Outcomes 8 years after preterm birth

Ruys, C.A.

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Chapter 8

Salt sensitivity of blood pressure at age 8 years in children born preterm

Charlotte A. Ruys, Joost Rotteveel, Monique van de Lagemaat, Harrie N. Lafeber, Martijn J.J. Finken

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ABSTRACT

Background Preterm birth and low birth weight have been associated with an increased risk of hypertension; postnatal growth and dietary salt intake may contribute to these associations. In adults, the change of blood pressure (BP) in response to modifications in salt intake, i.e., salt sensitivity of BP, has been independently associated with cardiovascular disease. Little is known about salt sensitivity in children. We hypothesize that it may partly explain the association between preterm birth and higher BP in later life.

Methods We assessed salt sensitivity of BP at age 8 years in 63 preterm-born children, and explored its association with postnatal growth, sodium intake and body composition from infancy onwards. BP was measured at baseline and after a 7-day high-salt diet. The difference in mean arterial pressure (MAP) was calculated; salt sensitivity was defined as an increase in MAP of ≥ 5%.

Results Ten children (16%) showed salt sensitivity of BP, which was associated with neonatal growth restriction as well as with lower fat mass and BMI from infancy onwards. At age 8 years, children classified as salt sensitive had a lower weight-for-age SD-score (-1.5 ± 1.3 vs. -0.6 ± 1.1) and BMI (13.8 ± 1.7 vs. 15.5 ± 1.8 kg/m^2) compared to their salt resistant counterparts. Sodium intake was not associated with (salt sensitivity of) BP.

Conclusion Salt sensitivity of BP was demonstrated in preterm-born children at age 8 years and may contribute to the development of cardiovascular disease at later age. Long-term follow-up studies are necessary to assess reproducibility of our findings and to explore clustering with other cardiovascular risk factors.

INTRODUCTION

Both preterm birth and (very) low birth weight have been associated with long-term consequences, such as an increased risk of cardiovascular disease, including hypertension and type 2 diabetes at later age;[1,2] rapid early postnatal weight gain could amplify this risk.[3,4] Several studies have attempted to unravel the underlying pathophysiological mechanisms, with specific interest for high blood pressure (BP), since this is considered a major risk factor for developing cardiovascular disease.[5,6]

Salt intake has been suggested to play a role in these associations. Lowering dietary salt intake has been shown to decrease both systolic and diastolic BP, irrespective of blood pressure status (normotensive or hypertensive).[7] However, there is a wide inter-individual variability in BP response to changes in salt intake, i.e., salt sensitivity of BP.[8] Salt sensitivity of BP has been independently associated with cardiovascular disease, even in case of normotension.[9,10]

To date, little is known about salt sensitivity of BP in children. Low birth weight has been associated with salt sensitivity of BP in studies with children and adults of whom the majority were born at term.[11,12] Furthermore, it has been suggested that sodium intake during infancy has permanent effects on (salt sensitivity of) later BP.[13,14] There are, to our knowledge, no studies that have explored these associations after preterm birth.

In addition to sodium intake, disruption of renal development may have permanent effects on later BP. Intrauterine growth restriction has been associated with persistent reductions in kidney volume – due to lower numbers of nephrons – and creatinine clearance.[15,16] Nephrogenesis normally continues up to the 36th week of gestation. Preterm birth, independent of size at birth, has also been associated with low nephron endowment[16,17] and morphologically abnormal nephrons.[18] In addition, rapid postnatal weight gain (catch-up growth), especially after intrauterine growth restriction, has been associated with accelerated ageing of kidneys in rats.[19] Furthermore, kidneys with lower nephron numbers may be unable to adapt sufficiently to dietary excesses because of less renal reserve capacity.[20] Together with compromised early renal development, this may exacerbate the impact of prematurity on later BP.

We hypothesize that a higher sodium intake and rapid weight gain in early postnatal life are associated with an increased risk of salt sensitivity of BP in preterm-born children at age 8 years, and that this may contribute to the increased risk of cardiovascular disease in later life. Therefore, the aim of our study was to describe the prevalence of salt sensitivity in our cohort of preterm-born children, and to explore the influence of sodium intake and early growth on salt sensitivity of BP at age 8 years.

METHODS

Study participants

Participants of this study were originally included in the 'Study Towards the Effects of Postdischarge nutrition on growth and body composition of infants born ≤ 32 weeks gestational age and/or ≤ 1500 g birth weight' (STEP). For this study, infants were randomized at term age (i.e., 40 weeks gestation) to receive either an isocaloric, protein- and mineral-enriched postdischarge formula (PDF, $n = 54$) or standard term formula (TF, $n = 48$) and were fed this diet until 6 months corrected age (CA). A control group of 50 human milk (HM) fed children was also included. At birth, term age, 3, 6, 12, and 24 months CA, weight, length and head circumference were measured using standard methods, and these data were subsequently converted to standard deviation scores (SDSs) according to the appropriate references. At term age and 6 months CA, body composition was measured with dual-energy X-ray absorptiometry (DXA).[21]

Blood pressure and salt sensitivity of BP were assessed as part of the follow-up study (STEP-2) at age 8 years. The main objective of the STEP-2 was to study the long-term effects of the nutritional intervention. The cohort retrieval is described elsewhere.[22] In short, 21 children were excluded, and 52 children refused to participate or could not be traced, resulting in 79 children who were included in the follow-up study (**Figure 8.1**). Exclusion criteria were severe physical impairment or conditions known to affect growth or body composition.

