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## **Preterm birth, early growth and adult metabolic health**

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## Preterm birth and blood pressure in adulthood:

high prevalence of hypertension but no effects of intrauterine or infancy growth

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## Abstract

### Objectives:

To determine whether intrauterine growth retardation (IUGR) is a predisposing factor for high blood pressure in 19-year-olds born (very) preterm.

### Methods:

Prospective follow-up study in 19-year-olds born preterm in The Netherlands in 1983. Systolic, diastolic, and mean blood pressure values and plasma renin activity concentration were obtained in 422 young adults born with a gestational age <32 weeks. Blood pressure was also measured in 174 individuals who were born with a gestational age of  $\geq 32$  weeks and a birth weight of <1,500 g.

### Results:

An increased prevalence of hypertension and probably also of prehypertensive stage was found. IUGR, birth weight, gestational age, and plasma renin activity were not associated with blood pressure. Current weight and BMI were the best predictors of systolic blood pressure at the age of 19 years.

### Conclusions:

The prevalence of hypertension is high in individuals who were born preterm when compared with the general population. In the individuals who were born very preterm, no support to the hypothesis that low birth weight is associated with increased blood pressure at young adult age can be given.

## Introduction

The suggested association between birth weight and adult diseases was studied in many epidemiological studies in the past decades (1;2). In these studies, an inverse relation has been described between birth weight and hypertension, dyslipidaemia, type 2 diabetes, and cardiovascular diseases in adult life. Individuals born after intrauterine growth retardation (IUGR) are thought to be at risk of developing high blood pressure compared with subjects with the same birth weight but no IUGR (3;4).

Besides low birth weight, 3 other early factors that are considered to be important risk factors for developing high blood pressure in adult life have been identified in individuals with IUGR. First, accelerated postnatal growth in weight and height is suggested to increase the risk of developing hypertension and type 2 diabetes in later life, especially in individuals with a low birth weight (5;6).

Second, it was postulated that altered angiotensin activity was an important factor underlying the “fetal origins of adult diseases” hypothesis (7;8). Also hypoxia, increased sympathetic nerve activity, and catecholamine production and proliferation of juxta-glomerular cells (and thus renin-producing cells) are suggested as factors in the pathogenesis.

Finally, preterms are probably at even greater risk for developing adult diseases compared with individuals who were born at term. A large Swedish study showed an inverse association between gestational age, ranging from 35 to 44 weeks, and systolic blood pressure (SBP) in 165,136 Swedish men (9). This correlation may be stronger in the lower range of gestation (gestational age 30 to 38 weeks), as demonstrated by Siewert-Delle et al (10). Very preterm infants who were born with a gestational age of <30 weeks were not included in this study. In contrast, other studies do not support these data. Singhal et al did not find an attributable risk to vascular disease at the age of 15 years in 216 preterm individuals (mean gestational age: 31 weeks) compared with individuals who were of the same age and born at term (11).

It is suggested that the underlying mechanism for prematurity’s influencing blood pressure and cardiovascular risk is related to an impaired (fetal) organ development. Many organ systems, such as kidneys and pancreas, develop until the third trimester of normal pregnancy. Preterm birth requires an increased energy of the neonate to grow and survive. Organ development, such as nephrogenesis and  $\beta$ -cell development in the pancreas, is not or only partly completed after preterm birth (12). Large studies that include the lowest ranges of gestation are needed to explore the role of prematurity and growth retardation with respect to the “fetal origins of adult disease” hypothesis.

Also, several maternal factors, such as maternal hypertension, smoking during pregnancy, and perinatal and postnatal factors, such as Apgar score and comorbidity after birth and drug use, are supposed to influence both neonatal and adult health. To our knowledge, no previous prospective studies were able to analyze these potential confounders in the relation to birth weight and blood pressure.

