

## Does Extremely Low Birth Weight Predispose to Low-Renin Hypertension?

Anke Raaijmakers, Zhen-Yu Zhang, Jolien Claessens, Nicholas Cauwenberghs, Theun Pieter van Tienoven, Fang-Fei Wei, Lotte Jacobs, Elena Levtchenko, Steven Pauwels, Tatiana Kuznetsova, Karel Allegaert,\* Jan A. Staessen\*

**Abstract**—Low birth weight and prematurity are risk factors for hypertension in adulthood. Few studies in preterm or full-term born children reported on plasma renin activity (PRA). We tested the hypothesis that renin might modulate the incidence of hypertension associated with prematurity. We enrolled 93 prematurely born children with birth weight <1000 g and 87 healthy controls born at term, who were all examined at ≈11 years. Renal length and glomerular filtration rate derived from serum cystatin C were 0.28 cm (95% confidence interval, 0.09–0.47) and 11.5 mL/min per 1.73 m<sup>2</sup> (6.4–16.6) lower in cases, whereas their systolic/diastolic blood pressure (BP) was 7.5 mm Hg (4.8–10.3)/4.0 mm Hg (2.1–5.8) higher ( $P<0.001$  for all). The odds of having systolic prehypertension or systolic hypertension associated with extreme low birth weight were 6.43 (2.52–16.4;  $P<0.001$ ) and 10.9 (2.46–48.4;  $P=0.002$ ). Twenty-four hours of urinary sodium excretion was similar in cases and controls (102.1 versus 106.8 mmol;  $P=0.47$ ). Sodium load per nephron was estimated as sodium excretion divided by kidney length (mmol/cm). PRA was 0.54 ng/mL per hour (0.23–0.85;  $P=0.001$ ) lower in cases. PRA, systolic BP, and sodium load were available in 43 cases and 56 controls. PRA decreased with systolic BP (slope  $-0.022$  ng/mL per hour/ $^{-\text{mmHg}}$ ;  $P=0.048$ ), but was unrelated to sodium load (slope  $+0.13$  mmol/cm $^{-\text{mmHg}}$ ;  $P=0.54$ ). The slope of PRA on systolic BP was similar ( $P=0.17$ ) in cases and controls. In conclusion, extremely low birth weight predisposes young adolescents to low-renin hypertension, but does not affect the inverse association between PRA and BP.

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Prematurity and low birth weight are risk factors for hypertension,<sup>1</sup> impaired kidney function,<sup>2</sup> and cardiovascular disease in adulthood.<sup>3</sup> Furthermore, a reduced nephron endowment early in life might increase the susceptibility to kidney disease in adulthood.<sup>1</sup> In children born at term, according to the Brenner hypothesis,<sup>2</sup> the nephron number decreases with lower birth weight. In prematurely born infants, nephron endowment at birth is not yet completed at delivery because nephrogenesis requires 32 to 36 weeks of gestation.<sup>4-6</sup> For the timely prevention of kidney disease, diagnosing hypertension and renal dysfunction early in life are of primordial importance. To the best of our knowledge, only 6 former studies in preterm or full-term born children reported on plasma renin activity (PRA)<sup>7-12</sup> or addressed the potential role of renin in the pathogenesis of hypertension.<sup>10,12</sup> To bridge knowledge gaps, we undertook the PREMATCH case–control study (Prematurity as Predictor of Children’s Cardiovascular and Renal Health).<sup>13</sup> Molecular, cellular, and physiological studies indicate

that renin is highly expressed during early kidney development.<sup>14</sup> One hypothesis we, therefore, tested was that renin might also modulate the incidence of hypertension associated with preterm birth and immature and abnormal glomerulogenesis. We enrolled prematurely born children with a birth weight of <1000 g (extremely low birth weight [ELBW]) and healthy controls, who we examined at a mean age of ≈11 years.<sup>15</sup> We measured blood pressure (BP) and PRA, performed renal ultrasonography and assessed renal function using glomerular filtration rate estimated from serum cystatin C and creatinine, while accounting for the 24-hour urinary sodium excretion.

### Methods

#### Study Participants

The study complied with the Helsinki declaration for investigations in human subjects.<sup>15</sup> The Ethics Committee of the University Hospitals Leuven (Belgium) approved the study. In line with good

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Departments of Pediatrics and Neonatology (A.R., E.L.) and Laboratory Medicine (J.C., S.P.), University Hospitals Leuven, Belgium; KU Leuven Department of Development and Regeneration (A.R., E.L., K.A.) and Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences (Z.-Y.Z., N.C., F.-F.W., L.J., T.K., J.A.S.), University of Leuven, Belgium; Department of Sociology, Vrije Universiteit Brussel, Belgium (T.P. v.T.); R&D Group VitaK, Maastricht University, The Netherlands (J.A.S.); and Intensive Care and Department of Pediatric Surgery, Erasmus Medical Center Sophia Children’s Hospital, Rotterdam, The Netherlands (K.A.).