Study procedures at age 8 years

Participants visited the outpatient clinic twice with a median interval between visits of 4 [IQR 2–7] weeks. Height and weight were measured and a DXA-scan was performed, as described previously.[22]

Blood pressure and salt sensitivity

The week before the first study visit, subjects were requested to stick to their regular diet. The week before the second study visit, all participating children were put on a high-salt diet. For this purpose, sodium chloride was provided in sachets in order to attain a dose of 0.12 g/kg body weight per day (which equals 2.1 mmol of sodium/kg per day). During both study visits, BP was measured after a 15 min rest in the supine position, every 5 min during 30 min. The measurements were performed at the non-dominant arm with an automatic device (Dinamap), using an appropriate cuff size for the upper arm circumference. Systolic and diastolic BP (SBP and DBP) were reported by the device and the mean arterial pressure

(MAP) was calculated as ((DBP x 2)+SBP)/3. The means for SBP, DBP and MAP were calculated from the 6 measurements, and subsequently converted to percentiles adjusted for sex, age and height.[23]

Salt sensitivity of BP was calculated as $MAP_{high\text{-}salt} - MAP_{regular}$ (ΔMAP). Subjects were classified as salt sensitive (SS) or salt resistant (SR) in case of an increase in MAP of ≥ 5% or < 5%, respectively, after the high-salt diet; $((MAP_{high\text{-}salt} - MAP_{regular})/MAP_{regular}) \times 100\%$.

Sodium intake

Sodium intake between birth and term age was calculated from all parenteral and enteral nutrition, including supplements (i.e., breast milk fortifier among others), given during that period. The sodium content of all types of nutrition was retrieved from product information and the total amount per type of nutrition per week was calculated. Sodium intake was adjusted for body size by dividing the total sodium intake per week by body weight measured during the same week. Missing data on body weight were extrapolated from measurements during the week before and after. The amount of sodium in the period from birth to term was presented as mmol/kg per day. For (partly) breastfed infants we estimated their intake, on the basis of a recommended mean intake of ≈160 mL/kg per day.[24] Furthermore, the sodium content of breast milk was estimated as 0.9 mmol/100 mL.[25]

To assess nutritional habits and sodium intake at age 8 years, parents and children filled in a 3-day nutritional diary. During 2 week days and 1 weekend day, all meals, snacks and beverages were recorded as precisely as possible. These data were entered in a digital nutrient-calculating tool on the website of 'The Netherlands Nutrition Centre',[26] which calculated daily intakes of energy, fat, protein, carbohydrates, sodium, and various other micronutrients.

Ethnicity and education level were reported by parents. Both variables were subsequently categorized; ethnicity was categorized as white in case both parents were white, and parental education level was categorized as 'higher education' if ≥ 1 parent(s) finished higher education (higher vocational or university).

The study protocol was approved by the Central Committee on Research Involving Human Subjects (CCMO), The Hague, The Netherlands. All parents of subjects gave written informed consent.

Statistical analysis

Normally distributed data are reported as means ± SDs and skewed data as medians [IQRs]. Skewed data were either log transformed or analyzed with non-parametric tests. SS and SR groups were compared using independent samples t-test, Mann-Whitney *U* or χ^2/Fisher's exact test as appropriate.

Weight gain between birth and age 8 years was assessed for various intervals and was calculated as the difference in weight SDS between two assessments (Δweight SDS). In line with previous analyses in this cohort, we also tested the effects of the following: (1) weight loss between birth and term age of ≥ 1 vs. < 1 SDS (extrauterine growth restriction), and (2) weight gain between term age and 6 months CA of ≥ 0.67 vs. < 0.67 SDS (early postnatal catch-up growth in weight).[22]

To assess associations of early life and childhood parameters with (salt sensitivity of) BP at age 8 years, regression analysis was used. Linear regression was used for baseline SBP at age 8 years and ΔMAP as continuous outcome variables, and logistic regression was used to assess associations with ΔMAP as a dichotomous outcome variable.

Baseline characteristics that were different between children classified as SS or SR ($P < 0.05$) were considered as possible confounders, and, if appropriate, included in the linear regression analyses as covariates. This was the case for parental ethnicity, birth length (in cm), and fat mass (in kg) at 6 months CA (**Table 8.1**). Also, a difference was found in type of feeding (PDF, TF or HM from term age to 6 months CA) between SS and SR groups ($P = 0.021$). Since this study is a post hoc study of a nutritional RCT, we subsequently examined associations between type of feeding (as categorical determinant) and (salt sensitivity of) BP by using linear regression analyses. These associations were non-significant (data not shown), and therefore 'type of feeding' was not included as a covariate in further analyses.

Furthermore, generalized estimating equations (GEEs) were used for longitudinal analysis of associations between growth parameters and salt sensitivity of BP (SS vs. SR). GEE is suitable for the assessment of differences between groups, adjusted for intra-individual variation over time, and it adjusts for grouped samples collected from the same subject at different times, by using a correlation structure. For our analyses, we chose an exchangeable correlation structure, in which one average within-subject correlation between samples over time is assumed. GEEs were performed with weight and length/height (SDS) over time (at birth, term age, 3, 6, 12 and 24 months CA, and 8 years) as dependent, continuous factors.

