALT study describes the relation between standardised measurements of blood pressure and 24 hour urinary sodium and potassium excretion in over 10,000 individuals at 52 centres around the world. The study showed that a 100 mmol/day difference in sodium intake is associated with a 2.2 mmHg difference in systolic blood pressure. This relation, however, was lost when four primitive societies with an extremely low salt intake were omitted from the analyses. Interestingly, however, sodium intake was related to the age-related slope of blood pressure also when the analysis was restricted to the 48 relatively high-salt centres. A 100 mmol/day lower sodium intake was associated with a 9 mmHg lesser rise in systolic blood pressure between the ages 25 and 55.[16]

Most epidemiologic studies *within* single populations have not been able to show a relation between sodium intake and blood pressure.[17] This could reflect inaccurate assessment of sodium intake or blood pressure,[18] or be due to the fact that the range of salt intake within a single population is too restricted to adequately study the effect of high and low intakes on blood pressure. Habitual sodium intake in Western populations varies between 100 and 250 mmol (6-15 grams of salt) per day.[19] Sodium intakes below 50 mmol per day are observed in primitive societies.[15] Possibly, the threshold above which sodium may start to affect blood pressure is somewhere between 50 and 100 mmol. Studies that do not include intakes both below and above the threshold level may therefore fail to demonstrate an effect of sodium on blood pressure. An alternative explanation for the lack of an association could be that a population consists of a heterogeneous group of individuals, whose blood pressures may react quite differently to dietary influences. Evidence is now accumulating that there are subgroups who are more sensitive to the effect of sodium on blood pressure than others.[20,21,22,23] Accordingly, in intervention studies of the effect of sodium restriction or supplementation on blood pressure, a large heterogeneity of blood pressure response has been observed: some people experience a

blood pressure reduction, whereas others do not respond or even show an increase in blood pressure.[24,25] However, part of the variability in response is random and has no biologic significance.[23] Persons whose pressures increase with a high sodium intake and decrease with a low sodium intake have been termed salt-sensitive. The issue of salt-sensitivity will be discussed in more detail later on in this chapter.

Potassium

An alternative explanation for the low blood pressure found in populations with a low dietary sodium intake is their generally high intake of potassium. Several epidemiological studies have pointed to an inverse relationship between potassium and blood pressure.[26,27] The INTERSALT study showed a decrease of 2.5 mmHg in systolic blood pressure, and a 1.7 mmHg decrease in diastolic pressure per 100 mmol increase in potassium intake across 52 centres around the world. In older subjects of the Rotterdam Study, we demonstrated a decrease in systolic pressure of 9.4 mmHg, and a decrease in diastolic pressure of 4.9 mmHg per 100 mmol potassium (Chapter 4.1). In a meta-analysis of 19 trials, Cappuccio and MacGregor reported an average fall in supine blood pressure of 5.9 mmHg systolic and 3.4 mmHg diastolic with a substantial experimental average increase in potassium intake of 86 mmol per day.[28] Not all clinical trials, however, were able to demonstrate an effect of potassium supplementation on blood pressure.[29,30] The blood pressure lowering effect of potassium has been attributed to an induced natriuresis, altered activity of the renin-angiotensin-aldosterone system and/or kallikrein-kinin system, or to a modulation of the sympathetic nervous system activity and alteration of the peripheral resistance.[31,32,33,34,35] The effect of a high potassium intake on blood pressure is more pronounced in blacks than in whites, in individuals consuming a high sodium chloride diet, and in hypertensive persons.[28,36,37] The INTERSALT study additionally showed stronger associations of potassium with blood pressure with increasing age.[38]

Electrolyte interaction

The renal handling of sodium and potassium is closely related, which argues for a concomitant consideration of these cations when studying their effect on blood pressure. The effects of a high sodium intake on blood pressure may be amplified by dietary deficiencies of potassium. In the NHANES I study, the sodium/potassium ratio was more strongly related to blood pressure than sodium and potassium alone.[39] Significant interactions between sodium and potassium have also been reported in studies by

others.[40,41] The study described in Chapter 4.3 of this thesis shows the effect of a moderate reduction in sodium intake and a moderate increase in potassium and magnesium intake on blood pressure in men and women aged 55 years and over. This simultaneous change in mineral intake resulted in a substantial, significant fall in systolic and diastolic blood pressure. The blood pressure effect was 3 to 4 times larger than expected on the basis of previous trials of either sodium restriction or potassium supplementation alone. This could be due to interaction between sodium and potassium. The increased magnesium intake of 7 mmol (168 mg) per day, resulting from use of the mineral salt, may have contributed to the relatively large reduction in blood pressure. A blood pressure lowering effect of magnesium has been reported in some observational and experimental studies, but results are inconsistent.[42,43,44] Several studies pointed to a possible interaction between sodium, potassium, and/or magnesium in determining blood pressure level.[45] Magnesium has been shown to be a modulator of sodium-potassium ion transport in numerous tissues.[46,47] The results of the mineral salt trial reported in this thesis suggest that multiple intervention on intake of several minerals may be more effective than changing the intake of sodium, potassium, or magnesium individually. However, because of the design of the trial interaction effects could not be studied. In our cross-sectional data (presented in Chapter 4.2) we could neither adequately study whether minerals interact, because the dietary intakes of minerals were too strongly intercorrelated. The methodological problem that arise in nutritional data analysis will be discussed later on.

Susceptibility

Markers of susceptibility

Hypertension is often considered to be a homogeneous condition. However, evidence is accumulating that there are several subtypes of hypertension with different pathophysiological and haemodynamical characteristics.[48] An intervention that could lower blood pressure in one subtype of hypertension may have no effect in other subtypes. For optimal treatment it seems worthwhile to identify subgroups of people who are likely to respond favourably to a specific intervention. Genetic factors could be related to the sensitivity of blood pressure to sodium and/or potassium intake. For example, several gene variants that give rise to higher levels of angiotensinogen have been observed more frequently in hypertensives than in normotensives. Raised levels of angiotensinogen could lead to overactivity of the renin-angiotensin system in response to

salt intake.[49] Carriers of the variant genes may therefore be more likely to benefit from sodium restriction than others. Several other variables, such as urinary kallikrein excretion, intracellular sodium concentration, sodium-lithium countertransport, and sodium-potassium cotransport have also been related in some way to sodium or potassium metabolism, or both.[50,51] Studies in this field may help to improve the understanding of a possible inherited susceptibility to hypertension resulting from an inadequate intake of sodium and/or potassium.