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\*These authors contributed equally to this work.

Correspondence to Jan A. Staessen, Research Unit Hypertension and Cardiovascular Epidemiology, KU Leuven Department of Cardiovascular Sciences, Studies Coordinating Centre, University of Leuven, Campus Sint Rafaël, Kapucijnenvoer 35, PO Box 7001, BE-3000 Leuven, Belgium. E-mail jan.staessen@med.kuleuven.be

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clinical practice guidelines and the national Belgian legislation, parents or custodians provided written informed consent and children informed assent. The study was registered at ClinicalTrials.gov (NCT02147457). We recruited cases from a cohort of 140 children born between 2000 and 2005, who survived premature birth after a gestation ranging from 23 to 33 weeks and who had a birth weight of <1000 g.<sup>13</sup> Of 140 children invited, 93 participated (66.4%). The 87 controls were either friends of the cases (n=41) or recruited at an elementary school close to the examination center located in Eksel, Belgium (n=46).<sup>13</sup> Cases and controls were examined at an age of  $\approx$ 11 years.<sup>13</sup>

### Clinical Measurements

BP was the average of 3 consecutive auscultatory readings obtained according to European guidelines<sup>16</sup> with a standard mercury sphygmomanometer after the children had rested in the sitting position for at least 5 minutes. The cuffs had a 9×18 cm inflatable bladder, but if upper arm circumference exceeded 22 cm, standard cuffs with 12×22 cm bladder were used. We checked the quality of the BP readings according to previously published criteria.<sup>17</sup> Prehypertension and hypertension were BPs exceeding the 90th and 95th percentiles of the distributions stratified according to sex, age, and body height.<sup>18,19</sup> Body weight was measured, using the Omron Karada Scan HBF511 (Omron Health Care, Kyoto, Japan) and body height by a wall-mounted ruler. Body mass index was weight in kilograms divided by height in meters squared. We also expressed the anthropometric measurements as Z scores based on Flemish growth charts.<sup>20</sup>

### Renal Ultrasonography

With participants in supine, left or right decubitus, one experienced ultrasonographer (T.K.) obtained renal gray scale images, using a Vivid7 Pro (GE 125 Vingmed, Horten, Norway) interfaced with a 1.5- to 4.5-MHz convex transducer according to standardized procedures.<sup>21,22</sup> One blinded observer (N.C.) postprocessed the digitally stored images, using a workstation running EchoPac software (version 4.0.4; GE Vingmed, Horten, Norway).<sup>22</sup> Renal length was the largest longitudinal distance in the sagittal plane and parenchymal thickness the distance between the outer margin and the renal sinus. Each participant was characterized by the average of 2 measurements obtained from optimal images. Intraobserver variability (N.C.) and interobserver (T.K. and N.C.) variability were assessed from repeated measurements in 20 subjects, using the Bland–Altman approach.<sup>23</sup> For renal length, the mean ( $\pm$ SD) absolute and relative differences between pairwise readings by the same observer were 0.07 $\pm$ 0.56 cm and 0.51 $\pm$ 5.0%, respectively. The corresponding estimates for interobserver variability were  $-0.03\pm 0.54$  cm and  $-0.29\pm 5.0\%$ , respectively.

### Biochemical Measurements

After the children had fasted for at least 6 hours and rested for 30 minutes in the supine position and after application of a Rapydan patch (70 mg lidocaine/70 mg tetracaine, Eurocept, Ankeveen, The Netherlands) to minimize discomfort, a study nurse collected a venous blood sample, which was immediately spun. Aliquots were stored at  $-20^{\circ}\text{C}$  until analysis. Serum creatinine was measured by the enzymatic Creatinine Plus Generation 2 kit and serum cystatin C by the particle-enhanced immunoturbidimetric Tina-Quant CysC Generation 2 assay, both running on a COBAS Integra 400 system (Roche Diagnostics, Basel, Switzerland). Measurements of serum creatinine and cystatin C were calibrated by isotope-dilution mass spectrometry<sup>24</sup> and the ERM-DA471/IFCC international standard,<sup>25</sup> respectively. Glomerular filtration rate was estimated from serum creatinine (eGFR<sub>cr</sub>) and cystatin C (eGFR<sub>cysc</sub>) by the Schwartz et al<sup>26</sup> and the Caucasian-Asian-Pediatric-Adult<sup>27</sup> equations, respectively. PRA was quantified by a radioimmunoassay reflecting the generation of angiotensin I (DRG Instruments, Marburg, Germany).<sup>28</sup> Blood samples were also analyzed for serum uric acid, total and high-density lipoprotein cholesterol and insulin and for plasma glucose, using automated methods in a single-certified laboratory. The children