All statistical analyses were performed with IBM SPSS Statistics version 22. Statistical significance was defined as a *P* value of < 0.05.

RESULTS

Of the 152 children originally included in the RCT, 79 were included in the follow-up study (**Figure 8.1**). Participants were 7.9 [7.6–8.3] years old, and 24% of them had at least one parent of non-white origin.

A total of 63 out of 79 children completed both study visits and participated in the salt sensitivity test. We compared children who participated in the salt sensitivity test to those who did not and found no significant differences in baseline characteristics (data not shown). However, mean SBP and SBP percentile at baseline (first study visit) were higher in the group not participating in the salt sensitivity test compared to the group that completed

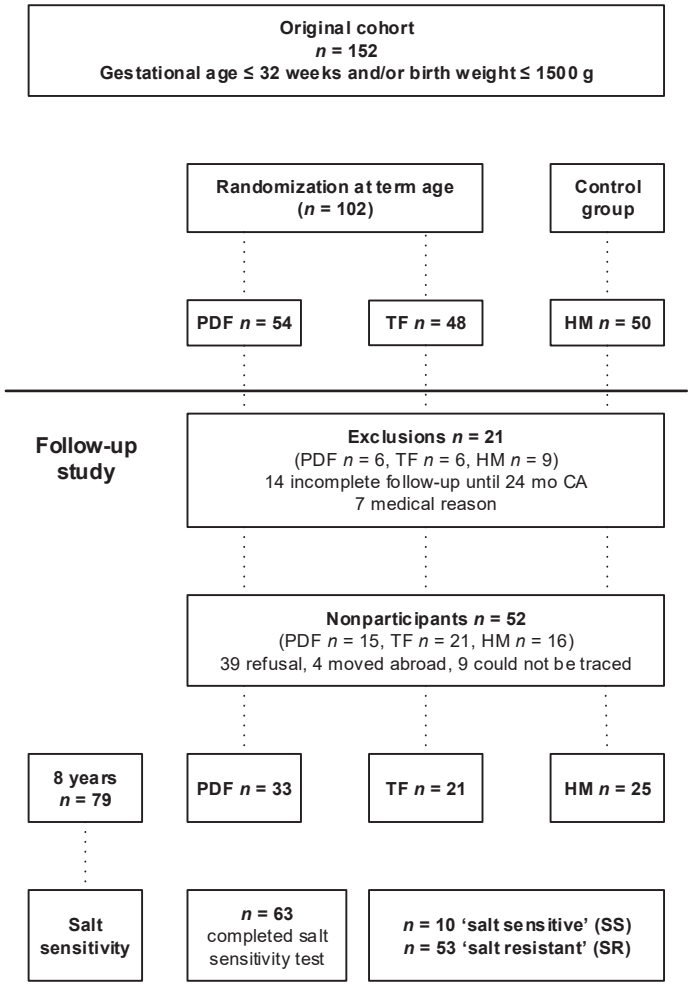

Figure 8.1. Flow chart of study population.
CA, corrected age; HM, human milk, PDF, postdischarge formula; TF, term formula.

both study visits, including the salt sensitivity test (107 ± 4 vs. 104 ± 7 mmHg; $P = 0.079$ and 74 ± 11 vs. 65 ± 20; $P = 0.025$, respectively). Other variables measured at 8 years were not different between the groups (data not shown).

Baseline characteristics of all participants are shown in **Table 8.1**. Ten of the 63 participants (16%) were classified as SS and 53 as SR. Sodium intake from birth to term age was similar in children classified as SS compared to those classified as SR. Sodium intake at age 8 years (**Table 8.2**) was also comparable in SS versus SR children; 3.3 ± 0.9 vs. 3.0 ± 0.8 mmol/

Table 8.1. Baseline characteristics

	Total population[a]	SS	SR	*P* value[b]
n	79	10	53	
Male	40 (51)	4 (40)	26 (49)	0.735
≥ 1 parent(s) of non-white origin	19 (24)	5 (50)	10 (19)	0.034
≥ 1 parent(s) finished higher education	37 (47)	4 (40)	26 (49)	0.314
Hypertensive disorder during pregnancy[c]	34 (43)	6 (60)	21 (40)	0.444
Gestational age, wks.	30.7 [29.3–31.6]	29.6 [27.6–30.8]	30.7 [29.1–31.6]	0.152
Birth weight, g	1314 ± 304	1150 ± 242	1320 ± 309	0.107
SDS	-0.4 ± 1.0	-0.5 ± 1.0	-0.4 ± 1.0	0.671
Birth length, cm	38.0 ± 3.1	35.9 ± 2.9	38.2 ± 3.1	0.031
SDS	-0.8 ± 1.3	-1.1 ± 1.2	-0.7 ± 1.3	0.356
SGA	16 (20)	2 (20)	13 (25)	1.000
NTISS score	23.6 ± 8.4	24.2 ± 10.1	23.9 ± 8.0	0.925
Sodium intake birth-term age mmol/kg/day	1.9 ± 0.3	2.1 ± 0.4	1.9 ± 0.2	0.189
Type of feeding term age – 6 months CA				0.021
PDF	33 (42)	3 (30)	26 (49)	
TF	21 (27)	6 (60)	10 (19)	
HM	25 (32)	1 (10)	17 (32)	
Body composition				
Term age fat mass, kg	0.31 ± 0.19	0.20 ± 0.16	0.33 ± 0.20	0.057
Lean mass, kg	3.03 ± 0.41	2.77 ± 0.30	3.01 ± 0.38	0.063
6 months CA fat mass, kg	1.89 ± 0.72	1.19 ± 0.50	1.98 ± 0.56	< 0.001
Lean mass, kg	5.75 ± 0.64	5.52 ± 0.75	5.72 ± 0.64	0.380