In this article, we describe the results of a large prospective follow-up study in which blood pressure was obtained in 19-year-olds who were born in 1983 with a gestational age of <32 weeks. Within this cohort, our objective was to determine whether IUGR is associated with increased blood pressure at age 19 years after very preterm birth and whether this is amplified as a result of accelerated growth postnatally and to determine whether IUGR is associated with alterations in renin activity at age 19 years after very preterm birth. In addition, the effect of potential maternal, perinatal, and postnatal confounders on blood pressure at young adult age were studied, as well as the relation between gestational age and blood pressure.

## Methods

### Population

Subjects were recruited from the Project On Preterm and Small-for-gestational-age infants (POPS) cohort. The POPS cohort comprises of 94% of all Dutch neonates (N=1,338) who were born alive in 1983 with a gestational age of <32 weeks (group 1) and/or a birth weight of <1,500 g (group 2) (13). All individuals who were alive at the age of 19 years (N=959) and not lost to follow-up until the age of 14 years (N=934) were invited to participate in a prospective follow-up study conducted from April 2002 until May 2003 in 10 outpatient clinics in The Netherlands. The ethics committees of all participating centers approved the study protocol.

Perinatal parameters (e.g., birth weight, gestational age, Apgar score, congenital anomalies) and obstetric parameters (e.g., maternal hypertension, medication during pregnancy, smoking during pregnancy) were known since birth. Follow-up data for height, weight, and BMI until the age of 10 years were also known in almost all subjects.

**Table 1. Characteristics of participants and non-responders.**

Characteristic	Participants			Non-responders
	All subjects	Group 1: <32 weeks	Group 2: ≥32 weeks and <1,500 g	
N	588	418	170	363
Males (%)	44.9	46.7	41.4	62.8
Birth weight (g)	1,303±302	1,314±338	1,274±177	1,328±251
Gestational age (weeks)	30.9±2.5	29.7±1.5	33.9±1.6	31.2±2.6
Age (yrs)	19.3±0.2	19.3±0.2	19.3±0.2	-
SBP (mmHg)	123±12	123±13	122±12	-
DBP (mmHg)	66±8	66±8	66±8	-
MAP (mmHg)	85±9	85±9	85±8	-

Values represent mean±SD or percent.

Birth weight and birth length were converted to SD score (SDS), using Swedish reference standards (14). Birth weight SDS was considered as a measure of IUGR. At follow-up visits at the ages of 3, 6, and 12 months, weight and length (measured in supine position), and at the ages of 2, 5, 10, and 19 years, data on weight and height (measured in standing position) were recorded. All of these parameters were converted to SDS, using Dutch reference standards (15).

The main statistical analyses included only participants of group 1 (gestational age <32 weeks). To study the relation between gestational age and blood pressure, also subjects of group 2 (gestational age  $\geq$ 32 weeks and birth weight <1,500 g) were included to increase the range of gestation until 40 weeks. Prevalence rates of hypertension were also calculated in both groups.

### Study protocol

Informed consent was obtained after oral and written information had been given. SBP and diastolic blood pressure (DBP) were obtained with an automatic blood pressure device (Dinamap, Critikon, Germany). Three measurements were performed at the non-dominant arm in supine position after 30 minutes of rest in the same position. The cuff-size was adjusted for arm length and circumference. Mean values were used in the statistical analysis. Mean arterial pressure (MAP) was calculated as:  $(\text{SBP} + 2 \times \text{DBP}) / 3$ . Information about medical history and drug use was obtained by an interview.

Individuals were excluded from the analyses when anti-hypertensive medication was used, individuals were pregnant, or blood pressure was not measured according protocol. Weight and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively, using calibrated scales. Participants were categorized into normal blood pressure (SBP <120 mmHg and DBP <80 mmHg), prehypertensive blood pressure (SBP 120-139 mmHg or DBP 80-89 mmHg), hypertension stage 1 (SBP 140-159 mmHg or DBP 90-99 mmHg) or hypertension stage 2 (SBP >160 mmHg or DBP >100 mmHg) according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure VII criteria (JNC VII) (16).

