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ORIGINAL RESEARCH

Early Determinants of Childhood Blood Pressure at the Age of 6 Years: The GECKO Drenthe and ABCD Study Birth Cohorts

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BACKGROUND: There is still uncertainty about the nature and relative impact of early determinants on childhood blood pressure. This study explored determinants of blood pressure at the age of 6 years in 2 Dutch birth cohorts.

METHODS AND RESULTS: Results of hierarchical multiple linear regression analyses in GECKO (Groningen Expert Center for Kids With Obesity) Drenthe study (n=1613) were replicated in ABCD (Amsterdam Born Children and Their Development) study (n=2052). All analyses were adjusted for child's age, sex, height, and body mass index (BMI), and maternal education and subsequently performed in the combined sample. No associations were found between maternal smoking during pregnancy and childhood blood pressure. In the total sample, maternal prepregnancy BMI was positively associated with systolic blood pressure (SBP) (β [95% CI], 0.09 [0.02–0.16] mm Hg) and diastolic blood pressure (β [95% CI], 0.11 [0.04–0.17] mm Hg). Children of women with hypertension had higher SBP (β [95% CI], 0.98 [0.17–1.79] mm Hg). Birth weight standardized for gestational age was inversely associated with SBP (β [95% CI], −6.93 [−9.25 to −4.61] mm Hg) and diastolic blood pressure (β [95% CI], −3.65 [−5.70 to −1.61] mm Hg). Longer gestational age was associated with lower SBP (β [95% CI] per week, −0.25 [−0.42 to −0.08] mm Hg). Breastfeeding for 1 to 3 months was associated with lower SBP (β [95% CI], −0.96 [−1.82 to −0.09] mm Hg) compared with no or <1 month of breastfeeding. Early BMI gain from the age of 2 to 6 years was positively associated with SBP (β [95% CI], 0.41 [0.08–0.74] mm Hg) and diastolic blood pressure (β [95% CI], 0.37 [0.07–0.66] mm Hg), but no effect modification by birth weight was found.

CONCLUSIONS: Higher maternal prepregnancy BMI, maternal hypertension, a relatively lower birth weight for gestational age, shorter gestational age, limited duration of breastfeeding, and more rapid early BMI gain contribute to higher childhood blood pressure at the age of 6 years.

Key Words: birth weight ■ childhood blood pressure ■ Developmental Origins of Health and Disease ■ fetal development ■ gestational age ■ postnatal development

Hypertension, as a major risk factor for cardiovascular diseases, such as stroke, myocardial infarction, and heart failure, has a high prevalence across the world.[1] Elevated blood pressure in childhood increases the risk of hypertension in adulthood and can also lead to target organ damage early in life, such as left ventricular hypertrophy.[2,3] Therefore, it is important to investigate determinants of childhood blood pressure and implement prevention strategies at an early age to reduce risk.

The "Developmental Origins of Health and Disease" hypothesis poses that hypertension has its origins in prenatal life and in early childhood.[4] This has been tested in studies investigating the influence of specific

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CLINICAL PERSPECTIVE

What Is New?

- Hierarchical regression analyses on the relation of prenatal factors, pregnancy outcomes, and postnatal factors with childhood blood pressure at the age of 6 years.
- Quantification of the relative contributions of length of gestation and intrauterine growth to blood pressure.

What Are the Clinical Implications?

- Identifying early determinants of blood pressure contributes to the understanding of developmental origins of blood pressure and helps to improve prevention strategies to reduce the risk of developing hypertension.

Nonstandard Abbreviations and Acronyms

ABCD	Amsterdam Born Children and Their Development
DBP	diastolic blood pressure
GECKO	Groningen Expert Center for Kids With Obesity
SBP	systolic blood pressure
std BW	standardized birth weight