Data are presented as mean ± SD, median [IQR], or *n* (%).CA, corrected age; HM, human milk; NTISS, neonatal therapeutic intervention scoring system; PDF, postdischarge formula; SDS, standard deviation score; SGA, small for gestational age, birth weight and/or length < -2 SD; SR, salt resistant; SS, salt sensitive; TF, term formula. [a] 16 children did not participate in the salt sensitivity test and can therefore not be determined as SS or SR; [b] SS and SR children were compared using independent samples t-test, Mann-Whitney U-test or χ^2/Fisher's exact test as appropriate; [c] Includes HELLP, (pre-)eclampsia, pregnancy induced hypertension, and pre-existent hypertension.

kg per day during the regular diet ($P = 0.365$) and 5.2 ± 1.2 vs. 4.7 ± 0.9 mmol/kg per day during the high-salt diet ($P = 0.142$). In addition, estimated glomerular filtration rate (eGFR) was comparable between the groups, both on day 1 and day 2 ($P = 0.921$ and $P = 0.549$, respectively, data not shown).

Table 8.2 shows the results of all measurements performed at age 8 years. Salt sensitive children had a lower weight, BMI and baseline SBP and DBP at age 8 years.

Table 8.2. Characteristics at age 8 years compared between salt sensitive and salt resistant groups

	Total population	SS	SR	*P* value[a]
n	79	10	53	
Age at follow-up, years	7.9 [7.6–8.3]	7.9 [7.7–8.3]	7.9 [7.5–8.2]	0.672
Weight, kg	25.7 ± 4.6	22.8 ± 4.1	26.17 ± 4.6	0.035
SDS	-0.6 ± 1.2	-1.5 ± 1.3	-0.6 ± 1.1	0.024
Height, cm	129.5 ± 5.6	128.3 ± 5.9	129.5 ± 5.8	0.531
SDS	-0.4 ± 0.8	-0.6 ± 0.7	-0.4 ± 0.9	0.412
BMI, kg/m^2	15.3 ± 2.1	13.8 ± 1.7	15.5 ± 1.8	0.008
SDS	-0.7 ± 1.7	-1.7 ± 1.3	-0.4 ± 1.0	0.001
Waist-hip ratio	0.91 ± 0.05	0.89 ± 0.04	0.92 ± 0.06	0.129
SDS	0.8 ± 1.0	0.5 ± 0.8	0.9 ± 1.1	0.221
Fat mass, kg	6.9 ± 2.3	5.2 ± 1.6	7.2 ± 2.3	0.013
Lean mass, kg	18.5 ± 2.8	17.2 ± 3.2	18.8 ± 3.0	0.131
Blood pressure[b]				
SBP 1, mmHg	104 ± 7	95 ± 8	105 ± 5	< 0.001
percentile	67 ± 19	39 ± 21	70 ± 16	< 0.001
DBP 1, mmHg	60 ± 7	51 ± 6	62 ± 5	< 0.001
percentile	53 ± 20	27 ± 14	58 ± 16	< 0.001
MAP 1, mmHg	75 ± 6	66 ± 6	76 ± 5	< 0.001
SBP 2, mmHg	106 ± 6	102 ± 6	104 ± 7	0.419
percentile	64 ± 19	60 ± 17	64 ± 20	0.527
DBP 2, mmHg	60 ± 5	63 ± 56	60 ± 4	0.105
percentile	54 ± 15	62 ± 18	53 ± 14	0.074
MAP 2, mmHg	75 ± 4	76 ± 4	75 ± 4	0.455
Δ MAP, mmHg (mean (range))	0.2 (-12.3, 16.8)	9.9 (4.9, 16.8)	-1.7 (-12.3, 3.7)	< 0.001
Dietary intake				
Sodium, mmol/kg per day				
Regular diet	3.1 ± 0.9	3.3 ± 0.9	3.0 ± 0.8	0.365
Supplements[c]	1.6 ± 0.5	1.9 ± 0.4	1.6 ± 0.5	0.121
Potassium, mmol/kg per day	2.4 ± 0.6	2.6 ± 0.6	2.3 ± 0.6	0.304

Data are presented as mean ± SD or median [IQR] unless indicated otherwise. BMI, body mass index; DBP, diastolic blood pressure; MAP, mean arterial pressure; SBP, systolic blood pressure; SDS, standard deviation score. [a] SS and SR children were compared using independent samples t-test, Mann-Whitney U-test or χ^2/Fisher's exact test as appropriate; [b] Measured after regular (1) and high-salt diet (2); [c] Supplementary sodium during high-salt diet ($n = 61$, 16 children did not participate in the salt sensitivity test, 2 missings on supplementary sodium intake).