also collected a 24-hour urine sample in a wide-neck container (BD Vacutainer, Franklin, NJ) for the measurement of volume, albumin, sodium, aldosterone (Beckman Coulter, Prague, Czech Republic), and creatinine.

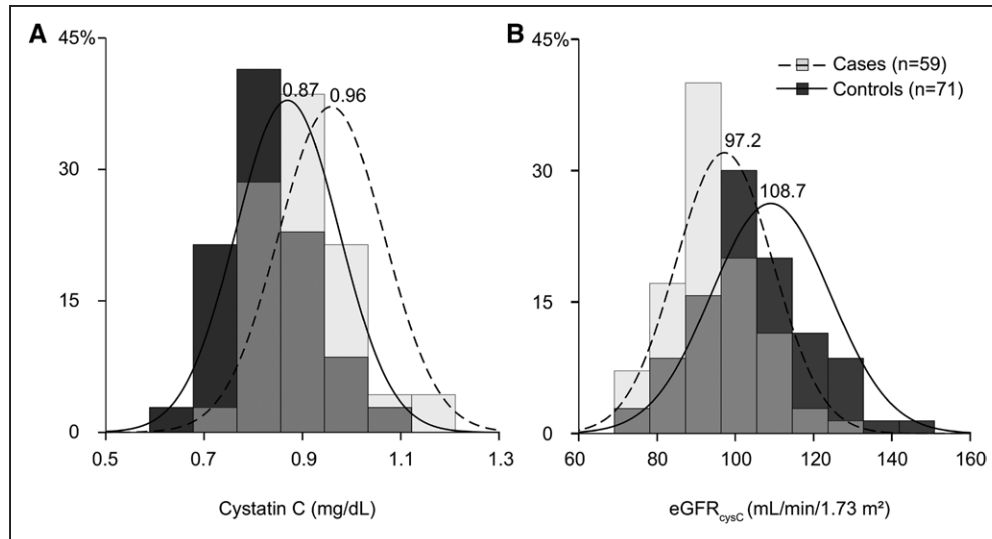
### Statistical Analysis

For database management and statistical analysis, we used SPSS software, version 23 (IBM, Armonk, NY). We assessed departure of the distributions from normality separately in cases and controls by the Shapiro–Wilk test and excluded outlying values by extending Tukey lower and upper hinges by 2.2 $\times$  the interquartile range. We compared means by Student's *t* test or Mann–Whitney *U* test, as appropriate, and proportions by the Fisher exact test. Multivariable-adjusted linear regression was used to analyze the association of BP with renal structure and function, sodium load, and PRA. The presence of prehypertension and hypertension was analyzed using logistic regression. We plotted distributions and 3-dimensional scatterplots, using XLSTAT