early factors on blood pressure in later life, such as maternal and fetal nutritional status, intrauterine smoke exposure, birth weight, postnatal growth, and breastfeeding.[5–8] However, some results are inconsistent or contradictory. For example, the relationship between birth weight and later blood pressure has been reported to be negative, positive, or absent, which may partly be because of the lack of control for potential confounders, such as maternal smoking.[7,9–13] Furthermore, the complicated interrelationships between above-mentioned factors make it difficult to disentangle their respective roles in epidemiological studies. For instance, as low birth weight can result from intrauterine growth restriction or from prematurity, most studies could not clearly distinguish between the effects of these 2 factors. Although some studies investigated the effect of intrauterine growth restriction on blood pressure in individuals born at term or the effect of preterm birth in individuals without intrauterine growth restriction (birth weight appropriate for gestational age), these studies failed to quantify the relative contributions of length of gestation and intrauterine growth.[14–16] In addition, there is increasing evidence for an association between early growth and childhood blood pressure, but whether this association is modified by birth weight remains unclear.[17] In summary, there is still much unknown on the early childhood origins of hypertension.

Therefore, the current study explored the association between early life determinants and blood pressure in children at around 6 years of age, to contribute to an understanding of their role in potentially causing elevated blood pressure. To this end, we standardized birth weight (hereafter called std BW) for sex and gestational age to create a proxy for intrauterine growth independent of gestational age. In a population-based Dutch birth cohort, we tested std BW, gestational age, early body mass index (BMI) gain, and other potential determinants in our analysis. We explored the following research questions: (1) what are the associations between prenatal factors and childhood blood pressure at the age of 6 years? (2) is low birth weight associated with elevated blood pressure in Dutch children after adjustment for other prenatal factors? (3) what is the association of gestational age and intrauterine growth with blood pressure at the age of 6 years? (4) what is the association between early BMI gain and blood pressure at the age of 6 years and is this association modified by birth weight? Furthermore, we performed replication analyses in another independent Dutch birth cohort to confirm the reliability of the results. Finally, we performed the analyses in the total sample combining participants from the 2 cohorts and tested if the associations between early determinants and blood pressure differ in the 2 cohorts.

METHODS

Data Sharing

This study used data from 2 birth cohorts: the GECKO (Groningen Expert Center for Kids With Obesity) Drenthe study and the ABCD (Amsterdam Born Children and Their Development) study. Data are available on request because of ethical restrictions related to protecting patient confidentiality. Researchers who are interested in using data for research purposes can find more information about the GECKO Drenthe study cohort on www.birthcohorts.net and can apply for access to the ABCD study data by contacting the research committee at abcd@amc.uva.nl.

Study Population

We derived data from the GECKO Drenthe study, a Dutch population-based birth cohort that studies risk factors associated with the development of overweight from birth to adulthood.[18] The cohort includes 2842 children born between April 2006 and April 2007. Of the 5326 newly born infants in the province, 2997 mothers consented to participate, 2842 of whom actively participated in the study. Data were collected from the last trimester of pregnancy onwards by midwives and gynecologists, and after birth during regular check-up visits to the Well Baby Clinics and municipal health services as part of the nationwide Youth Health Care program, which monitors the health, growth, and development of children from birth to 18 years. The GECKO Drenthe study cohort is described in detail by L'Abee et al[18] and registered at www.birthcohorts.net. Written informed consent was obtained from parents, and this study was approved by the Medical Ethics Committee of the University Medical Center Groningen in accordance with the 1975 Declaration of Helsinki, as amended in 1983. In the current analysis, 1613 children with Dutch ethnicity and complete information on age, sex, and blood pressure were included (Figure S1 shows the flowchart of study inclusions).

Outcome: Blood Pressure

The outcome variable in the study is blood pressure, which was measured by healthcare professionals when children were around 6 years old. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) (in mm Hg) were measured using a digital automatic blood pressure monitor (M3 intellisense; OMRON Healthcare Co, Japan) with the smallest cuff. The cuff was placed on the bare (or in light clothing) left arm of the relaxed and seated child. The child was sitting for 5 minutes, then the measurements were repeated up to 3 times with 1-minute intervals. Individual measurements were considered valid only if the coefficients of variance between the measurements were <15%. Subsequently, the mean SBP and DBP were calculated. According to the American Academy of Pediatrics 2017 guideline (Clinical Practice Guideline for Screening and Management of High Blood Pressure in Children and Adolescents), children were categorized as having hypertension if their SBP or DBP ≥95th percentile for sex, age, and height.[19]