Besides genetic factors, physiological or pathological alterations in the cardiovascular system may increase the sensitivity of blood pressure to sodium and/or potassium. These changes could be related to age, blood pressure level itself, or other factors. Besides neural vasomotor control mechanisms,[52] hormonal systems involved with salt and water balance alter with age.[53] The number of functional nephrons in the kidney has been shown to be reduced at older age. This may lead to an increased delivery of sodium to the macula densa in surviving nephrons, resulting in an inhibition of renin synthesis and secretion by the juxtaglomerular cells.[54] The renin-angiotensin system plays a major role in the water and sodium balance, and its major function is to allow wide variations in sodium intake and excretion without large fluctuations in blood pressure. If the renin-angiotensin system becomes less responsive, blood pressure rises when large amounts of sodium are ingested to maintain sodium balance via pressure natriuresis. Sustained hypertension has been shown to induce structural changes in blood vessels, heart, and kidney.[55] Again, damage of renal tissue may affect the renin-angiotensin system, which could increase the sensitivity of blood pressure in hypertensives to intake of electrolytes. An increased sensitivity of blood pressure to sodium intake with age and blood pressure level was confirmed by a meta-analysis of intervention trials by Grobbee and Hofman.[24] In the next paragraph, blood pressure response to intake of sodium and/or potassium in different age groups will be discussed in more detail.

Susceptible time periods in life

Experiments in genetic strains of salt-sensitive rats have shown that a high salt intake at the time of weaning could have a major impact on the early development of hypertension.[56] Similarly in humans, exposure to high sodium levels in infancy may adversely affect the development of blood pressure during growth and maturation. In Chapter 2 of this thesis special attention has been paid to sodium intake in infancy in relation to blood pressure in adolescence. The original trial on which the follow-up study was based showed a positive relationship between sodium intake and blood pressure

development during the first six months of life. The follow-up study showed that higher blood pressure levels were still present 15 years later in children who had been assigned to the diet that contained the usual amount of salt. Sodium may have played a critical role in early blood pressure development in these children, possibly through an adverse effect on immature kidney tissue.[57] An alternative explanation could be that the preference for a certain level of salt intake is set early in life and maintained thereafter, eventually resulting in higher blood pressure levels. From our study we cannot infer which etiologic factors may have been involved in the blood pressure rising process. McGarvey *et al.* observed an independent, inverse relation between maternal prenatal potassium intake and infant diastolic blood pressure at 6 and 12 months, which provides evidence for a very early role of potassium in blood pressure regulation.[58] In the follow-up study of infants mentioned above, potassium intake was not taken into account as the difference in sodium intake resulted from random allocation. Data on the relation between nutrient intakes in infancy and future blood pressure are scarce. Studies in this field may provide clues for the prevention of hypertension and a further understanding of its causes.

As discussed previously in this chapter, the age-related blood pressure rise is most pronounced in children. As the result of a possible self-perpetuating process of blood pressure level on blood pressure, small differences in rate of blood pressure change in childhood may yield substantial differences in blood pressure level later in life.[7,8] Studies on determinants of blood pressure development at young age are therefore of particular relevance. In Chapter 3 the relation between sodium and potassium intake and rate of blood pressure change was studied in a follow-up study among children aged 5 to 19 years. Change in blood pressure was assessed in two time periods, *i.e.* between 1978 and 1985 ('early phase') and between 1986 and 1991 ('late phase'). The relation between mean urinary electrolyte excretions in the early phase and blood pressure changes in both the early phase (Chapter 3.1) and late phase (Chapter 3.2) was studied. The associations with change in blood pressure appeared to be stronger for potassium than for sodium in both the early and late phase of the study. This finding corroborates the report by Lever *et al.* who hypothesised that in the early stages of hypertension blood pressure is raised by a process more closely related to potassium than to sodium.[59]

The elderly is of particular interest in light of the sodium-blood pressure relation. A number of physiological alterations occur when people grow older, making them particular susceptible to a high intake of salt.[60,61,62,63] Low plasma renin levels, a decreased renin response to stimulation, and volume expansion have repeatedly been demonstrated in older people.[64] Besides a reduction of functional neurons leading to an inhibition of

renin synthesis, as discussed in the previous section, the decline in plasma renin levels with age may be explained by a decrease either of renin storage or of sympathetic nervous system activity on renin release.[65] The cross-sectional study, reported in Chapter 4.1, suggests a positive association of sodium excretion and an inverse association of potassium excretion with blood pressure in people above 55 years of age. The observed association between electrolyte excretion and blood pressure was probably underestimated, because electrolyte intakes were assessed by a single overnight urine collection and hypertensive subjects were excluded from the analysis. In Chapter 4.2 intakes of electrolytes were estimated from a semiquantitative food frequency questionnaire. Potassium intake again was inversely related to blood pressure. Intake of sodium was not measured in this study. The intervention study described in Chapter 4.3 showed that blood pressure in older, mildly hypertensive subjects is sensitive to multiple changes in mineral intake.

Intervention

Target groups for intervention

As indicated in Chapters 2 and 3 of this thesis, the roots of hypertension may be found in childhood. Children who experience a large rise in blood pressure are more likely to develop hypertension in later life.[9] Intervention at (very) young age with the aim to prevent or diminish the age-related rise in blood pressure could therefore yield a significant contribution to the prevention of hypertension.

In adults, higher blood pressure levels have been associated with an increased mortality due to heart disease and stroke. The combined results of nine prospective studies, generally among middle-aged men, show that the relative risk for a heart attack is more than twice as high for diastolic blood pressures above 105 mmHg compared to pressures of 90 mmHg, and almost four times as high compared to pressures of 80 mmHg. The relative risk for stroke increases even more dramatically with blood pressure level.[66] Once hypertension has developed, it tends to be self-perpetuating via amplifying mechanisms, mediated by secondary structural changes in the blood vessels, heart, and kidney. Lowering blood pressure, also of mildly elevated levels, leads to a decrease in coronary heart disease and stroke in middle-aged adults.[67,68] Intervention on blood pressure level and change in hypertensive adults is likely to prevent or delay end organ damage. A decrease in blood pressure in mildly hypertensive and normotensive adults will probably result in a reduction of the cardiovascular risk and may prevent a future rise in

blood pressure. A clear benefit in total and cardiovascular mortality of blood pressure reduction has been shown also in older, hypertensive people below the age of 70-80.[69] With respect to the very old, however, there is debate about whether blood pressure reduction should be advocated or not.[70,71,72,73]

Intervention approaches

With regard to the prevention of cardiovascular complications, two main intervention approaches are generally considered. The 'high risk' approach aims at lowering blood pressure specifically in individuals at an increased risk for cardiovascular disease, as judged by their blood pressure levels. In this approach, hypertensive patients within the population are identified and treated. This approach is of large benefit to the individual because a reduction in blood pressure will substantially reduce the patient's cardiovascular risk. On the other hand, 60% of cardiovascular complications occur in people with diastolic blood pressure levels below 95 mmHg.[74] In other words, the burden of cardiovascular disease occurs predominantly in people with only mildly elevated blood pressure levels who do not easily come to the attention of the medical care system. The prevalence of severe hypertension in the general population is low, whereas that of mild hypertension is much higher. Consequently, if significant reductions in cardiovascular disease rates in the community are to be achieved, attention should be paid to reduction of blood pressure in the large group of mild hypertensives.[75] The 'whole population approach' aims at shifting the distribution of blood pressure levels to lower levels in the community as a whole. The community benefits of lowering the average blood pressure have been estimated by Wilkins and Calabrese.[76] In white US males aged 35 to 75, a 5 mmHg reduction in systolic blood pressure would reduce the number of major coronary events by approximately 35,000 per year.