Early life parameters and (salt sensitivity of) BP

Of all early life parameters (**Table 8.3**), only Δweight (SDS) in different time periods was associated with SBP and salt sensitivity of BP at age 8 years. A decrease in weight of ≥ 1 SDS ('extrauterine growth restriction') as compared to < 1 SDS between birth and term age, was associated with a higher odds of salt sensitivity of BP at age 8 years (OR, 6.1; 95% CI, 1.2, 31.6; $P = 0.031$). An increase of ≥ 0.67 SDS in weight ('early catch-up growth') as compared to < 0.67 SDS between term age and 6 months CA was associated with a higher SBP at age 8 years (β, 4.1; 95% CI, 1.3, 6.9; $P = 0.005$), but not with salt sensitivity of BP.

Sodium intake between birth and term age was not associated with any of the outcomes. Because we estimated the intake of (partly) breastfed children, we repeated the analyses with only those children who had definite data on intake ($n = 49$). The results of these sensitivity analyses did not differ from the analyses within the entire sample (data not shown).

Childhood parameters and (salt sensitivity of) BP

Higher weight and BMI (SDS) at age 8 years were associated with a higher SBP and a lower odds of salt sensitivity of BP. Analyzing fat mass and lean mass separately did not explain these associations, since both were independently associated with a higher SBP and a lower odds of salt sensitivity of BP. Sodium intake at age 8 years was not associated with SBP or salt sensitivity of BP (**Table 8.4**).

Adjusted analyses

We adjusted the linear regression models with SBP for birth length and parental ethnicity, and associations between childhood parameters and SBP were additionally adjusted for fat mass at 6 months CA. The results of these adjusted models were all similar to the crude models (data not shown). Likewise, associations with ΔMAP (mmHg) were adjusted for birth length and parental ethnicity, and these results were similar to the crude analyses, with the exception of the associations with Δweight SDS 6–12 months CA and Δweight SDS 6–24 months CA, which became non-significant after adding birth length to the model (crude models $P = 0.029$ and $P = 0.047$, adjusted models $P = 0.126$ and $P = 0.095$, respectively). The association between BMI SDS at 8 years and ΔMAP (mmHg) became non-significant after adding either birth length, parental ethnicity or fat mass at 6 months CA to the model (crude model $P = 0.036$, adjusted models $P = 0.079$, $P = 0.067$, and $P = 0.255$, respectively).

Logistic regression analyses were not adjusted because of small numbers (i.e., $n = 10$ for SS).

Table 8.3. Associations between early life parameters and (salt sensitivity of) blood pressure at age 8 years

	Blood pressure		Salt sensitivity of blood pressure			
	SBP, mmHg		Δ MAP, mmHg continuous		Δ MAP, <5% vs. ≥5%	
	β (95% CI)[a]	*P* value	β (95% CI)[a]	*P* value	OR (95% CI)[b]	*P* value
Gestational age, weeks	0.5 (-0.4, 1.4)	0.255	-0.1 (-1.0, 0.7)	0.748	0.8 (0.6, 1.2)	0.257
Birth weight, kg	1.8 (-3.1, 6.6)	0.464	-2.1 (-6.9, 2.7)	0.393	0.1 (0.0, 1.6)	0.112
SDS	-0.3 (-0.4, 0.7)	0.687	-0.5 (-1.9, 1.0)	0.531	0.9 (0.4, 1.7)	0.665
SGA	0.9 (-2.7, 4.5)	0.624	1.4 (-2.0, 4.8)	0.405	1.3 (0.3, 5.6)	0.767
NTISS score	0.0 (-0.2, 0.2)	0.937	-0.1 (-0.3, 0.1)	0.210	1.0 (0.9, 1.1)	0.924
Sodium intake birth – term age mmol/kg per day	-3.7 (-9.9, 2.6)	0.249	3.9 (-1.5, 9.4)	0.161	NA	NA
Early postnatal growth						
Δ weight SDS birth – term age						
continuous	2.1 (0.0, 4.3)	0.050	-1.7 (-3.9, 0.4)	0.118	0.2 (0.1, 0.9)	0.034
< -1 vs. ≥ -1 SDS	-2.2 (–5.2, 0.7)	0.140	2.4 (-0.5, 5.2)	0.099	6.1 (1.2, 31.6)	0.031
Δ weight SDS term – 6 months CA						
continuous	2.0 (0.6, 3.5)	0.007	-0.3 (-1.8, 1.2)	0.684	0.6 (0.3, 1.3)	0.162
< 0.67 vs. ≥ 0.67 SDS	4.1 (1.3, 6.9)	0.005	-1.2 (-4.1, 1.7)	0.417	0.2 (0.1, 1.2)	0.089
Infancy – childhood growth						
Δ weight SDS 6–12 months CA	-1.9 (-4.6, 0.8)	0.155	2.7 (0.3, 5.2)	0.029	3.2 (1.0, 10.5)	0.059
Δ weight SDS 6–24 months CA	-1.9 (-3.9, 0.1)	0.056	1.9 (0.0, 3.8)	0.047	2.2 (0.8, 5.6)	0.111
Δ weight SDS 12–24 months CA	-1.9 (-4.9, 1.1)	0.216	0.7 (-2.2, 3.7)	0.623	1.1 (0.3, 4.2)	0.916
Δ weight SDS 24 months CA–8 years	1.8 (0.2, 3.5)	0.027	-1.2 (-2.8, 0.4)	0.137	0.8 (0.4, 1.6)	0.541
Body composition						
Fat mass term age, kg	3.8 (-4.0, 11.6)	0.333	-9.0 (-16.1, -1.9)	0.014	0.0 (0.0, 1.3)	0.062
Fat mass 6 months CA, kg	3.0 (1.0, 4.9)	0.004	-3.4 (-5.7, -1.2)	0.003	0.0 (0.0, 0.3)	0.002
Lean mass term age, kg	1.8 (-1.8, 5.3)	0.322	-1.8 (-5.7, 2.0)	0.339	0.1 (0.0, 1.1)	0.064
Lean mass 6 months CA, kg	2.4 (0.1, 4.6)	0.043	-0.4 (-2.6, 1.9)	0.751	0.6 (0.2, 1.8)	0.375