Selection of Potential Determinants of Childhood Blood Pressure

Prenatal exposures, pregnancy outcomes, and postnatal factors with a high probability of being related to blood pressure later in life were selected, as based on the literature (Table 1).[4–8,10,20–24]

Prenatal Exposures: Prepregnancy BMI, Maternal Hypertension, and Maternal Smoking During Pregnancy

Mothers joined the study in their third trimester of pregnancy. Mother's prepregnancy BMI (in kg/m^2) was self-reported. Mother's overweight was defined as BMI between 25 and 30 kg/m^2 and obesity as ≥30 kg/m^2. Maternal hypertension was self-reported or was partly derived from healthcare files, which was assessed as ever or never diagnosed by a physician in the past or during the pregnancy. Whether the mother smoked during pregnancy was obtained via questionnaires administered to the parents during the third trimester.

Pregnancy Outcomes: Gestational Age and Birth Weight

Gestational age was recorded by midwives. Birth weight and sex in the GECKO Drenthe study was recorded in the delivery room or abstracted from obstetric records and/or birth notifications. Birth weight was used as a continuous variable (in kilograms) and was standardized (std BW) for sex and gestational age using updated reference values in 2019 from the Dutch Perinatal Registration (https://www.perined.nl) as a proxy for intrauterine growth.[25]

Postnatal Factors: Breastfeeding and Early BMI Gain

Duration of breastfeeding was self-reported by parents and was categorized into 4 subgroups: no breastfeeding or <1 month (up to 1 month), 1 to 2.9 months (up to 3 months), 3 to 5.9 months (up to 6 months), and ≥6 months (>6 months).

Children's height and weight were measured by trained youth healthcare nurses at the age of 2 and 6 years during a regular check-up. BMI was calculated as weight divided by the square of height (kg/m^2). On the basis of BMI, age, and sex of children, the BMI z scores at 2 and 6 years of age (using the growth analyzer; reference: the Netherlands 1977) were calculated.[26,27] A child's early BMI gain depicts the BMI for age z-score change from 2 to 6 years of age. A positive z-score change indicates a higher BMI gain than expected based on the growth curve (incline), whereas a negative z-score change indicates a lower BMI gain than expected based on the growth curve (decline).

Covariates: Child BMI and Maternal Education

Sex, age, height, the child's BMI z score at 6 years of age, and maternal education were included as covariates in the regression analyses. Height is always used as covariate because it is a major determinant of blood pressure in growing children. We included BMI as covariate as it is strongly associated with blood pressure, so the effects of early determinants estimated in our models were adjusted for the child's