The 'whole population approach', but also the 'high risk approach' when judging blood pressure levels only, disregard the fact that a population consists of a heterogeneous group of individuals. The mechanisms involved in blood pressure elevation may differ across subgroups. As a consequence, the blood pressure response to a specific intervention will differ among individuals with a different etiology of hypertension. For optimal treatment (and possibly also from the viewpoint of cost-effectiveness), it is worthwhile to identify groups of people who are likely to respond favourably to a specific intervention. A preventive strategy focusing for example on specific age groups might be considered. In case that susceptibles cannot readily be identified within a population, screening for indicators of susceptibility will have to take place. The practical

implications of this strategy need more detailed consideration.

Dietary intervention

One of the most important potentially modifiable determinants of blood pressure is the diet. This thesis focuses on the role of mineral intake in blood pressure regulation. Chapter 2 showed that the blood pressure levels in adolescence could in part be determined by the amount of salt in baby food. Reducing salt intake in infancy is a measure which can easily be achieved with help of the food industry and which is not expected to impair the quality of life or affect other important metabolic or physiologic mechanisms in these young children. We did not study the effect of potassium in this cohort of infants, but others have suggested that potassium may have a favourable effect on blood pressure at very young age,[58] as has been discussed previously in this chapter.

Lifestyle modifications in other age groups are more difficult to achieve and compliance could be poor in the long-term. This is especially the case if the subject does not (yet) experience health problems or is unaware of being at increased risk for cardiovascular disease. As demonstrated in Chapters 2 and 3 by the high urinary sodium/potassium ratios of around three to four, the diets of children and young people tend to be dominated by processed foods high in sodium, and are low in potassium-rich foods such as fruits and vegetables. It would seem prudent to move towards a lower sodium/higher potassium diet for children, as already advocated for adults,[77] for the primary prevention of high blood pressure and hypertension in later life. In older people also, the ratio of sodium to potassium in the diet of around two to three is substantially larger than the preferred level of one. Substitution of common sodium salt by a low sodium, high potassium, high magnesium mineral salt offers an effective and feasible approach to lowering blood pressure in older people as has been shown in Chapter 4.3. Furthermore, this mild dietary intervention did not adversely affect the blood lipid profile (Chapter 4.4). Changing the sodium/potassium balance in the diet by means of a salt substitute has not yet been studied in infants and children, but could be a useful measure also in these age groups to attenuate the rise in blood pressure.

Pharmacological or nonpharmacological treatment?

According to the Dutch guidelines for general practitioners, patients with a diastolic pressure above 105 mmHg should be treated with blood pressure lowering medication. Patients with diastolic blood pressures between 100-104 mmHg should receive treatment in case several other risk factors are present.[78] In subjects with clearly elevated blood

pressure levels, *i.e.* diastolic blood pressures above 105 mmHg, the benefits of drug treatment clearly outweigh their potential negative side-effects and there is little discussion whether the administration of drugs to these patients is acceptable or not. However, in patients with high-normal or mildly elevated blood pressure levels, *i.e.* diastolic blood pressures between 90 and 105 mmHg, the need for drug therapy is still subject to debate.[79,80] The potential benefits of antihypertensive therapy in mildly hypertensive individuals, which in absolute terms are smaller than in subjects with severe hypertension, may be offset by the occurrence of side-effects and the impaired quality of life.[81] Nonpharmacological therapy, including weight reduction, dietary interventions, use of nutrient supplements, limitation of alcohol intake, regular moderate exercise, and relaxation therapy, are possibly preferable in mild hypertension.[82] Also in severe hypertension, the use of one or more nondrug therapies could be considered as an adjunct treatment to antihypertensive medication.[83,84,85] Because of the diminished clearance capacity of the body, the elderly could be especially susceptible to unfavourable side-effects of drugs. Furthermore, older patients are more likely to be under drug treatment for coexisting diseases and therefore at higher risk for adverse drug interactions. Treatment of high blood pressure in this age group by nonpharmacologic means deserves even more attention than in younger patients.[86] However, one should be careful that long-term nonpharmacological therapy does not lead to suboptimal prevention of cardiovascular complications.[87] Through dietary and other lifestyle modifications, diastolic blood pressure is often lowered to levels between 90 and 100 mmHg and drug use is avoided. Prevention in this case, however, is not optimal as blood pressure remains too high. As for drug therapy, the target diastolic blood pressure level should be below 90 mmHg. If this cannot be achieved by single lifestyle modifications, multifactorial intervention could be applied and drugs added if necessary.

Little is known about the efficacy of pharmacological compared to nonpharmacological therapy in mild hypertension. Only few studies have directly compared the effect of drugs with nonpharmacological measures on cardiovascular risk status.[88,89,90,91] The evidence from these trials is not conclusive. With regard to blood pressure, reductions achieved by lifestyle modifications seem somewhat smaller than those observed with drug treatment. In our mineral salt trial presented in Chapter 4.3, diastolic blood pressure was reduced by 3-4 mmHg. Moderate weight loss (of about 4 kg) has been shown to lower diastolic blood pressure by 2-3 mmHg in subjects with high-normal blood pressure in the Trials of Hypertension Prevention.[92] Mean reductions of 5-6 mmHg in diastolic blood pressure are generally achieved with antihypertensive drugs.[68] However, anti-hypertensive

drugs, though generally effective in lowering blood pressure, could adversely affect the serum lipid profile and other metabolic indices.[89,90,93] When taking these undesirable effects into account, the overall effect on cardiovascular risk status in mild hypertension may not be very much different between both therapies.

Methodological aspects

Introduction

In this part of the general discussion, a few methodological problems will be considered that were encountered in the studies described in this thesis. The topics that are subsequently dealt with are: the effect of measurement errors on the observed associations of urinary electrolyte excretions with blood pressure, the study of blood pressure status compared to blood pressure change, etiologic versus pragmatic studies, and multicollinearity and energy-adjustment in nutritional research.

Measurement errors of urinary electrolyte excretion and blood pressure

In the cross sectional study reported in Chapter 4.1 of this thesis, we observed only a weak association of sodium with blood pressure after adjustment for potassium excretion. From this one may conclude that sodium intake is of little importance in relation to blood pressure. However, measurement errors may have affected the observed associations in our study and should be considered as an alternative explanation, as discussed below.