**Table 1. Characteristics of Controls and Cases**

Characteristic	Cases		Controls		P Value
	n	Estimate	n	Estimate	
Anthropometric measurements					
Age, y	93	11.3 $\pm$ 1.4	87	10.9 $\pm$ 1.3	0.029
Height, cm	93	145.1 $\pm$ 9.3	87	149.2 $\pm$ 10.1	0.005
Z score for height	93	$-0.45\pm 0.96$	87	0.56 $\pm$ 1.05	<0.001
Weight, kg	93	36.5 $\pm$ 9.4	87	40.6 $\pm$ 9.5	0.004
Z score for weight	93	$-0.52\pm 1.05$	87	0.34 $\pm$ 0.87	<0.001
Body mass index, kg/m <sup>2</sup>	93	17.7 $\pm$ 2.8	87	18.0 $\pm$ 2.5	0.47
Heart rate, bpm	93	72.0 $\pm$ 12.5	87	72.2 $\pm$ 9.9	0.54
Measurements on blood					
Serum creatinine, mg/dL	59	0.57 $\pm$ 0.10	71	0.56 $\pm$ 0.08	0.74
Serum cystatin C, mg/dL	59	0.96 $\pm$ 0.12	71	0.87 $\pm$ 0.11	<0.001
Plasma glucose, mg/dL	58	76.7 $\pm$ 5.8	68	77.1 $\pm$ 6.8	0.70
Serum insulin, mU/L	55	5.65 $\pm$ 2.92	66	5.66 $\pm$ 3.09	0.98
Serum total cholesterol, mg/dL	58	155.6 $\pm$ 19.8	69	154.6 $\pm$ 25.8	0.82
Serum HDL cholesterol, mg/dL	58	59.1 $\pm$ 13.8	69	59.8 $\pm$ 12.9	0.78
Serum uric acid, mg/dL	58	4.16 $\pm$ 0.83	69	3.97 $\pm$ 0.88	0.20
24-h urinary measurements					
Volume, L	88	1.03 $\pm$ 0.53	83	1.15 $\pm$ 0.56	0.15
Sodium, mmol	71	102.1 $\pm$ 39.2	67	106.8 $\pm$ 38.7	0.47
Creatinine, g	86	0.71 $\pm$ 0.23	81	0.73 $\pm$ 0.23	0.64
Aldosterone, $\mu$ g	85	4.81 $\pm$ 3.12	82	4.70 $\pm$ 2.76	0.82
Microalbuminuria, mg	82	4.59 $\pm$ 2.89	74	5.02 $\pm$ 3.21	0.38

Values are mean $\pm$ SD. Z scores were based on Flemish growth charts.<sup>20</sup> HDL indicates high-density lipoprotein.



**Figure 1.** Frequency distributions of (A) serum cystatin C and (B) the glomerular filtration rate (eGFR<sub>cysC</sub>) derived from serum cystatin C by the Caucasian-Asian-Pediatric-Adult equation.<sup>27</sup> Compared with controls (n=71), cases (n=59) had higher serum cystatin C levels (0.96 vs 0.87 mg/dL; *P*<0.001) and lower eGFR<sub>cysC</sub> (97.2 vs 108.7 mL/min per 1.73 m<sup>2</sup>; *P*<0.001).

(version 2016.03.31336) and R (version 3.2.3). Significance was a 2-sided *P* value <0.05.

**Results**

**Characteristics of Study Participants**

The number of girls was similar among controls and cases (44 [50.6%] versus 44 [47.3%]; *P*=0.66). Cases were 0.44 years (95% confidence interval [CI], 0.04–0.83) older than controls (Table 1). Compared with controls, cases were 4.12 cm (CI, –6.97 to –1.28) smaller and 4.13 kg (CI, –6.91 to –1.35) lighter. The corresponding differences for height and weight derived from Z scores were –1.01 (CI, –1.31 to –0.72) and –0.86 (CI, –1.14 to –0.57), respectively. Measured birth weight averaged 795 g in cases (5th–95th percentile interval, 766–823 g), whereas measured birth weight in controls averaged 3448 g (3347–3549).

Reasons for the unavailability of blood samples were refusal of the child (n=10), too low sample volume (n=12) or inability to collect blood after one or two attempts (n=28). Serum insulin and 24-hour urinary creatinine, aldosterone and microalbuminuria were not normally distributed and required nonparametric testing. There were no differences between cases and controls (Table 1; *P*≥0.20) in the mean values of cardiovascular and renal risk factors, including markers of the carbohydrate and cholesterol metabolism. Serum creatinine was similar in cases and controls (difference cases minus controls, –0.005 mg/dL; CI, –0.037 to 0.026; Table 1), whereas cases had significantly higher serum cystatin C levels (mean difference 0.087 mg/dL; CI, 0.048–0.126; Table 1; Figure 1).

**Blood Pressure**

Two children had no BP reading. Diastolic BP was not measurable in another two participants. Of 1062 systolic plus diastolic BP readings, 176 (16.6%) terminated on 0, 229 (21.6%) on 2, 234 (22.0%) on 4, 215 (20.2%) on 6, and 208 (19.6%)

on 8. None of the readings ended on an odd number. Of the 3 consecutive systolic and diastolic BPs obtained in individual study participants, none were identical.