Table 1. Study Population Characteristics

Characteristics	GECKO Drenthe Study Cohort				ABCD Study Cohort			
	Total (n=1613)	Boys (n=814)	Girls (n=799)	*P* Value	Total (n=2052)	Boys (n=1041)	Girls (n=1011)	*P* Value
General characteristics								
Child age, y	5.85±0.33	5.87±0.33	5.83±0.32	0.011	5.72±0.47	5.72±0.46	5.72±0.48	0.978
Outcome								
Blood pressure, mm Hg								
Systolic	104.0±8.6	104.3±8.7	103.7±8.5	0.177	97.2±8.0	97.6±7.9	96.8±8.0	0.032
Diastolic	61.9±7.5	60.9±7.6	63.0±7.2	<0.001	57.1±6.7	56.3±6.4	57.9±6.8	<0.001
Hypertension, n (%)								
SBP based (SBP ≥95th percentile)	327 (20.3)	179 (22.0)	148 (18.5)	0.095	109 (5.3)	60 (5.8)	49 (4.8)	0.408
DBP based (DBP ≥95th percentile)	166 (10.3)	85 (10.4)	81 (10.1)	0.905	46 (2.2)	21 (2.0)	25 (2.5)	0.584
Total (SBP or DBP ≥95th percentile)	391 (24.2)	207 (25.4)	184 (23.0)	0.286	135 (6.6)	72 (6.9)	63 (6.2)	0.591
Elevated blood pressure, n (%)								
SBP based (SBP ≥90th percentile)	516 (32.0)	284 (34.9)	232 (29.0)	0.014	206 (10.0)	115 (11.0)	91 (9.0)	0.142
DBP based (DBP ≥90th percentile)	339 (21.0)	166 (20.4)	173 (21.7)	0.576	144 (7.0)	66 (6.3)	78 (7.7)	0.257
Total (SBP or DBP ≥90th percentile)	635 (39.4)	330 (40.5)	305 (38.2)	0.356	287 (14.0)	147 (14.1)	140 (13.8)	0.909
Prenatal factors								
Maternal BMI prepregnancy, median (IQR), kg/m^2	23.74 (21.45–26.75)	23.73 (21.46–26.69)	23.77 (21.45–26.82)	0.845	22.03 (20.42–24.10)	22.04 (20.44–24.07)	21.97 (20.38–24.22)	0.888
Maternal BMI prepregnancy categories, n (%)								
Low (<18 kg/m^2)	18 (1.1)	9 (1.1)	9 (1.2)	1	39 (1.9)	20 (1.9)	19 (1.9)	0.642
Normal (18–25 kg/m^2)	965 (61.4)	486 (61.4)	479 (61.4)		1642 (80.0)	841 (80.8)	801 (79.2)	
High (>25 kg/m^2)	588 (37.4)	296 (37.4)	292 (37.4)		371 (18.1)	180 (17.3)	191 (18.9)	
Maternal smoking during pregnancy, n (%)	236 (14.6)	117 (14.4)	119 (14.9)	0.822	183 (8.9)	103 (9.9)	80 (7.9)	0.134
Maternal hypertension during pregnancy, n (%)	187 (11.6)	95 (11.7)	92 (11.5)	0.984	311 (15.7)	166 (16.5)	145 (14.9)	0.35
Gestational diabetes mellitus, n (%)	36 (2.5)	17 (2.3)	19 (2.6)	0.814	12 (0.6)	6 (0.6)	6 (0.6)	1
Pregnancy outcomes								
Gestational age, median (IQR), wk	40.00 (39.00–40.86)	40.14 (39.00–41.00)	40.00 (39.00–40.86)	0.619	40.14 (39.29–41.00)	40.14 (39.29–41.00)	40.14 (39.29–41.00)	0.623
Preterm (gestational age <36 wk), n (%)	73 (4.7)	40 (5.1)	33 (4.3)	0.507	88 (4.3)	48 (4.6)	40 (4.0)	0.537
Birth weight, kg	3.56±0.55	3.63±0.55	3.49±0.53	<0.001	3.52±0.54	3.59±0.56	3.45±0.51	<0.001
Low birth weight (<2.5 kg), n (%)	48 (3.0)	24 (3.0)	24 (3.1)	1	69 (3.4)	34 (3.3)	35 (3.5)	0.888
Std BW*	1.02±0.13	1.02±0.13	1.02±0.13	0.888	1.01±0.13	1.00±0.13	1.01±0.13	0.458
Small for gestational age, n (%)†	135 (9.0)	61 (8.0)	74 (9.8)	0.235	206 (10.4)	111 (11.1)	95 (9.7)	0.353

(*Continued*)

Table 1. Continued

Characteristics	GECKO Drenthe Study Cohort				ABCD Study Cohort			
	Total (n=1613)	Boys (n=814)	Girls (n=799)	*P* Value	Total (n=2052)	Boys (n=1041)	Girls (n=1011)	*P* Value
Postnatal factors								
Breastfeeding, n (%)								
No breastfeeding or <1 mo	552 (36.0)	286 (37.0)	266 (35.0)	0.609	406 (19.8)	198 (19.0)	208 (20.6)	0.105
1–2.9 mo	261 (17.0)	137 (17.7)	124 (16.3)		322 (15.7)	179 (17.2)	143 (14.2)	
3–5.9 mo	314 (20.5)	152 (19.7)	162 (21.3)		622 (30.4)	326 (31.3)	296 (29.3)	
≥6 mo	406 (26.5)	198 (25.6)	208 (27.4)		699 (34.1)	337 (32.4)	362 (35.9)	
Early BMI gain, kg/m^2‡	0.05±0.84	0.02±0.83	0.08±0.85	0.209	−0.16±0.84	−0.17±0.84	−0.16±0.84	0.962
Child BMI, kg/m^2	16.03±1.49	16.05±1.47	16.00±1.51	0.557	15.35±1.29	15.37±1.22	15.32±1.37	0.336
Child BMI categories, n (%)§								
Underweight	76 (4.7)	40 (4.9)	36 (4.5)	0.693	289 (14.1)	142 (13.6)	147 (14.5)	0.277
Normal weight	1310 (81.2)	665 (81.7)	645 (80.7)		1627 (79.3)	838 (80.5)	789 (78.0)	
Overweight/obesity	227 (14.1)	109 (13.4)	118 (14.8)		136 (6.6)	61 (5.9)	75 (7.4)	
BMI z score	0.25±0.82	0.25±0.84	0.24±0.81	0.742	−0.17±0.83	−0.17±0.82	−0.18±0.85	0.869
Sociodemographic factors								
Maternal age at birth, y	30.93±4.18	30.95±4.14	30.92±4.22	0.886	32.72±3.85	32.67±3.91	32.76±3.79	0.592
Maternal educational level, n (%)								
Low/middle	993 (62.1)	504 (62.3)	489 (61.8)	0.884	496 (24.3)	243 (23.5)	253 (25.2)	0.4
High	607 (37.9)	305 (37.7)	302 (38.2)		1542 (75.7)	791 (76.5)	751 (74.8)	