In Western populations, intake of salt within an individual shows a large day-to-day variation. Habitual sodium intake of an individual cannot accurately be assessed by a food frequency questionnaire, because salt use during cooking and dining is hard to quantify and not all salt is actually consumed. More than 90% of the ingested salt is excreted in urine within the next few days. Urinary excretion of sodium is therefore often used as the proxy of intake in epidemiologic studies, even though this relates only to recent intake. Because of the difficulties in the assessment of sodium intake, individuals are often grossly misclassified with respect to their true habitual sodium intake. In our large population study, participants collected one overnight urine sample from which daily salt intake was estimated. Overnight urinary values show a moderate degree of correlation with 24 hour excretions, but are a crude measure of habitual sodium intake. The inaccurate assessment of sodium intake in our study has probably lead to misclassification and biased the regression coefficients towards zero ('regression-dilution').[17] The quantitative estimates of the sodium-blood pressure relation could be considerably

improved by a more accurate assessment of sodium intake. Multiple 24 hour urine samples, collected over a longer period of time and checked for completeness, will yield considerably better information than the single overnight urine collection that we used in our study. Some techniques are available to adjust for the regression dilution bias.[18,66] We did not apply these techniques in our analysis because subjects collected only one urine sample, but they are worth being considered. The relation of urinary potassium excretion with blood pressure in our study was relatively strong when compared to sodium. If potassium intake is less variable than sodium intake, this finding could in part be explained by the smaller measurement error.

Blood pressure, as other physiological characteristics, is subject to variation. The blood pressure within a single individual may vary in different seasons, from day to day, and even at different time points during the day. Besides that, the ambient temperature, blood pressure observer, measuring device, size of the cuff, posture of the subject (sitting, standing or lying), as well as the subject's mental and physical state, could influence the outcome of the measurement. From this it follows that it is impossible to reliably assess a person's blood pressure by a single blood pressure reading. In the Rotterdam Study blood pressure was measured twice on one occasion with a random-zero sphygmomanometer, and the average was used in our cross sectional analyses reported in Chapters 4.1 and 4.2. The participants had been sitting quietly for at least 5 minutes before the measurements were performed. Nevertheless, these measures did not completely remove random error in the assessment of the subjects' blood pressure levels. This will have caused imprecision in the estimated effects, resulting in relatively wide 95% confidence intervals. Multiple measurements on several separate occasions, preferably over a longer period of time, could further reduce the random variation and provide a more reliable estimate of the true individual blood pressure levels. However, this appeared not feasible in our large population study among elderly people.

Blood pressure: level versus change

In a randomised intervention study, the effect of an experimentally achieved exposure on blood pressure is studied. The main end point for analysis in such study is usually change in blood pressure due to the exposure. The blood pressure level at the end of the trial will be the result not only of blood pressure change due to intervention, but also of several factors unrelated to the intervention that may have existed before the start of the study. For this reason, in the mineral salt trial described in this thesis (Chapter 4.3) the main focus was on change in blood pressure during intervention. The time structure of an

etiologic study differs from that of an intervention study. The exposure of interest is not introduced at baseline and will probably have existed for a shorter or longer period before the start of the study. Whether to study blood pressure level or blood pressure change in an etiologic study depends on the exposure at issue and the research question. A stable exposure that has been present for a longer time, but that no longer affects current blood pressure change (for example a genetic factor that determines blood pressure early in life) can only come to the attention when studying blood pressure level. This would argue for the choice of level rather than change as the end point in data analysis. In the study among children described in Chapter 3, blood pressure change was chosen as the study outcome for the following reasons. The major part of the lifetime increase in blood pressure occurs in childhood, and it is likely that determinants of the blood pressure increasing process can be identified in particular during this period of life. Furthermore, change rather than actual blood pressure in children may be a predictor of adult blood pressure and of hypertension.[3,94] We did not examine the association of change in blood pressure with change in electrolyte excretions over time. Values for urinary sodium and potassium appeared to be relatively constant within individuals during the follow-up period, and for this reason we averaged electrolyte excretions over the whole time span and used this measure of cumulative exposure.

The study described in Chapter 2 had initially been set up as a randomised trial. Because of the differential selection of subjects for the follow-up study, the randomisation was lost. It is therefore more appropriate to consider the follow-up study described in this chapter as an observational (cohort) study, in which the exposure of interest is an experimentally manipulated difference in sodium intake early in life. Blood pressure level at 15 years of age, rather than change in blood pressure from birth to adolescence, was chosen as the end point. The main reason for this was the different procedure for blood pressure measurement in the first and late part of the study. Whereas the early measurements had been performed with a Doppler device attached to a random-zero sphygmomanometer, the latter measurements were performed with a automatic blood pressure measuring device. This may be one of the reasons that blood pressure at birth appeared to be only weakly correlated to blood pressure in adolescence in this cohort. The use of achieved blood pressure level was therefore preferable to the use of blood pressure change as the end point in the analysis of this study.

In later life, changes in blood pressure become less pronounced. Probably, stable risk factors that have been present for a long time do no longer cause large changes in blood pressure in adulthood. Therefore, for a number of determinants one may decide to study

their effect on blood pressure level rather than change. Different rates of blood pressure change early in life will eventually result in different blood pressure levels in later life. Blood pressure level at older age could be considered the cumulative endpoint of lifetime blood pressure change. In Chapters 4.1 and 4.2 of this thesis electrolyte intake was studied in relation to blood pressure level in a population aged 55 and over. The study of blood pressure level becomes more complicated in the very old. In this age group, the cardiovascular disease process itself may cause a decline in blood pressure. Consequently, blood pressure level in the very elderly is the result of different processes with their own specific determinants that have been acting for a longer or shorter period of time. As these factors cannot easily be disentangled, the study of blood pressure change is to be preferred to blood pressure level.

Etiologic versus pragmatic studies

The objective of the study has bearings on its design. When studying determinants of blood pressure to come to a better understanding of the etiology of hypertension, one may often wish to directly link the findings of the study to biological mechanisms. Intervention studies designed for this purpose aim to study the solitary effect of (change in) a determinant on the outcome. Extraneous effects related to intervention are not of interest and should, in fact, be excluded. These effects may therefore be avoided, or be equally distributed over the study groups so that they differ with regard to the determinant only. In trials, comparability of extraneous effects can be increased by 1) the inclusion of a placebo-control group, and 2) blinding of the observer and the participant towards the assigned intervention. In nutritional research, one could either study foods or individual nutrients as the determinant of interest. Foods are a mixture of numerous compounds and it is difficult to relate intake of individual nutrients directly to possible biological pathways. Therefore, in etiologic studies total intakes of individual nutrients derived from the foods or, alternatively, total 24 hour urinary excretions are mostly the determinant of interest.