Systolic and diastolic BPs were 7.5 mm Hg (CI, 4.8–10.3) and 4.0 mm Hg (CI, 2.1–5.8) higher in cases than in controls (Table 2). With adjustments applied for sex, age, and height, these estimates were 1.2 mm Hg (CI, 0.2–2.2; *P*=0.021) systolic and 0.9 mm Hg (CI, 0.4–1.5; *P*=0.002) diastolic. Cases compared with controls (Table 2), had a 5- and 9-fold higher prevalence of systolic prehypertension (n=30 [33.0%] versus 6 [6.9%]) and hypertension (n=19 [20.9%] versus 2 [2.3%]), respectively. The odds of having systolic prehypertension or systolic hypertension associated with ELBW were 6.43 (CI, 2.52–16.4; *P*<0.001) and 10.9 (CI, 2.46–48.4; *P*=0.002). There was no difference between cases and controls in the prevalence of diastolic prehypertension and hypertension (*P*≥0.15; Table 2).

**Table 2. Blood Pressure in Controls and Cases**

Characteristic	Cases		Controls		P Value
	n	Estimate	n	Estimate	
Systolic blood pressure					
Mean, mm Hg	91	114.4±10.2	87	106.9±8.2	<0.001
Prehypertension, %	30	33.0%	6	6.9%	<0.001
Hypertension, %	19	20.9%	2	2.3%	<0.001
Diastolic blood pressure					
Mean, mm Hg	90	69.0±6.4	86	65.0±6.4	<0.001
Prehypertension, %	8	8.9%	3	3.5%	0.21
Hypertension, %	1	1.1%	0	0%	>0.99

Values are mean±SD or number of children with characteristic (%). Prehypertension and hypertension were blood pressures exceeding the 90th and 95th percentiles of the distributions stratified according to sex, age, and body height.<sup>18</sup>

**Table 3. Renal Size and Function in Controls and Cases**

Characteristic	Cases		Controls		P Value
	n	Estimate	n	Estimate	
<b>Renal length</b>					
Left, cm	84	8.69±0.69	79	9.00±0.60	0.011
Right, cm	84	8.76±0.67	79	9.02±0.62	0.002
Mean of left and right, cm	84	8.73±0.66	79	9.01±0.59	0.004
<b>Parenchymal thickness</b>					
Left, cm	84	1.07±0.09	79	1.09±0.10	0.089
Right, cm	84	1.06±0.09	79	1.08±0.09	0.16
Mean of left and right, cm	84	1.06±0.09	79	1.09±0.09	0.089
<b>Estimated glomerular filtration</b>					
From creatinine, mL/min per 1.73 m <sup>2</sup>	59	111.0±17.2	59	111.7±15.3	0.80
From cystatin C, mL/min per 1.73 m <sup>2</sup>	59	97.2±13.6	59	108.7±15.3	<0.001
UVNa/average renal length, mmol/cm	67	11.93±4.43	65	11.85±4.43	0.93
Plasma renin activity, ng/mL per h	56	1.21±0.71	71	1.75±0.98	0.001

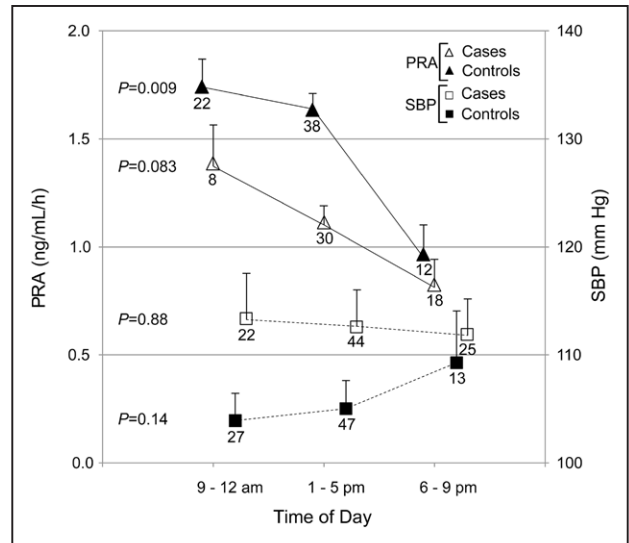
Values are mean±SD. UVNa indicates 24-h urinary sodium excretion.

**Renal Size and Function**

Images were not optimal in children in 9 cases and 8 controls and were, therefore, excluded from analysis. Renal length was 0.28 cm (CI, 0.09–0.47;  $P \leq 0.011$ ) lower in cases compared with controls (Table 3), whereas renal parenchymal thickness did not differ between the 2 groups ( $P \geq 0.089$ ). While averaging left and right kidney size, cases compared with controls had a 0.28 cm (CI, 0.09–0.47;  $P = 0.004$ ) shorter renal length. With adjustment for body height, sex, and age, the difference was 0.15 cm (CI, 0.05–0.25;  $P = 0.005$ ).  $eGFR_{cr}$  was similar in both groups, but  $eGFR_{cysC}$  was 11.5 mL/min per 1.73 m<sup>2</sup> (CI, 6.4–16.6) lower in cases (Table 3; Figure 1).