CA, corrected age; CI, confidence interval; MAP, mean arterial pressure; NTISS, neonatal therapeutic intervention scoring system; OR, odds ratio; SBP, systolic blood pressure; SDS, standard deviation score; SGA, small for gestational age, birth weight and/or length < -2 SDS. [a] Unadjusted linear regression analyses; [b] Unadjusted logistic regression analyses.

Table 8.4. Associations between childhood parameters and (salt sensitivity of) blood pressure at age 8 years

	Blood pressure		Salt sensitivity of blood pressure			
	SBP, mmHg		Δ MAP, mmHg continuous		Δ MAP, < 5% vs. ≥ 5%	
	β (95% CI)[a]	*P* value	β (95% CI)[a]	*P* value	OR (95% CI)[b]	*P* value
Weight, kg	0.6 (0.3, 0.9)	< 0.001	-0.2 (-0.5, 0.1)	0.181	0.8 (0.7, 1.0)	0.038
SDS	2.2 (1.1, 3.4)	< 0.001	-1.0 (-2.2, 0.2)	0.101	0.5 (0.3, 1.0)	0.033
BMI, kg/m^2	1.3 (0.6, 2.0)	< 0.001	-0.6 (-1.4, 0.1)	0.109	0.4 (0.2, 0.8)	0.011
SDS	2.5 (1.3, 3.7)	< 0.001	-1.4 (-2.6, -0.1)	0.036	0.3 (0.1, 0.6)	0.004
Body composition						
Fat mass, kg	0.9 (0.3, 1.5)	0.003	-0.4 (-1.1, 0.2)	0.206	0.5 (0.3, 0.9)	0.016
Lean mass, kg	0.8 (0.3, 1.3)	0.002	-0.2 (-0.7, 0.3)	0.477	0.8 (0.6, 1.1)	0.133
Sodium intake, mmol/kg per day	-1.6 (-3.3, 0.1)	0.069	0.3 (-1.5,2.2)	0.727	1.5 (0.6, 3.3)	0.361

BMI, body mass index; CI, confidence interval; MAP, mean arterial pressure; OR, odds ratio; SBP, systolic blood pressure; SDS, standard deviation score. [a] Unadjusted linear regression analyses, [b] Unadjusted logistic regression analyses.

Longitudinal analyses of growth parameters and salt sensitivity of BP

Length/height in cm and SDS over time were not associated with salt sensitivity of BP (*P* = 0.113 and *P* = 0.323, respectively). Weight (in kg and SDS) over time was lower in SS compared to SR subjects (β, -1.04; 95% CI, -1.67, -0.42; *P* = 0.001 and β, -0.76; 95% CI, -1.21, -0.32; *P* = 0.001, respectively) (**Figure 8.2**).

DISCUSSION

To our knowledge, this is the first cohort of preterm-born children in which salt sensitivity of BP was determined and linked to other characteristics suggested to play a role in the development of cardiovascular disease. We found a prevalence of 16% for salt sensitivity of BP in our study cohort and an association between infant and childhood growth and salt sensitivity. Furthermore, a lower fat mass from term age onwards was associated with a higher odds of salt sensitivity; at age 8 years, children classified as SS had a lower weight (SDS) and BMI (SDS) compared to those classified as SR. Sodium intake in neither the neonatal period nor at age 8 years was associated with (salt sensitivity of) BP.