In a pragmatic study the aim may not primarily be to come to a better understanding of etiologic factors involved in the disease process, but to estimate the change in the disease status itself with a given change in diet. The intervention itself is guided by what can be achieved in practice. In pragmatic studies, issues such as long-term feasibility of the intervention receive considerable attention. Dietary regimens and combined interventions are often studied rather than single nutrients. An advantage of studying foods in stead of individual nutrients is that they are in general more directly translated to dietary

recommendations. In the intervention study presented in Chapter 4.3, a simultaneous change in dietary intake of sodium, potassium, and magnesium was achieved by means of a salt substitute. From this study we could not conclude whether it was the decreased intake of sodium, the increased intake of potassium or magnesium, or the combined changes in mineral intake that accounted for the observed fall in blood pressure. For this reason, the study contributes little to the understanding of the mechanisms of blood pressure reduction in the hypertensive elderly. On the other hand, the study is highly pragmatic in the sense that the results can be easily translated into practical, dietary guidelines.

Multicollinearity and energy-adjustment in nutritional research

A problem may arise in nutritional epidemiologic research when the intake of nutrients is highly intercorrelated. Potassium and magnesium, for example, are often ingested together through the same vegetables and fruits. Furthermore, a diet that includes many salty foods is often an 'unhealthy' diet that contains fewer potassium- and magnesium-rich foods. High intercorrelations of nutrients make it difficult to estimate the impact of one single nutrient on blood pressure. In statistical data analysis, the simultaneous inclusion of strongly correlated variables in a multivariate model may give rise to unanticipated, spurious results. This problem of *multicollinearity* occurs when the residual variation in one of the nutrients is substantially reduced because of the inclusion of one or more other nutrients.[95] In case that there is little variation left for the estimation of the regression coefficient for the nutrient of interest, no reliable estimate can be obtained. When studying electrolyte intake and blood pressure this is for example the case when dietary potassium and magnesium are included in the multivariate model together with intake of calcium and fibre. The problem of multicollinearity cannot adequately be solved by statistical methods as it is due to a lack of variation in the study base. Disentangling the individual contributions of highly correlated nutrients on blood pressure is therefore a true challenge, if not impossible, in the analysis of cross-sectional data of epidemiologic studies. Better information will be obtained by intervention studies, in which the effect of individual mineral intakes on blood pressure can truly be compared with the effect of combined intakes in parallel groups. People consume foods, not nutrients. Therefore, inference from observational studies can probably best focus of mixtures of nutrients rather than on individual factors.

The consumption of nutrients is positively related with total energy intake and individual differences in caloric intake may produce variation in intake of nutrients

unrelated to dietary composition. Total caloric intake may be a primary determinant of disease and it is therefore desirable to adjust electrolyte intakes for total energy to avoid confounding. In case that total caloric intake is not related to the study outcome, adjustment is still preferable because it will increase the precision of the estimate for the nutrient of interest. Several methods for energy correction are available.[96] In our cross sectional analysis of dietary electrolyte intake and blood pressure (Chapter 4.2) we used a two-step approach as proposed by Willett and Stampfer.[97] First, total caloric intake was used as the independent variable in a linear regression model with the nutrient as the dependent variable. The corresponding residuals for each individual were added to the expected nutrient intake for the mean energy intake of the study population, resulting in a nutrient intake unrelated to total energy. Second, the energy-adjusted nutrient intakes were included in the multivariate model. When one is interested also in the effect of total energy intake on the outcome, this variable can additionally be included in the model. The coefficients for pure nutrient intake and total energy obtained by this method are interpretable and have biological significance.

New research areas

As pointed out previously in this chapter, specific genetic or physiological characteristics could be associated with the sensitivity of blood pressure to electrolyte intake. Studies especially designed for this purpose are warranted to identify possible hormonal and biochemical indicators of sensitivity, or specific genotypes that are likely to show a blood pressure response to electrolyte intake. Until now, research in this field has mainly focused on sodium. The studies presented in this thesis provide evidence that potassium is at least equally important in determining blood pressure and the age-related blood pressure rise. The study of potential markers of blood pressure sensitivity to potassium intake therefore deserves more attention.

When markers for susceptibility become available, it is worthwhile to investigate whether individuals who are expected to be susceptible show a larger blood pressure response to changes in sodium and/or potassium intake than non-susceptibles. It has been suggested that age could be one of the modulators of blood pressure response to dietary electrolyte intakes. Intervention studies including parallel age groups could further address this hypothesis.

How the susceptibility concept could be implemented in current preventive strategies needs further investigation. In addition to the 'high risk' and 'whole population' approach, a preventive strategy focusing on susceptible target groups within a population,

e.g. school children or nursing home residents, might be considered. In case that susceptible subgroups cannot readily be identified within a population, large-scale screening for indicators of susceptibility probably has to take place. How this could be realised in practice needs further detailed consideration.

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CHAPTER 6

SUMMARY

6
Summary

Hypertension is an important risk factor for cardiovascular disease, the leading cause of death in Western societies. Blood pressure level in these countries rises sharply from birth until old age. In populations with a low intake of sodium and a high intake of potassium, the age-related rise in blood pressure is less pronounced and the prevalence of hypertension is low. This suggests a possible role of sodium and potassium in determining blood pressure. Whereas this hypothesis has been confirmed in ecologic studies, studies within single populations have often failed to demonstrate a relation between intake of sodium and/or potassium and blood pressure. One possible explanation could be the fact that a population consists of a heterogeneous group of individuals, whose blood pressures may respond quite differently to dietary influences. Age could be one of the modulators of blood pressure response to electrolyte intake. This thesis focuses on two phases in life that seem of particular interest in this respect, namely childhood and old age.

At young age, the hypertensive process is probably initiated and it is worthwhile to investigate whether electrolytes could affect the rate of blood pressure change. *Chapter 2* describes the role of salt intake during the first six months of life in determining blood pressure level 15 years later in life. Blood pressure was measured in a group of 167 adolescents who had participated in a randomised double blind trial of the effect of a low or normal sodium diet on blood pressure in infancy. After adjustment for confounders, systolic blood pressure level at follow-up was 3.6 mmHg lower (95% confidence interval 0.5 - 6.6 mmHg) and diastolic blood pressure level was 2.2 mmHg lower (95% CI -0.2 - 4.5 mmHg) in children who had been assigned to the low sodium diet compared to the controls. These findings suggest that sodium intake in infancy could be related to the development of hypertension later in life.

Chapter 3 focuses on sodium and potassium intake in relation to the change in blood pressure from childhood into adulthood, using data from a large Dutch population study of risk factors for cardiovascular disease (EPOZ). From the study cohort, a group of 596 children was randomly selected for yearly follow-up of blood pressure and its determinants. For 233 children aged 5 to 17 at entry at least six yearly blood pressure measurements were performed between 1978 and 1985 (early phase of the study). For 167 children at least three additional yearly measurements were available between 1986 and 1991 (late phase). Mean sodium and potassium intakes were estimated from six overnight urine samples that had been collected during the early phase of the study.