Descriptive variables are either mean±SD or median (IQR), depending on the distribution of the variable. An independent Student *t* test was used to assess differences between boys and girls for continuous variables with normal distributions, a Wilcoxon test was used for nonnormally distributed variables, and the χ^2 test was used for categorical variables. ABCD indicates Amsterdam Born Children and Their Development; BMI, body mass index; DBP, diastolic blood pressure; GECKO, Groningen Expert Center for Kids With Obesity; IQR, interquartile range; SBP, systolic blood pressure; and Std BW, standardized birth weight.

*Std BW: birth weight standardized for sex and gestational age using updated reference values in 2019 from the Dutch Perinatal Registration (https://www.perined.nl).

†Small for gestational age: birth weight <10th percentile.

‡Early BMI gain: BMI for age z-score change from 2 to 6 years of age.

§BMI categories were defined using the sex- and age-specific BMI cutoffs defined by the International Obesity Task Force.

BMI at the age of 6 years. BMI categories at the age of 6 years (overweight, normal weight, and underweight) were defined using the sex- and age-specific BMI cutoffs defined by the International Obesity Task Force.[27] Maternal education was also included as a covariate because it is suggested to be related to childhood blood pressure in the literature.[24] The education level of the mothers (low/middle education or higher vocational education) was registered during pregnancy.

Replication Cohort

We performed replication analyses in an independent birth cohort called ABCD study.[28] In brief, between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in the ABCD study at their first visit to an obstetric care provider. Women were asked to fill out a questionnaire, including sociodemographic characteristics, medical history, and lifestyle. When the children turned 5 years, the mothers received another questionnaire and an invitation for a health check. Anthropometry and blood pressure were measured by trained research assistants during the health check at 5 to 6 years. The age of 5 or 6 years is a common age to measure blood pressure in early childhood (ie, after being an infant or a toddler but before puberty) in longitudinal birth cohorts, such as GECKO Drenthe and ABCD studies. For the replication analyses, 2052 children from the ABCD study cohort with Dutch ethnicity and complete information on age, sex, and blood pressure were included. Details of measurements have been described elsewhere.[28–31] Calculation and standardization of variables in ABCD study cohort were performed in the same way as in the GECKO Drenthe study cohort.

Statistical Analysis

An independent Student *t* test was used to compare basic characteristics between boys and girls in both cohorts for continuous variables with normal distributions, and Wilcoxon tests were used for nonnormally distributed variables. The χ^2 test was used for categorical variables.

Hierarchical linear regression analyses were used to test whether prenatal factors, pregnancy outcomes, and postnatal factors contribute to childhood blood pressure. Blocks of variables were added to the models in the same order they had appeared over time, starting with prenatal and ending with postnatal factors:

Model 1: SBP/DBP=covariates (age, sex, height, maternal education, and child's BMI at the age of 6 years)+prenatal factors (maternal smoking, maternal prepregnancy BMI, and maternal hypertension).

Model 2: SBP/DBP=covariates+prenatal factors+pregnancy outcomes (std BW and gestational age).