**Plasma Renin Activity**

PRA was 0.54 ng/mL per hour (0.23–0.85;  $P = 0.001$ ) lower in cases compared with controls (Table 3). In controls ( $P$  for linear trend,  $P = 0.009$ ), there was diurnal variation in PRA with a similar trend in cases ( $P = 0.083$ ). Neither in controls or in cases systolic BP varied over the day ( $P \geq 0.14$ ; Figure 2). The 24-hour urinary sodium excretion was similar in cases and controls ( $P = 0.47$ ; Table 1). To estimate sodium load per nephron, we divided sodium excretion by average kidney length (Table 3). The number of cases and controls with data available on PRA, systolic BP, and the sodium load per nephron amounted to 43 and 56, respectively. In a multivariable model, PRA decreased with systolic BP (slope =  $-0.022$  ng/mL per hour/ $^{-mmHg}$ ; CI,  $-0.004$  to  $-0.040$ ;  $P = 0.048$ ), but was not associated with sodium load per nephron (slope =  $+0.011$ ;  $-0.027$  to  $0.049$  ng/mL per hour/ $^{-mmol/cm}$ ;  $P = 0.56$ ). There was no difference between cases and controls in the slope of PRA on systolic BP (0.003 versus  $-0.013$  ng/mL per hour/ $^{-mmHg}$ ;  $P \geq 0.45$ ). Figure 3 shows the regression plane ( $P = 0.048$ ) relating PRA

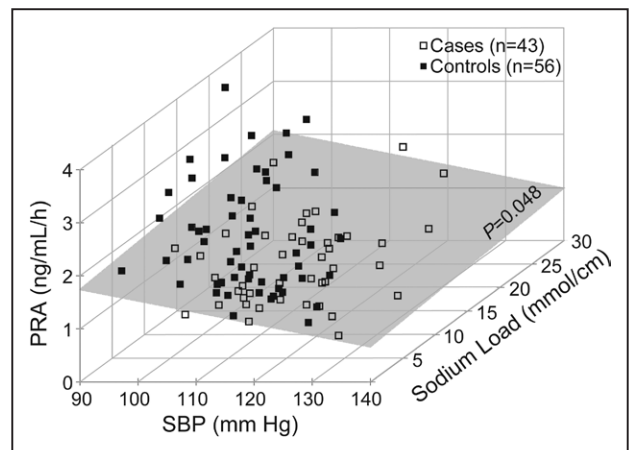


**Figure 2.** Plasma renin activity (PRA) and systolic blood pressure (SBP) as function of time of day in cases (open symbols) and controls (closed symbols). Plotted values are means. Vertical lines indicate 95% confidence boundaries. The number of children contributing to the means is given alongside the plotted data points.  $P$  values are for linear trend.

to systolic BP, while accounting for sodium load per nephron. In addition, heart rate as a proxy of the balance between sympathetic and parasympathetic tone did not alter the regression plane.

**Discussion**

The key findings of our study were that among young adolescents, ELBW children, compared with those born at term, had higher BP, a 5- to 9-fold higher risk of prehypertension or hypertension and smaller kidney size with lower  $eGFR_{cysC}$ . Although these observations are in line with previous reports,<sup>3,29-33</sup> the most salient and hitherto unreported outcome of our study was that the high BP in ELBW children was associated with lower



**Figure 3.** The plane shows the independent associations of plasma renin activity (PRA) with systolic blood pressure (SBP) and the sodium load per nephron. To estimate sodium load per nephron, we divided 24-h sodium excretion by average kidney length. The number of cases and controls with data available on PRA, SBP, and the estimated sodium load per nephron amounted to 43 and 56, respectively. The  $P$  value refers to the significance of the modeled regression plane.

PRA, which was not explained by any difference in the 24-hour sodium excretion. Our study, therefore, suggests that the pathogenesis of hypertension after premature birth is unlikely to be mediated through a mechanism dependent on the renin-angiotensin system.