Individual blood pressure slopes over time (mmHg/year) were calculated by linear regression analysis. The relation between mean urinary electrolyte excretions, assessed in the early phase, and blood pressure changes in both the early and late phase was studied *(Chapters 3.1 and 3.2)*. Sodium was positively associated, and potassium inversely associated with blood pressure change in this cohort of children and adolescents. The associations with change in blood pressure appeared to be stronger for potassium than for sodium in both the early and late phase of the study. This study shows that electrolytes may play a role in determining blood pressure change at young age.

At old age, a number of physiological changes occur that may increase the sensitivity of blood pressure to an inadequate intake of electrolytes. In *Chapter 4* several studies are presented on the relation between electrolyte intake and blood pressure in older people. Data were obtained from participants of the Rotterdam Study, a population-based study among 7,983 residents of a suburb of Rotterdam aged 55 and over. In *Chapter 4.1* the association of urinary sodium and potassium excretion with blood pressure was studied in 1,006 subjects who were not on antihypertensive treatment. Findings were adjusted for age, sex, and body mass index. An independent inverse association of urinary potassium excretion with blood pressure was observed. An increase of 100 mmol in potassium excretion was related to a 9.4 mmHg (95% CI 2.2 - 16.5 mmHg) lower systolic blood pressure, and a 4.9 mmHg (95% CI 1.1 - 8.7 mmHg) lower diastolic blood pressure after adjustment for sodium excretion. A weak positive association was observed for sodium after adjustment for potassium excretion: a 100 mmol increase in urinary sodium was associated with a 2.2 mmHg (95% CI -0.1 - 4.5 mmHg) higher systolic, and a 0.8 mmHg (95% CI -0.4 - 2.0 mmHg) higher diastolic blood pressure level. In *Chapter 4.2*, dietary intakes of potassium, magnesium, and calcium as assessed by a semiquantitative food frequency questionnaire were studied in relation to blood pressure in 3,239 subjects who were not on antihypertensive treatment. Findings were adjusted for age, sex, body mass index, alcohol intake, and total energy intake. Dietary intake of potassium and magnesium appeared to be inversely and independently related to blood pressure level. Per gram increase in potassium intake, a 0.9 mmHg (95% CI -0.2 - 2.1 mmHg) decrease in systolic blood pressure, and a 0.8 mmHg (95% CI 0.2 - 1.4 mmHg) decrease in diastolic blood pressure was observed. For magnesium, values were 1.2 mmHg (95% CI -0.002 - 2.5 mmHg) and 1.1 mmHg (95% CI -0.003 - 1.9 mmHg) per 100 mg, respectively.

Dietary measures to reduce blood pressure may be more effective when the intake of several nutrients is changed simultaneously. In a double blind, randomised, multifactorial trial we investigated whether moderate sodium restriction combined with an increase in

potassium and magnesium intake would reduce blood pressure in older people with mild to moderate hypertension. The findings of this trial are presented in *Chapter 4.3*. Changes in mineral intake were achieved by substituting common sodium salt in the diet with a low sodium, high potassium, high magnesium mineral salt for six months. Complete follow-up was achieved by 97 of the 100 randomised subjects. In subjects who used the mineral salt, mean systolic blood pressure during intervention was 7.6 mmHg (95% CI 4.0 - 11.2 mmHg) lower, and diastolic blood pressure was 3.3 mmHg (95% CI 0.8 - 5.8 mmHg) lower than in controls who used common salt. After adjustment for change in body weight during intervention, values were 8.7 and 3.6 mmHg respectively. The compliance with the intervention was satisfactory, which was reflected in a persistent difference in 24 hour urinary sodium and potassium excretion between the study groups. The blood lipid profile was not adversely affected by the intervention with the mineral salt *(Chapter 4.4)*.

In *Chapter 5* the development of blood pressure during life and the role of electrolyte intake in determining blood pressure level and rise are described. This is followed by a discussion of intervention approaches, with a special focus on blood pressure sensitivity to electrolyte intake. In the next part of the discussion, methodological aspects of research into blood pressure and nutrient intake, and the implications of the findings for public health, are considered. Finally, some directions for future research in this field are delineated.

CHAPTER 7

SAMENVATTING

7
Samenvatting

Hypertensie is een belangrijke risicofactor voor hart- en vaatziekte, de meest voorkomende doodsoorzaak in westerse samenlevingen. In deze landen wordt een sterke bloeddrukstijging waargenomen met de leeftijd. Bij 'primitieve' volkeren met een lage natrium- en een hoge kaliuminneming is deze bloeddrukstijging minder uitgesproken en is de prevalentie van hypertensie laag. Dit suggereert een mogelijk effect van natrium en kalium in de voeding op de bloeddruk. Deze hypothese is in ecologisch onderzoek bevestigd, maar epidemiologische onderzoeken *binnen* bevolkingsgroepen kunnen vaak geen verband tussen de inneming van natrium en/of kalium en de bloeddruk aantonen. Eén van de mogelijke verklaringen zou kunnen zijn dat personen binnen een bevolking sterke onderlinge verschillen vertonen in bloeddrukgevoeligheid voor bepaalde nutriënten. De leeftijd is mogelijk één van de factoren die van invloed zijn op deze gevoeligheid. De onderzoeken beschreven in dit proefschrift zijn uitgevoerd binnen twee specifieke leeftijdsgroepen die interessant lijken in dit opzicht, namelijk kinderen en ouderen.

Reeds op jonge leeftijd wordt een bloeddrukstijging ingezet die mogelijk leidt tot hypertensie. Het is daarom zinvol om te onderzoeken of inneming van elektrolyten de bloeddrukverandering vroeg in het leven beïnvloedt. Het onderzoek beschreven in *Hoofdstuk 2* richt zich op de relatie tussen de inneming van natrium tijdens de eerste levensmaanden en de bloeddruk 15 jaar later. Hiertoe werd de bloeddruk gemeten bij 167 adolescenten die in 1980 deelgenomen hadden aan een gerandomiseerde studie bij zuigelingen naar het effect van zoutarme voeding op de bloeddruk. Na correctie voor verstorende variabelen was de systolische bloeddruk op 15-jarige leeftijd 3,6 mmHg lager (95% betrouwbaarheidsinterval 0,5 - 6,6 mmHg) en de diastolische bloeddruk 2,2 mmHg lager (95% BI -0,2 - 4,5 mmHg) bij adolescenten die als zuigeling zoutarme voeding hadden ontvangen vergeleken met controlepersonen die normale voeding hadden ontvangen. Deze bevinding suggereert dat de inneming van natrium tijdens de eerste levensmaanden bij zou kunnen dragen aan het ontstaan van hoge bloeddruk op latere leeftijd. *Hoofdstuk 3* richt zich op de inneming van natrium en kalium in relatie tot de bloeddrukverandering tijdens de jeugd. De gegevens zijn verzameld in een vervolgonderzoek bij een willekeurige groep van 596 kinderen die deel uitmaakten van het cohort van het Epidemiologisch Preventief Onderzoek Zoetermeer (EPOZ). Bij 233 kinderen in de leeftijd van 5 tot 17 jaar werden tenminste zes jaarlijkse bloeddrukmetingen verricht tussen 1978 en 1985 ("vroege fase"). Bij 167 kinderen uit dit cohort werden nog minstens drie extra jaarlijkse metingen verricht in de periode van 1986 tot 1991 ("late