### Laboratory analysis

A blood sample was obtained after blood pressure measurement, in which plasma renin activity (PRA) was measured by quantification of the generated angiotensin I with a radioimmunoassay (Incstar, Stillwater, MN, USA). The sensitivity was 0.05  $\mu\text{g/l/h}$ , and the coefficient of variation ranged from 5.6 to 7.6% at different levels.

### Statistical analysis

Unpaired t tests were performed to compare blood pressure means. Because birth weight is positively associated with adult weight and adult weight influences blood pressure (causal pathway) (17), we used a multivariate regression model to analyze the effect of birth weight

on blood pressure and the effect of growing more (or less) in weight than would be expected from a given birth weight. Therefore we first used linear regression to calculate the expected size (weight or height), on the basis of birth weight, and then subtracted the actual size. This “residual” was entered in the final linear regression model (18). Recently, we explained the algebraic concept of this regression model (19). The coefficient of birth weight SDS shows the effect of birth weight SDS on adult blood pressure, and the coefficient of the residual weight shows the effect of gaining more (or less) weight than expected on adult blood pressure. Likewise, multiple logistic regression analyses were applied to evaluate the effect of birth weight SDS and residual weight adjusted for gender on the prevalence of hypertension. The effect of gestational age and gender on blood pressure and the prevalence of hypertension was analyzed separately with linear and logistic regression models. Statistical significance was defined as a P value <0.05.

**Table 2. Regression analyses of birth weight SDS and postnatal weight gain on blood pressure at age 19 years.**

Outcome	Birth weight	Weight						
	SDS	3 mo	6 mo	1 yr	2 yrs	5 yrs	10 yrs	19 yrs
SBP	0.500 (-0.667 to 1.668)	0.556 (-0.375 to 1.487)	0.696 (-0.395 to 1.788)	0.667 (-0.439 to 1.773)	0.383 (-0.790 to 1.556)	1.736 <sup>a</sup> (0.708 to 2.764)	2.212 <sup>a</sup> (1.102 to 3.321)	2.324 <sup>a</sup> (1.433 to 3.215)
DBP	0.281 (-0.490 to 1.051)	0.155 (-0.461 to 0.770)	0.024 (-0.745 to 0.696)	-0.435 (-1.167 to 0.296)	-0.519 (-1.294 to 0.256)	0.013 (-0.667 to 0.703)	0.395 (-0.373 to 1.163)	0.165 (-0.441 to 0.771)
MAP	0.354 (-0.472 to 1.180)	0.288 (-0.372 to 0.949)	0.216 (-0.557 to 0.988)	-0.068 (-0.851 to 0.715)	-0.219 (-1.051 to 0.641)	0.588 (-0.149 to 1.324)	1.000 <sup>b</sup> (0.194 to 1.807)	0.885 <sup>b</sup> (0.240 to 1.529)

Values represent  $\beta$  (95% CI). All analyses were adjusted for sex.

<sup>a</sup> P <0.01.

<sup>b</sup> P <0.05.

**Table 3. Regression analyses of birth length SDS and postnatal length/height gain on blood pressure at age 19 years.**

Outcome	Birth length	Length/height						
	SDS	3 mo	6 mo	1 yr	2 yrs	5 yrs	10 yrs	19 yrs
SBP	0.877 (-0.283 to 2.037)	0.636 (-0.544 to 1.817)	0.359 (-0.889 to 1.606)	0.686 (-0.597 to 1.970)	0.267 (-1.027 to 1.580)	0.313 <sup>a</sup> (0.149 to 0.478)	1.126 (-0.158 to 2.409)	0.822 (-0.548 to 2.192)
DBP	0.641 (-0.121 to 1.403)	0.258 (-0.509 to 1.025)	-0.126 (-0.923 to 0.672)	0.030 (-0.869 to 0.810)	0.100 (-0.951 to 0.751)	0.153 <sup>b</sup> (0.044 to 0.263)	-0.182 (-1.068 to 0.703)	-0.400 (-1.017 to 0.501)
MAP	0.720 (-0.096 to 1.536)	0.384 (-0.445 to 1.214)	0.036 (-0.832 to 0.904)	0.209 (-0.696 to 1.114)	0.026 (-0.886 to 0.938)	0.207 <sup>b</sup> (0.090 to 2.005)	0.254 (-0.679 to 1.186)	0.007 (-0.959 to 0.973)

Values represent  $\beta$  (95% CI). All analyses were adjusted for sex.