Model 3: SBP/DBP=covariates+prenatal factors+pregnancy outcomes+postnatal factors (breastfeeding and early BMI gain).

The 3 models were performed in both the GECKO Drenthe and ABCD study cohorts. Next, we combined participants from the 2 cohorts into a total sample, then performed these 3 models in the total sample and added an extra cohort covariate (0, ABCD study; 1, GECKO Drenthe study). In addition, we tested if the effects of early determinants on blood pressure differ in the 2 cohorts by testing determinant-by-cohort interactions for each determinant. In the total sample, we also tested interactions between std BW and early BMI gain in relation to childhood blood pressure. For model 3, we also performed sensitivity analyses excluding participants with gestational diabetes mellitus (36 in GECKO Drenthe study and 12 in ABCD study).

The variance inflation factor was used to diagnose the possibility of multicollinearity among all the variables included in the models. In the current study, all variance inflation factors were <2, indicating no problematic multicollinearity.

In addition, using the same blocks of variables as above in linear regression analyses, hierarchical logistic regression analyses were performed in the 2 cohorts as well as the total sample to explore associations between early determinants and hypertension.

$P<0.05$ was considered statistically significant. We did not apply a multiple testing correction in our study, because our study was hypothesis based with all potential determinants carefully selected on the basis of the literature. Inclusion of ABCD study afforded evaluation of consistency and replication of results, but results of the combined sample were considered the most important as it provided the most power. Statistical analyses were performed in R version 3.4.3.

RESULTS

Basic Characteristics

A total of 1613 children from the GECKO Drenthe study cohort and 2052 from the ABCD study cohort were included in our study. Table 1 shows maternal/child characteristics by sex in both cohorts. The average SBP and DBP values were 104.0 and 61.9 mm Hg in the GECKO Drenthe study cohort, which were higher than SBP and DBP values of 97.2 and 57.1 mm Hg in the ABCD study cohort. Consequently, hypertension (SBP or DBP ≥95th percentile) prevalence in children at the age of 6 years was also higher in GECKO Drenthe study (24.2%) than in the ABCD study (6.6%) cohort.

Prenatal Factors and Childhood Blood Pressure at the Age of 6 Years

Tables 2 and 3 show the linear regression results of individual cohorts and total sample between prenatal factors and childhood SBP and DBP, respectively, at the age of 6 years. No associations were found between maternal smoking during pregnancy and childhood blood pressure. In the total sample, maternal prepregnancy BMI was positively associated with SBP and DBP after adjusting for covariates, other prenatal factors, pregnancy outcomes, and postnatal factors (model 3). The increase in SBP and DBP per unit (kg/m^2) of maternal prepregnancy BMI was 0.09 and 0.11 mm Hg, respectively. Children of women with hypertension during pregnancy had higher SBP (1.30 mm Hg) and DBP (0.80 mm Hg) at the age of 6 years (model 1). After adding pregnancy outcomes to the model, the independent effect size of maternal hypertension on SBP and DBP decreased by >10% and even became insignificant for DBP (model 2). Further adjustment for postnatal factors only influenced the effect size of maternal hypertension on blood pressure slightly (model 3).

Birth Weight, Gestational Age, and Childhood Blood Pressure at the Age of 6 Years

Tables 2 and 3 also illustrate the linear regression results of birth weight and gestational age with childhood SBP and DBP at the age of 6 years. Birth weight was negatively associated with SBP and DBP after adjustment for prenatal factors. In the total sample, per unit std BW (from 1 to 2), there was a decrease in SBP of 7.28 mm Hg and a decrease in DBP of 3.79 mm Hg (model 2). Gestational age was inversely associated only with SBP, and the decrease in SBP per extra gestational week was 0.26 mm Hg (model 2). To compare the effect of birth weight and gestational age on SBP, we calculated the 2.5th and 97.5th percentiles for birth weight and gestational age in the total sample. For instance, for std BW, the decrease in SBP from the 2.5th percentile (std BW, 0.77 in the total sample) to the 97.5th percentile (std BW, 1.28) would be 3.71 mm Hg; and for gestational age, the decrease in SBP from the 2.5th percentile (35.57 weeks in the total sample) to the 97.5th percentile (42.00 weeks) would be 1.67 mm Hg. After adding postnatal factors to the model, the association between std BW and SBP/DBP was slightly attenuated but remained significant (model 3).