fase"). De gemiddelde inneming van natrium en kalium gedurende de onderzoeksperiode werd geschat uit zes overnachtsurines die verzameld werden in de vroege fase van het onderzoek. Met behulp van lineaire regressie-analyse werden individuele bloeddrukveranderingen over de tijd (mmHg/jaar) bepaald. De relatie tussen de uitscheiding van elektrolyten en bloeddrukverandering in de vroege en late fase van het onderzoek staat beschreven in de *Hoofdstukken 3.1 en 3.2*. Voor natrium werd een positief verband en voor kalium een negatief verband met de bloeddrukverandering waargenomen. Het verband was sterker voor kalium dan voor natrium, zowel in de vroege als in de late fase van het onderzoek. De resultaten van dit onderzoek suggereren dat elektrolyten de bloeddrukstijging tijdens de jeugd kunnen beïnvloeden.

Op oudere leeftijd treden er verschillende fysiologische veranderingen in het lichaam op die de gevoeligheid van de bloeddruk voor een inadequate inneming van elektrolyten kunnen verhogen. *Hoofdstuk 4* laat de resultaten zien van verschillende onderzoeken naar de relatie tussen inneming van elektrolyten en de bloeddruk bij ouderen. De gegevens zijn verkregen van deelnemers aan het Erasmus Rotterdam Gezondheid en Ouderen onderzoek (ERGO), een bevolkingsonderzoek bij 7.983 mannen en vrouwen van 55 jaar en ouder in de wijk Ommoord in Rotterdam. In het onderzoek dat beschreven wordt in *Hoofdstuk 4.1* werd het verband tussen de natrium- en kaliumuitscheiding in de urine en de bloeddruk bestudeerd bij 1.006 ouderen. De bevindingen zijn gecorrigeerd voor leeftijd, geslacht en Quetelet-index. Een onafhankelijk omgekeerd verband tussen kalium en de bloeddruk werd waargenomen, waarbij een 100 mmol toename in kaliumuitscheiding gepaard ging met een 9,4 mmHg (95% BI 2,2 - 16,5 mmHg) lagere systolische en een 4,9 mmHg (95% BI 1,1 - 8,7 mmHg) lagere diastolische bloeddruk na correctie voor natrium-uitscheiding. Een zwak direct verband tussen natriumuitscheiding en bloeddrukniveau werd waargenomen na correctie voor kaliumuitscheiding, waarbij een 100 mmol hogere natriumuitscheiding gepaard ging met een 2,2 mmHg (95% BI -0,1 - 4,5 mmHg) hogere systolische en een 0,8 mmHg (95% BI -0,4 - 2,0 mmHg) hogere diastolische bloeddruk. In het onderzoek vermeld in *Hoofdstuk 4.2* werd de inneming van kalium, magnesium en calcium (gemeten met een voedingsvragenlijst) bestudeerd in relatie tot de bloeddruk bij 3.239 ouderen. De bevindingen zijn gecorrigeerd voor leeftijd, geslacht, Quetelet-index, alcoholgebruik en totale energie-inneming. De inneming van kalium en magnesium was omgekeerd gerelateerd aan de bloeddruk. Per gram toename in kaliuminneming werd een 0,9 mmHg (95% BI -0,2 - 2,1 mmHg) lagere systolische en een 0,8 mmHg (95% BI 0,2 - 1,4 mmHg) lagere diastolische bloeddruk waargenomen. Voor magnesium bedroegen deze waarden respectievelijk 1,2 mmHg (95% BI -0,002 - 2,5 mmHg) en 1,1 mmHg

(95% BI -0,003 - 1,9 mmHg) per 100 mg toename.

Veranderingen in de voeding om de bloeddruk te verlagen zouden meer effect kunnen hebben wanneer niet de inneming van één, maar van meerdere nutriënten gelijktijdig beïnvloed wordt. In een dubbelblind, gerandomiseerd, multifactorieel onderzoek, beschreven in *Hoofdstuk 4.3*, werd onderzocht of matige natriumbeperking gecombineerd met een matige toename van de kalium- en magnesiuminneming de bloeddruk zou kunnen verlagen bij ouderen met lichte tot matige hypertensie. De verandering in de inneming van mineralen werd bereikt door gewoon keukenzout in de voeding gedurende zes maanden te vervangen door een mineraalzout met een verlaagd natrium- en een verhoogd kalium- en magnesiumgehalte. Er werden 100 deelnemers in het onderzoek opgenomen, waarvan 97 personen het gehele onderzoek afrondden. Bij de deelnemers die het mineraalzout gebruikten was de gemiddelde systolische bloeddruk tijdens de onderzoeksperiode 7,6 mmHg (95% BI 4,0 - 11,2 mmHg) lager en de diastolische bloeddruk 3,3 mmHg (95% BI 0,8 - 5,8 mmHg) lager in vergelijking met de controlegroep die gewoon zout gebruikte. Na correctie voor verschillen in gewichtsverandering tijdens het onderzoek bedroegen deze waarden respectievelijk 8,7 en 3,6 mmHg. Het consistente verschil in natrium- en kaliumuitscheiding in de urine tussen de twee groepen gedurende de gehele onderzoeksperiode wees op een goede "therapietrouw". Het lipidenprofiel in het bloed werd niet ongunstig beïnvloed door de interventie met het mineraalzout *(Hoofdstuk 4.4)*.

In *Hoofdstuk 5* wordt de bloeddrukontwikkeling tijdens het leven en de invloed van elektrolyten op de bloeddruk beschreven. Vervolgens worden mogelijkheden voor interventie aangegeven, waarbij speciale aandacht wordt besteed aan eventuele inter-individuele verschillen in bloeddrukgevoeligheid voor elektrolyten. Daarna worden enkele methodologische aspecten belicht die aan de orde kwamen in de hierboven beschreven onderzoeken, gevolgd door enkele suggesties voor vervolgonderzoek.

Dankwoord

De laatste pagina's van een proefschrift worden vaak als eerste gelezen. Ik zal deze ruimte daarom niet onbenut laten om iedereen te bedanken die ervoor gezorgd heeft dat het boekje meer is geworden dan enkel een kaft.

Mijn promotor, Prof. dr D.E. Grobbee, maakte mij enthousiast voor het onderzoek toen ik in 1988 als verdwaalde student stage liep op het Instituut Epidemiologie en Biostatistiek. Hij zag er heil in mij na een aantal jaren opnieuw het instituut binnen te halen. Rick, dank je wel voor het vertrouwen en voor je kundige begeleiding.