<sup>a</sup> P <0.01.

<sup>b</sup> P <0.05.



## Results

Of 934 eligible subjects, 596 participated in this study (63.8% response rate). Of the 338 non-responders, 59 were lost to follow-up, 53 were not able, 177 did not feel like, and 27 did not have time to participate. Thirteen subjects could not be included within the research period, and in 9 subjects the reason for non-response is unknown.

Five subjects mentioned that they had had increased blood pressure in the past, but none was treated for hypertension at the time of the study. Eight subjects were excluded from the data analysis: 4 because of use of anti-hypertensive medication for other reasons than hypertension (e.g., restless legs, nervousness), 2 because of protocol violation, 1 because of pregnancy, and 1 because of unreliable blood pressure measurement. Therefore, SBP and DBP data of 588 subjects were analyzed, 264 of whom were male and 324 of whom female (Table 1). The mean age was 19.29 (range: 18.63 to 20.18) years. A total of 418 subjects were born at a gestational age of <32 weeks (group 1); 170 were born with a gestational age of  $\geq 32$  weeks and with a birth weight <1,500 g (group 2). Gestational age and birth weight of the subjects in group 1 were  $29.7 \pm 1.53$  weeks and  $1,314 \pm 338$  g and in group 2 were  $33.9 \pm 1.63$  weeks and  $1,274 \pm 177$  g, respectively.

Of all subjects who were alive at 19 years, birth weight and gestational age did not differ between the responders and non-responders. Baseline characteristics of the non-responders are shown in Table 1. Compared with the subjects in the original cohort (including those who died and were lost to follow-up), the responders had a higher mean birth weight (101 g; 95% CI of mean difference: 67 to 134 g) and a longer duration of gestational age (1.2 week; 95% CI of mean difference: 0.9 to 1.5 weeks).

Data of blood pressure values are shown in Table 1. SBP, DBP, and MAP in participants in group 1 was  $123 \pm 13$  mmHg,  $66 \pm 8$  mmHg, and  $85 \pm 9$  mmHg, respectively. Participants in group 2 had SBP, DBP, and MAP of  $122 \pm 12$  mmHg,  $66 \pm 8$  mmHg, and  $85 \pm 8$  mmHg, respectively. SBP was higher in men ( $126 \pm 12$ ) than in women ( $120 \pm 12$ ). DBP was lower in men ( $64 \pm 8$ ) than in women ( $68 \pm 8$ ). Prenatal (maternal hypertension and maternal smoking during pregnancy) and perinatal and postnatal parameters (alterations on cardiocotographic measurement, Apgar score, neonatal use of corticosteroids, sepsis, and respiratory distress status) all were related to birth weight SDS but not to SBP and DBP values (data not shown). Therefore, no statistical adjustment for these parameters was required.

In a linear regression analysis of subjects born with a gestational age of <32 weeks, blood pressure was not associated with birth weight, birth weight SDS, birth length, and birth length SDS, all adjusted for gender. Regression coefficients are given in Tables 2 and 3. Increased postnatal weight gain and BMI after the age of 5 years both were predictors for SBP at the age of 19 years. The strength of this relation increased with age. Height at 5 years of age predicted SBP, DBP, and MAP at age 19 years. However, the actual effect on both SBP and DBP was very



small (0.3-mmHg increase in SBP per 1 SD more increase in height than expected at age 5). Current weight SDS and current BMI SDS were the strongest predictors for SBP ( $\beta=2.3$  mmHg per 1 residual weight SDS and 2.4 mmHg per 1 residual BMI SDS, respectively). Early postnatal weight gain (birth to 2 years) and increase in length were not related to blood pressure at the age of 19 years.