Previous data have shown that prematurity is associated with higher BP later in life. In our population of preterm-born children, we found no associations of gestational age, birth

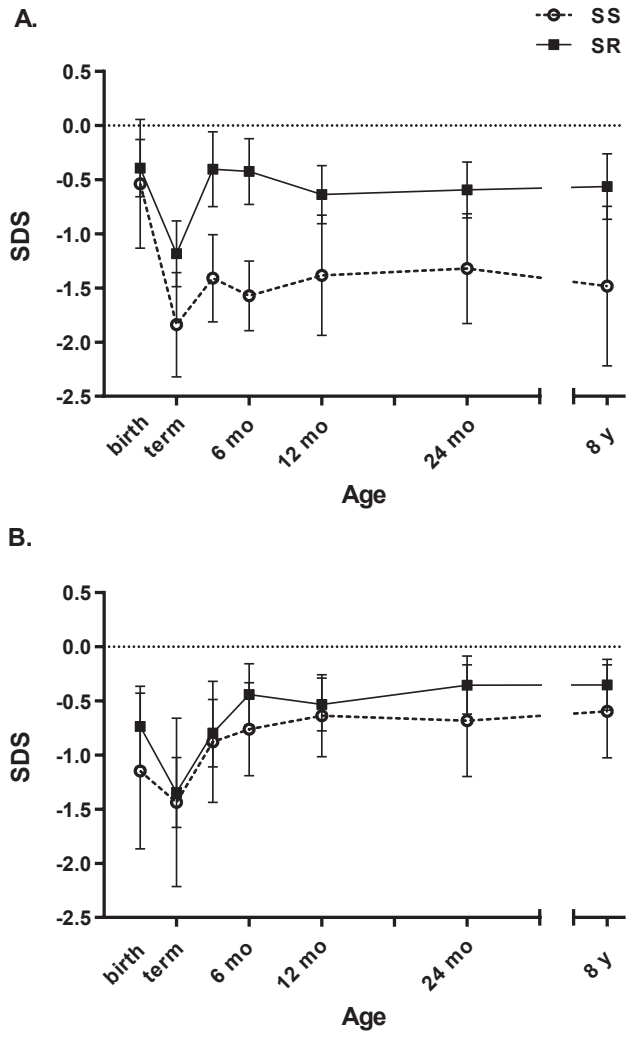

Figure 8.2. Weight (A) and length/height (B) standard deviation scores (SDS) over time in children classified at age 8 years as salt sensitive (SS) versus salt resistant (SR).
Growth trajectories were compared using GEE analyses, $P = 0.001$ for weight SDS and $P = 0.323$ for length/height SDS. Dotted line = reference population mean.

weight (in kg or SDS), or being born small-for-gestational-age with SBP. However, weight gain between term age and 6 months CA was positively associated with SBP. Many studies that investigated associations between birth weight and BP showed that low birth weight was associated with an increased BP at later age in both term and preterm populations, although the relationship may not be linear.[2,3,27,28] At age 8 years, we found that higher weight and BMI were associated with higher SBP, and these results are consistent with

other papers reporting on the importance of current weight and BMI as risk factors for higher BP in childhood or adolescence.[29,30]

Early sodium intake, although essential for adequate growth in preterm newborns, has been suggested to play a role in the development of higher BP in later life.[31] We did not find associations of sodium intake in the neonatal period or at age 8 years with SBP at age 8 years. In term-born children, however, this association was found for sodium intake in the first months of life and BP at age 7 years,[13] as well as in children aged 8–18 years in whom a higher sodium intake was associated with an increased SBP, with a more pronounced effect in overweight/obese children.[32] Whether salt sensitivity of BP could be a mediator in these relationships, and possibly also in the association between low birth weight and increased (S)BP, is not known.

Classifying individuals as either SS or SR is complex, since salt sensitivity of BP is a normally distributed trait in humans, and arbitrary cut off points for BP-changes in response to salt intake are used to classify subjects as SS or SR.[33] There is no gold standard for the classification of salt sensitivity, therefore, in literature, various definitions have been used.[10] Because of the exploratory nature of our study, we chose to analyze salt sensitivity of BP both continuously and dichotomously. As cut-off for salt sensitivity of BP, we chose a percentage change in MAP (also called 'salt sensitivity index') of < 5% vs. ≥ 5%, as opposed to an absolute change in MAP, a cutoff criterion often used in adult studies.[10] Using a percentage change is probably more feasible in pediatric populations, since it is unknown to which extent absolute changes in BP can be effectuated by differences in dietary salt intake in children.

The prevalence of salt sensitivity of BP in our cohort is difficult to compare with current literature, since most research towards salt sensitivity of BP was performed in adults, and it has been described that salt sensitivity of BP increases with age.[33,34] Moreover, definitions and testing protocols of salt sensitivity are highly heterogeneous, which hampers a valid comparison.[35] Simonetti et al. found a salt sensitivity prevalence of 37% (n = 9) at age 11 years in children born with a birth weight < 2500 g, based on an increase in MAP of ≥ 3 mmHg after a high-salt diet during 7 days.[12] In adult populations, depending on the definition, the proportion of normotensive individuals classified as SS ranges from 18% to 26%, with greater proportions being reported in hypertensive and black populations.[36,37] Consistent with the latter, 50% of the children defined as SS in our study had at least one parent from African origin.

Interestingly, we found that children classified as SS had a lower baseline BP, also when expressed as a percentile value adjusted for sex, age and height. This seems to contradict

with observations showing that salt sensitivity of BP is more prevalent in hypertensive individuals,[33] however, mean BP values of both SS and SR children in our study were well below the 95th percentile. Birth weight and catch-up growth between term age and 6 months CA were not associated with salt sensitivity of BP in our cohort. This finding contradicts with the conclusion of Wesseling et al. that low birth weight and its consequences, such as catch-up growth, should be seen as modifiable risk factors for developing salt sensitivity of BP.[38] Accordingly, Simonetti et al. found that children born with a low birth weight had a reduced renal mass dependent on the degree of growth restriction, and this was associated with elevated BP and increased salt sensitivity of BP at age 11 years.[12] Possibly, our sample size was insufficient to find such associations, especially because of the low number of children classified as SS.