Our findings confirm several seminal studies published in the 1970s and 1980s,<sup>3,29–33</sup> showing an inverse relationship between BP and birth weight. In the Dunedin cohort of 692 seven-year-old children, those in top third of the BP distribution compared with those with lower levels had a significantly lower birth weight.<sup>29</sup> In a 10-year follow-up study of 143 low birth weight infants and 139 controls,<sup>30</sup> mean systolic/diastolic BP increased from 107/70 mmHg to 112/74 mmHg for birth weights increments from 740 to 2000 g to >2500 g. British birth cohort studies,<sup>31–33</sup> including children followed-up for 10 years<sup>32</sup> or into adult life,<sup>31,33</sup> reported similar observations. A narrative review of the literature summarizing the evidence published from 1996 until 2000 included 444,000 women and men of all ages and ethnicities. Across 80 studies, the effect size was  $\approx 2$  mmHg lower systolic BP at follow-up for each 1-kg increment in birth weight.<sup>34</sup> In our current study, a mean difference in birth weight of  $\approx 2600$  g resulted in a 8 mmHg gradient in systolic BP at the age of 11 years, which is of the same order of magnitude as in the aforementioned meta-analysis.<sup>34</sup>

Brenner was the first to offer a possible explanation for the inverse association between BP and birth weight.<sup>34</sup> According to his hypothesis, hypertension supervenes when the number of nephrons decreases by acquired disease during adult life, unilateral nephrectomy, for instance for allograft transplantation, or impaired nephron development during intrauterine life. According to Guyton's model, a smaller number of nephrons necessitates a higher BP to excrete sodium.<sup>35</sup> Few studies described the relationship between kidney weight and the number of nephrons. Kidney length is one of the dimensions required to calculate kidney volume and weight. According to published evidence, renal length is an appropriate measure to assess renal dimensions in children,<sup>36</sup> and is proportional to renal volume.<sup>37</sup> A subject-level meta-analysis of 190 adults (mean age, 51 years) demonstrated that the number of nephrons augments with kidney weight ( $r=0.17$ ;  $P=0.03$ ).<sup>38</sup> In our current study, we assumed that renal length reflected the number of nephrons. Even after adjustment for sex, age, and body height, kidney length was still 0.15 cm smaller in cases than controls. However, we cannot exclude that the association between kidney length and nephron number is more complex than can be explained by simple geometry.

In the majority of preterm infants, nephrogenesis is still ongoing at the time of birth.<sup>4–6</sup> Two studies investigated postnatal glomerulogenesis either in ELBW infants weighing <1000 g<sup>4</sup> or after preterm birth with a gestational age of <35 weeks.<sup>6</sup> In Rodríguez et al<sup>4</sup> study of 56 ELBW infants and 10 full-term controls, glomerulogenesis, as measured by computer-assisted radial glomerular counts was markedly decreased in all preterm infants and correlated significantly with gestational age ( $r=0.87$ ;  $P<0.001$ ). Active glomerulogenesis was absent in preterm infants surviving for 40 days or longer and in all term infants.<sup>4</sup> In Sutherland et al<sup>6</sup> study, renal maturation accelerated in 22 infants after preterm birth,

with an increased number of glomerular generations and a decreased width of the nephrogenic zone in kidneys of pre-term neonates. Our current findings are in line with these two studies in that our ELBW children likely had fewer functional nephrons, thereby increasing their vulnerability to impaired renal function in both the early postnatal period and later in life. A secondary, but clinically relevant finding in this study was that  $eGFR_{cysC}$  was 11.5 mL/min per 1.73 m<sup>2</sup> lower in cases than controls, whereas  $eGFR_{cr}$  was similar in both groups. Serum creatinine often fails to identify people at risk of renal impairment or with subclinical renal dysfunction.<sup>39</sup>  $eGFR_{cysC}$  is a validated and sensitive biomarker of glomerular filtration in children.<sup>40</sup> Its clinical use in pediatric medicine should be promoted for the timely prevention of progression to renal impairment.

In the early 1970s, Brunner et al<sup>41</sup> group coined the terms low-renin, normal-renin, and high-renin hypertension by relating PRA to the daily sodium excretion. Compared with a standardized nomogram generated in 52 healthy volunteers, PRA among 219 patients with essential hypertension was subnormal, normal, and elevated in 27%, 57%, and 16%, respectively.<sup>41</sup> Under normal conditions, PRA increases with sodium restriction, but decreases with BP. In our current study, PRA was 0.54 ng/mL per hour lower in cases than in controls, decreased with systolic BP, but was unrelated to the sodium load. The slope of PRA on systolic BP was similar in cases and controls. Overall, our observations suggest that ELBW predisposes to low-renin hypertension, but does not affect the normal inverse association between PRA and BP. After the clinical development of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, the interest in the renin-angiotensin system waned. This probably explains why our extensive literature search only identified 7 studies that reported on PRA in preterm<sup>9,10,12</sup> or full-term<sup>7,8,10,11</sup> born children. PRA peaks in the healthy newborns and falls with aging reaching mean values similar to those in adults around 8 years of age.<sup>7,8,11</sup> At birth, PRA is higher in prematurely born infants compared with neonates born at term.<sup>9</sup> As in our current study, the relationship between PRA and BP is negative<sup>9,10</sup> and in full-term infants is possibly mediated by prostacyclin.<sup>10</sup> Keijzer-Veen and coworkers reported that in 20-year adults the 24-h ambulatory BP (118.8 versus 115.9 mmHg) and daytime BP (122.9 versus 119.6 mmHg) were higher in 50 participants prematurely born, compared with 30 controls, but they did not observe a difference in PRA between cases and controls.<sup>12</sup> However, in Keijzer-Veen et al<sup>12</sup> study, body position and urinary sodium were not reported as being controlled.