Blood pressure was also not related to gestational age, both when only participants in group 1 were included ( $\beta$  for SBP: -0.251 mmHg per week increase in gestational age; 95% CI: -1.016 to 0.514) and when all subjects were included ( $\beta$  for SBP: -0.149 mmHg per week increase in gestational age; 95% CI: -0.542 to 0.245) or when only subjects with a birth weight of <1,500 g were included ( $\beta$  for SBP: -0.150 mmHg per week increase in gestational age; 95% CI: -0.553 to 0.254).

PRA was inversely related to blood pressure adjusted for gender. The  $\beta$  for SBP was -0.02 (95% CI: -0.032 to -0.011) mmHg per 1  $\mu\text{g/l/h}$ ; the  $\beta$  for DBP was -0.0133 (95% CI: -0.037 to -0.005) mmHg per 1  $\mu\text{g/l/h}$ ; the  $\beta$  for MAP was -0.024 (95% CI: -0.039 to -0.009) mmHg per 1  $\mu\text{g/l/h}$ . Regression coefficients were not different between subjects with low and high birth weight SDS. PRA was not related with birth weight SDS or gestational age (Table 4 for mean values within birth weight SDS tertiles).

The prevalence of hypertension was 10.5% and of prehypertensive stage was 45.9% within group 1 and 8.8% and 37.6%, respectively, within group 2 (Table 5). The crude risk for hypertension was higher in men (odds ratio: 2.7; 95% CI: 1.4 to 5.3) compared with women. Birth weight SDS and gestational age both did not affect the risk for hypertension. Increased postnatal weight gain and BMI after 5 years were predictors for the risk of hypertension at the age of 19 years, but current weight affected the risk the most.

## Discussion

This article describes the results of the first large scale prospective study on the suggested association between IUGR and blood pressure at the age of 19 years in individuals who were born with a gestational age of <32 weeks and/or birth weight of <1,500 g. Our main finding was that we could not show a relation between birth weight SDS, Birth length SDS, or gestational age and adult blood pressure. Adjustment for height, a common procedure in paediatric blood pressure interpretation, did not reveal a relation between birth weight SDS and blood pressure either. Also accelerated postnatal growth or weight gain during the first months in life did not influence blood pressure at the age of 19 years. Current weight and BMI were the best predictors for blood pressure at age 19 years.

A remarkable finding was that in our 19-year-old cohort (group 1), the mean SBP was high. In our cohort (mainly white), the SBP in men was 126 mmHg and in women was 120 mmHg. In

**Table 4.** Blood pressure, plasma renin activity, and BMI SDS within tertiles of birth weight SDS in participants of group 1.

Outcome	Tertiles of birth weight SDS			P for trend <sup>a</sup>
	Lowest	Middle	Highest	
SBP (mmHg)	122±13	123±12	124±13	0.73
DBP (mmHg)	66±8	66±8	66±8	0.91
MAP (mmHg)	85±9	85±8	85±9	0.95
PRA (µg/l/h)	2.5±1.3	2.2±1.0	2.3±1.5	0.33
BMI SDS	-0.3±1.3	-0.2±1.4	0 ±1.1	0.07

Values represent mean±SD.  
<sup>a</sup>ANOVA.

comparison, the SBP of subjects of the same age (18 to 19 years) participating in the Bogalusa heart study was 115 mmHg in white men and 109 mmHg in white women (20). The Third National Health And Nutrition Examination Survey (NHANES III) reported a mean SBP in 17-year-olds of 117 mmHg in white boys and 107 mmHg in white girls (21). So, in both men and women, SBP was higher in our cohort. Other studies, such as NHANES and Framingham heart studies, reported mean blood pressure values in larger age categories (29 to 37 and 18 to 39 years), making comparison with our results difficult.