Mijn copromotor, dr ir J.C.M. Witteman, was in de afgelopen jaren mijn vraagbaak. Jacqueline, jij zorgde ervoor dat ik nooit "zo maar" iets opschreef en prikte moeiteloos door elk verzinsel heen. Soms was ik bang dat er nooit een proefschrift zou komen... Niettemin ben ik dankbaar dat je mijn grijze cellen hebt laten werken.

Een deel van dit proefschrift is tot stand gekomen doordat ik gebruik kon maken van databestanden van anderen. Ik wil Prof. H.A. Valkenburg bedanken dat ik de gegevens van het Epidemiologisch Preventief Onderzoek Zoetermeer (EPOZ) kon gebruiken. Cuno Uiterwaal heeft mij hierbij geholpen, waarvoor mijn hartelijke dank. Ik wil Prof. A. Hofman bedanken dat ik een vervolgonderzoek kon uitvoeren bij "zijn" zuigelingen De hulp van Ria Rijneveldshoek en Joke Jansen bij dit onderzoek heb ik erg op prijs gesteld.

Het Erasmus Rotterdam Gezondheid en Ouderen onderzoek (ERGO) heeft een belangrijke bijdrage geleverd aan dit proefschrift. Ik dank de vertegenwoordigers van de ERGO-onderzoekslijnen, Prof. A. Hofman, Prof. D.E. Grobbee, Prof. P.T.V.M. de Jong en dr H.A.P. Pols, dat ook ik uit het ERGO-vaatje mocht tappen. De artsen en overige ERGO-medewerkers ben ik dankbaar voor het verzamelen van de gegevens. De computergroep onder leiding van Michael Koenders wil ik danken voor het verwerken en gebruikersvriendelijk maken van de grote berg gegevens. Ton de Bruijn en Jeanette Vergeer van het lab dank ik voor het verrichten van de natrium- en kaliumbepalingen.

Ik dank de mannen en vrouwen uit Ommoord die bereid waren een half jaar lang mee te werken aan het mineraalzoutonderzoek. "SAGA" bleef niet langer een mythe, maar werd een groot succes door de inspanning van velen. Hanneke den Breeijen was vanaf het allereerste begin betrokken bij het onderzoek en een onmisbare steun wanneer het voedingszaken betrof. Bij Annette Bak kon ik met alle praktische problemen terecht en ik ben haar dankbaar voor de hulp als ik het even niet zag zitten. Lorette Hulsman, door jouw enthousiasme liep het in het onderzoekscentrum op rolletjes en werden we regelmatig verwend met chocolade en gebak. Onze publicaties in "De Ongezouten Waarheid" vond ik minstens zo leuk als in de BMJ. De kennis en gezelligheid van de diëtisten Janet Dollekamp en Wendy Vos hadden niet gemist kunnen worden! Het verstrekken van de voedingsmiddelen vereiste een geheel eigen logistiek. Annemarie van

Muyden en Dick Slof lieten alles perfect verlopen. De dames Westerhof, Van der Sluijs, Goetgeluk, Wensing, Roëll, Kruif, Pot en De Bie zorgden ervoor dat ons winkeltje "De Zoute Inval" reilde en zeilde. Zij lieten zich niet uit het veld slaan temidden van de broden, kazen, vleeswaren en soepen met geheime codes. Mevrouw R. Witteman dank ik voor de administratieve werkzaamheden. De heren J. Pontier en M. Copier van "Wijkgebouw Romeijnshof" waren zo vriendelijk om ruimte beschikbaar te stellen voor het winkeltje. De contactpersonen bij Akzo Nobel, de heren De Jong, Bosch en De Vries, dank ik voor de prettige intensieve samenwerking.

Dr Deborah Chee and Prof. Paul Elliott of the London School of Hygiene and Tropical Medicine (U.K.) made a valuable contribution to this thesis. Deborah, thank you for preparing one of the manuscripts.

I would like to thank Prof. Jukka T. Salonen and his staff for the pleasant time at Kuopio University (Finland). The experience in data analysis that I have obtained at your department appeared to be useful in later research work. My friends Sari Pekkarinen and Paula Pakarinen and their families made me feel at home in Finland. It was because of them that I could survive the dark cold winter. Kiitoksia paljon, oli tosi hauskaa!

I am grateful to Prof. Roger Williams and his staff at the University of Utah (Salt Lake City, U.S.A.) for their enthusiasm and interest in my research work. I hope that our fruitful collaboration on indicators of salt sensitivity will be continued in the future.

I would like to thank the MSc-fellows Shireen Fahim, Angélika Velkova and Jama Warsame Jama for their interest in me personally and in my research work. I hope our contact will be continued and I wish you a lot of success in your scientific career.

Het bestaan als epilady in de afgelopen jaren werd veraangenaamd door de prettige contacten met collega's. Enkelen wil ik bij name noemen. Paul Steegmans was van het begin af aan mijn gezellige kamergenoot. Paul, ik ben blij dat het toch geen dubbel-promotie geworden is want dan had je mijn paranimf niet kunnen zijn! Caroline van Rossum, ik vind het heel leuk dat ook jij mij terzijde wil staan bij dit spannende gebeuren. De periode voorafgaand aan de "dubbele bevalling" was niet altijd gemakkelijk. Maarten de Rijk en Daniëlle Majoor boden op kamer 2132 een luisterend oor en een helpende hand, waarvoor ik ze erg dankbaar ben. Chris de Ruiter dank ik dat hij op de meest ongelegen momenten bereid was mijn proefschrift van de elektronische ondergang te redden. Marcel Eijgermans behoedde mij voor hoge bloeddruk door het ontcijferen van cryptische databestanden en door het aanleveren van eigengebakken SAGA-broden!

Een speciaal woord van dank voor mijn familie en vrienden die altijd geïnteresseerd bleven in mijn werk, ook al was het niet duidelijk wat ik nu precies deed.

Mijn ouders dank ik voor hun liefde en al het andere dat ze mij gegeven hebben.

Robbert, ik ben blij dat ik voor jou geen woorden nodig heb.

Ik dank God dat Hij mij alles gaf wat nodig was om dit werk te kunnen doen.

About the author

Marianne Geleijnse was born on 27 April 1967 in The Hague. She attended secondary school (Atheneum ß) at 'Christelijk Lyceum' in Alphen aan den Rijn. She studied Biomedical Sciences at Leiden University and graduated in 1991. During her studies, she spent one year in Finland at the University of Kuopio (head: Prof. J.T. Salonen) where she was involved in the Kuopio Ischemic Heart Disease Risk Factor Study. In April 1992 she started her training in epidemiology at the Department of Epidemiology & Biostatistics of Erasmus University Rotterdam (head: Prof. A. Hofman). At that time the work on this thesis was initiated. She received her Master of Science degree in Epidemiology at the Netherlands Institute of Health Sciences in 1995. She is married to Robbert den Bleker and they have a son.