Strong points of our study are that we standardized body position at the time of blood sampling, that we confirmed the diurnal variation in PRA, that we measured 24-hour urinary sodium, and that we reported on the quality of our BP readings. However, our study must also be interpreted within the context of its potential limitations. First, 11-year-old children are a special target study population to be approached with restraint. This explains why we could not obtain blood samples in all study participants and why the participants with data available varied across our analyses. However, missing measurements unlikely introduced bias, because they occurred randomly with similar proportions among

cases and controls. Second, we only measured in-office BP. However, Keijzer-Veen et al<sup>12</sup> obtained results similar to ours based on ambulatory BP monitoring. Third, a case-control study can show association, but not causation. However, our findings are in line with the well-known physiology of the renin-angiotensin system, but cannot exclude the contribution of other pathophysiological mechanisms, such as sympathetic activation in the early stages of hypertension in adolescence.<sup>42</sup> Finally, we used the ratio of 24-hour urinary sodium excretion to kidney length as an index reflecting sodium load per nephron. Although plausible based on studies relating nephron number to prematurity,<sup>4-6</sup> the latter index remains to be validated.

### Perspectives

On the basis of our findings, we propose that ELBW children compared with children born at term are at high risk to develop a type of hypertension associated with lower glomerular filtration and, for the same amount of dietary sodium intake, also with decreased circulating PRA levels. American<sup>18</sup> and European<sup>19</sup> guidelines recommend lifestyle changes, but do not support the use of diuretics as first-line treatment of hypertension in children. Their usage relies on expert opinion. ELBW children, probably having a low-renin volume-expanded type of hypertension might be salt sensitive and benefit from a life-course reduction in salt intake. They might also be more responsive to diuretics than inhibitors of the renin-angiotensin system, the currently recommended first-line treatment in hypertensive children.<sup>18,19</sup> Above all, our study highlights the importance to screen for hypertension in all prematurely born infants to avoid the complications associated with high BP, the overriding reversible cardiovascular risk factor.<sup>43-45</sup> Finally, information on birth weight and on the perinatal history of patients might provide clinically relevant cues to physicians managing hypertension in adults. Making better use of antenatal, perinatal, and neonatal information would comply with the *Lancet* Commission on Hypertension's call to implement a life-course strategy to address the global burden of raised BP and associated complications.<sup>46</sup>

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### Disclosures

None.

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## Novelty and Significance

### What Is New?

- Low birth weight and prematurity are forerunners of hypertension in adulthood.
- Few studies reported on plasma renin activity (PRA) in preterm or full-term born children.
- In prematurely born children with birth weight <1000 g (extremely low birth weight) and healthy controls, we tested the hypothesis whether renin might modulate the pathogenesis of hypertension associated with preterm birth.

### What Is Relevant?

- In cases compared with controls, renal length and glomerular filtration rate derived from serum cystatin C were 0.28 cm and 11.5 mL/min per 1.73 m<sup>2</sup> lower, blood pressure was 7.5/4.0 mm Hg higher, and PRA was 0.54 ng/mL/h lower.

- Sodium load per nephron, expressed as the ratio of sodium excretion divided by kidney length was similar in cases and controls.
- PRA decreased with systolic blood pressure but was unrelated to sodium load or heart rate. There was no difference between cases and controls in the slope of PRA on systolic blood pressure.

### Summary

Extremely low birth weight predisposes young adolescents to low-renin hypertension, but does not affect the inverse association between PRA and blood pressure. Extremely low birth weight children might be salt sensitive, benefit from a life-course reduction in salt intake, and more responsive to diuretics than inhibitors of the renin–angiotensin system.

## Does Extremely Low Birth Weight Predispose to Low-Renin Hypertension?

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