The prevalence of hypertension in our study was 10.5%. The overall prevalence of hypertension in subjects between 18 and 39 years of age was 7.2% in the NHANES III (22). Moreover, as it has been reported that the prevalence of hypertension increases by 1.3% with a 1-year increase of age (22), the prevalence of hypertension in the general population between ages 18 and 39 would be higher than the prevalence in 19-year-olds. The prevalence of prehypertension in our cohort was 45.9%. Such individuals are suggested to have a 2-fold risk for progression toward hypertension in later life (16). Therefore, monitoring of blood pressure in these subjects is recommended. However, whether the prevalence of prehypertensive stage (45.9% in our cohort) was also high compared with the general population and/or with a random 19-year-old reference group is not known. Population-based reports on blood pressure prevalences according to the most recent criteria are needed. To compare our data with the Muscatine Study, we needed to categorize our data according to the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure V criteria (23). Then, the prevalence of normal blood pressure (SBP <130 mmHg and DBP <85 mmHg) in our cohort was lower compared with the subjects in the Muscatine Study (62.4% versus 72%) and the prevalence of high blood pressure (SBP 130-139 mmHg or DBP 85-89) and hypertension stage I (SBP 140-159 mmHg or DBP 90-99) was higher (22.2% and 15.5% in our cohort versus 18% and 9% in the Muscatine, respectively) in both men and women (24). Again, the mean age of the subjects in our cohort was much lower: 19 years in our study versus 29 to 37 years in the Muscatine Study.

Several factors may have influenced our results. First, our protocol of blood pressure measurements to minimize variability deviated from other studies. We measured blood pressure 3 times in rest, in supine position, and at the non-dominant arm. Blood pressure values are suggested to be lower when measured in supine position, but when the arm is supported at the heart level (which is the case in supine position), no significant error is expected (25).

Second, our blood pressure values may have been influenced because of the use of automatic oscillometric device (Dinamap). Two studies that compared manometric and Dinamap blood pressure measurements reported an underestimation of the DBP values between 2.4 and 8.2 mmHg when this automatic device was used (26;27). However, inconsistency on the SBP values exists. Coppieters et al reported that SBP was systematically 3.6 mmHg lower in Dinamap measurements, but Pavlik et al reported a systematic overestimation of SBP between 1.0 and 6.7 mmHg when the Dinamap was used (26;27). When we adjusted for the systematic error as reported by Coppieters et al, the prevalence of hypertension increased to 18.9% and the prevalence of prehypertensive stage to 48.5%. When the Dinamap systematically overestimated the SBP with 6.7 mmHg and underestimated DBP with 2.4 mmHg (26;27), the mean blood pressure in our cohort decreased to 120±12 for SBP and 67±8 for DBP in men and 114±12 for SBP and 70±8 for DBP in females. The prevalence of hypertension within group 1 dropped to 4.3% and of prehypertensive stage to 31.8%. Still, mean SBP and DBP were higher compared with the subjects in the NHANES III and Bogalusa Heart Study (21;28).

Third, it is recommended that blood pressure be measured at least 2 times independently before mean SBP and DBP are calculated and a person is defined as hypertensive. Our 3 blood pressure measurements were performed on 1 day and are evidently not independent. However, the reference data that we used to compare prevalence rates and mean blood pressure values were also based on 1 initial screening and the mean of at least 3 measurements (21;22). Therefore, our data are comparable, showing both high prevalence and high mean blood pressure.

**Table 5.** Prevalence of hypertension using the blood pressure criteria according to the JNC VII.

Outcome	All subjects		Group 1: <32 weeks		Group 2: ≥32 weeks and <1,500 g	
	N	%	N	%	N	%
Normal blood pressure	273	46.4	182	43.5	91	53.5
Prehypertensive stage	256	43.5	192	45.9	64	37.6
Hypertension stage 1	55	9.4	42	10.0	13	7.6
Hypertension stage 2	4	0.7	2	0.5	2	1.2
Total	588	100.0	418	100.0	170	100.0