Strengths and limitations

The main strength of our study is that we had extensive information available in this birth cohort on (neonatal) nutritional intake, growth parameters from birth until childhood, and body composition. Moreover, we had the opportunity to compare a variety of perinatal, early life and childhood characteristics between children classified as SS or SR.

There are several limitations. First, this study was a post hoc analysis of an RCT. Second, a term-born control group was not included and, as a consequence, we were unable to compare our results with norm data. Third, the relatively small sample size did not allow to adjust our statistical analyses for multiple potential confounders. Nevertheless, considering the exploratory aspect of our study, reporting only crude analyses seemed appropriate. Even so, sometimes wide CI's were found and, therefore, results should be interpreted with caution. Fourth, the method for determining salt sensitivity may not have been optimal. The amount of supplementary salt intake during the high-salt diet was reported afterwards by parents, which may have caused a recall bias. An objective measure, such as 24-h urine collection for assessment of sodium excretion, would have had our preference; however, it was very difficult to obtain reliable samples from 8 year-old children. In addition, even though supplementary salt intake appears to be comparable between SS and SR children, it could be that the SS children are relatively overdosed considering the similar sodium intake in mmol/kg per day at a lower body weight. It was recommended by Elijovich et al. that the high sodium diet should contain around 250 mmol of sodium per day, followed by a low sodium diet containing no more than 50 mmol per day.[33] The children in our cohort did not reach the suggested amount during the high-salt diet, but these recommendations may not apply to a pediatric study population. Furthermore, since we did not have a specific low-salt diet, the difference in sodium intake between the regular diet and the high-salt

diet may have been too small to detect salt sensitivity in children with a less responsive BP to changes in salt intake. Fifth, another important aspect of the salt sensitivity test that is subject to a number of possible influences, is BP measurement. Electronic devices generally overestimate (S)BP, however, because we were interested in a BP difference this may not be a substantial limitation. The advantage of using an electronic device is that it is less sensitive to inter-observer bias than auscultatory measurement of BP.[39] Moreover, by standardizing the circumstances and performing the measurement 6 times, we tried to limit the influence of individual variability on our outcomes.

Perspectives

Salt sensitivity has been suggested to be a risk factor for increasing BP with age, however, it was also associated with cardiovascular morbidity and mortality, irrespective of BP status. Considering the increased risk of cardiovascular diseases in preterm-born individuals,[1] salt sensitivity of BP may be of interest to take into account in future research towards elucidating underlying pathophysiological processes. Salt sensitivity has been associated with other metabolic risk factors such as insulin resistance and could therefore be designated as a feature of the 'metabolic syndrome profile'.[40,41] However, when looking at our results, the SS children appear to be more lean and growth restricted from birth onwards compared to the children classified as SR. This may support the idea that salt sensitivity of BP is also an independent risk factor for developing cardiovascular disease, regardless of BP status and possibly also of other metabolic parameters, or that mechanisms for salt sensitivity in (preterm-born) children are different from those in adults. Further research investigating mechanisms that mediate salt sensitivity of BP in both children and adults seems necessary. Other than assuming a direct relation between increased sodium intake and volume expansion leading to a rise in BP, novel theories about the pathophysiology of salt sensitivity have been proposed.[42] First, endothelial dysfunction may cause an increase in (renal) vascular resistance and consequently a rise in BP. Mechanisms suggested to contribute to endothelial dysfunction in SS individuals include a decreased nitric oxide-mediated vasodilation and insulin insensitivity.[42-44] Second, it has been shown that sodium could accumulate in the interstitium of the skin, without the accompanying water retention. Failing of this mechanism may play a role in salt sensitivity of BP.[45]

CONCLUSION

In our cohort of preterm-born children, 16% showed salt sensitivity of BP at age 8 years, which was associated with growth restriction in the neonatal period as well as with a

lower fat mass and BMI from infancy onwards. Long-term follow-up is necessary to assess reproducibility of our current findings, to explore the association with cardiovascular risk factors later in life, and to track the suggested age-related increase in salt sensitivity of BP. Altogether this may contribute to unraveling the complex mechanisms underpinning the association between preterm birth, early growth, and cardiovascular diseases later in life.

Summary Table

What is known about the topic

- Preterm-born children are at higher risk for developing hypertension and other cardiovascular diseases later in life
- Salt sensitivity of blood pressure is an independent risk factor for developing cardiovascular disease in adults

What this study adds

- This is the first study to explore salt sensitivity of blood pressure in a preterm-born population
- Salt sensitivity of blood pressure at age 8 years was found in 16% of our preterm-born study population and was associated with growth restriction in the neonatal period as well as with lower fat mass and BMI from infancy onwards
- Identifying early risk factors for salt sensitivity and high blood pressure in this population could contribute to prevention of long-term adverse health outcomes

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