Our study indicates that individuals who were born preterm have elevated mean blood pressure values and that the prevalence of hypertension is increased at the age of 19 years. This is not related to the extent of IUGR (birth weight SDS), birth weight, or gestational age. In our cohort, the range of birth weight is 560 to 2,580 g. Most studies in which the relation between birth weight and adult blood pressure was found included subjects with a birth weight ranging between 2,000 and 5,000 g (29-31). This suggests that the relation among birth weight, prematurity, and blood pressure may be diminished in the lower birth weight ranges or gestational ages and is not a continuously linear but a curved dose-response relation. This would explain the increased mean blood pressure values, increased prevalence of hypertension, and the absence of the relation between birth weight and blood pressure in the participants of group 1 in our cohort. This trend has not been described in other studies that included preterm individuals who were born at gestational age of 30 weeks. Future studies may help to confirm our findings.

A few other reasons can be encountered for the absence of the association between IUGR and blood pressure. First, at 19 years of age, our cohort may have been too young to detect a relation. Possibly, the differences were not present at this age yet, or differences were too small to detect with our tools (which measures blood pressure 1 to 2 mmHg accurate). However, changes in blood pressure as a result of IUGR have been shown in other studies at even younger age (32). Law et al described that the effect of low birth weight on blood pressure may be obscured during adolescence (33;34). Follow-up of our subjects therefore is recommended.

Second, a selection bias could have been introduced because of a response of 64%. Of all subjects who were alive at 19 years of age, no differences in baseline characteristics were present. However, compared with the original cohort, the responders had a slightly higher birth weight and were born after a longer duration of gestation compared with the non-responders. So those with the suggested highest risk for increased blood pressure were less included in the study, possibly leading to negative results. Even if this bias were introduced and a relation between IUGR and blood pressure were concealed, our results concerning mean blood pressure values and prevalence rates are probably underestimated, and conclusions would not change much.

Finally, it is possible that the relation between birth weight and blood pressure does not exist at all and therefore was not found in our cohort. Indeed, authors have debated on contradictory results in several studies. Huxley et al stated that most studies that found a relation between birth weight and adult blood pressure included small numbers of subjects. With increasing study size, the relation diminished (35), suggesting a publication bias (36). Furthermore, most studies failed to account for possible appropriate adjustment for potential confounders, such as current weight (35). As birth weight is positively correlated with current weight and current weight with blood pressure, also in our cohort, current weight cannot be

designated as a potential confounder (causal pathway) (35;37;38). Therefore, we studied the effect of birth weight and current weight separately, using a multivariate regression model using “unexplained residuals” for current weight as adjusting variable (18). Using this model, no relation could be found.

Several authors suggested that other prenatal, perinatal, and postnatal parameters could influence the association of birth weight and blood pressure (35;38). In our study, we were able to show that maternal hypertension, smoking during pregnancy, neonatal corticosteroid use, presence of respiratory distress syndrome, and alterations on cardiocardiographic measurement were associated with birth weight SDS. These factors were all not associated with blood pressure at 19 years. We therefore conclude that these parameters are not confounders in our study.

As expected, PRA was negatively correlated to blood pressure. Individuals with high levels of active renin will have lower blood pressure values. However, neither birth weight SDS nor gestational age was associated with PRA. These data are not in agreement with the findings of Martyn et al (8), who showed increased plasma concentrations of (in)active renin at adult age in subjects who were large at birth. Konje et al found that active renin concentrations in the umbilical vein in neonates after delivery was higher in individuals who were small-for-gestational-age (7). Both authors concluded that the renin-angiotensin system is altered in individuals with IUGR. Possibly, the relation between birth weight and PRA in our cohort is not found because the relation between birth weight and blood pressure is not present. Contribution to the pathophysiological mechanism of the renin-angiotensin system therefore cannot be given.

## Conclusions

In conclusion, in this large cohort of young adults born prematurely, the mean SBP and the prevalence of hypertension were high at 19 years of age. No relation with IUGR was found. Therefore, in individuals who were born prematurely, no support for the “fetal origins of adult diseases” hypothesis can be given. Whether the relation between birth weight and blood pressure is a curved dose-response curve needs to be studied, using subjects in all birth weight ranges and gestational ages and sophisticated blood pressure tools.

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