Postnatal Factors and Childhood Blood Pressure at the Age of 6 Years

Tables 2 and 3 present the linear regression results of breastfeeding and early BMI gain with childhood SBP and DBP at the age of 6 years. In the total sample, compared with no or <1 month of breastfeeding, only 1 to 2.9 months of breastfeeding was significantly associated with lower SBP, when adjusted for prenatal and pregnancy predictors (model 3). Although no significant association was found between duration of breastfeeding for 3 to 5.9 or ≥6 months and childhood SBP, the 95% CIs of effect sizes for the 3 subgroups of breastfeeding overlapped, indicating that the association with SBP may not differ significantly in breastfeeding groups.

BMI gain from 2 to 6 years of age was positively associated with both childhood SBP and DBP, when adjusted for prenatal, pregnancy predictors, and other covariates, including the child's BMI at the age of 6 years. In the total sample, per SD BMI gain, SBP increased 0.41 mm Hg and DBP increased 0.37 mm Hg. The increase of blood pressure from the 2.5th percentile of BMI gain at 2 to 6 years (–1.64 SD in the total sample) to the 97.5th percentile (1.72 SD) would be 1.38 mm Hg in SBP and 1.24 mm Hg in DBP. No evidence was found to support effect modification by birth weight (*P* interaction >0.05).

The Figure shows the standardized effect sizes of early determinants on blood pressure (model 3), which indicates that std BW and duration of breastfeeding (1–2.9 months) had relatively large effects on blood pressure. In general, the results were consistent between the 2 cohorts, and no significant differences of effects of early determinants on blood pressure were found between the 2 cohorts (*P* interaction >0.05). Sensitivity analyses excluding participants with gestational diabetes mellitus yielded similar results compared with analyses including all participants, and did not lead to different conclusions (data not shown).

Hierarchical logistic regression analyses showed that a higher maternal prepregnancy BMI (OR, 1.04; 95% CI, 1.01–1.06), lower std BW (OR, 0.26; 95% CI, 0.11–0.64), and faster BMI gain (OR, 1.18; 95% CI, 1.03–1.34) from 2 to 6 years were also associated with an increased risk of hypertension at 6 years of age (Table S1).

DISCUSSION

The current study showed that higher maternal prepregnancy BMI, maternal hypertension during pregnancy, lower birth weight and gestational age, <1 month of breastfeeding, and faster early BMI gain contribute to higher childhood blood pressure at the

Table 2. Results of Hierarchical Regression Analyses With Childhood SBP at the Age of 6 Years as Outcome in Individual Cohorts and Total Sample

Determinants	β (95% CI), mm Hg		
	Model 1	Model 2	Model 3
Prenatal factors			
Maternal smoking during pregnancy			
GECKO Drenthe study	1.09 (−0.19 to 2.38)	0.72 (−0.59 to 2.02)	0.80 (−0.50 to 2.11)
ABCD study	0.44 (−0.81 to 1.68)	−0.05 (−1.30 to 1.19)	−0.07 (−1.32 to 1.17)
Total sample	0.81 (−0.07 to 1.70)	0.35 (−0.54 to 1.24)	0.38 (−0.52 to 1.27)
Maternal prepregnancy BMI			
GECKO Drenthe study	0.06 (−0.04 to 0.16)	0.08 (−0.02 to 0.18)	0.07 (−0.03 to 0.17)
ABCD study	0.06 (−0.04 to 0.16)	0.10 (0.00 to 0.20)	0.10 (0.00 to 0.20)
Total sample	0.07 (0.00 to 0.14)	0.09 (0.02 to 0.16)†	0.09 (0.02 to 0.16)*
Maternal hypertension			
GECKO Drenthe study	1.73 (0.31 to 3.15)*	1.46 (0.04 to 2.88)*	1.36 (−0.06 to 2.79)
ABCD study	1.10 (0.13 to 2.07)*	0.78 (−0.19 to 1.75)	0.78 (−0.19 to 1.74)
Total sample	1.30 (0.49 to 2.11)†	1.01 (0.21 to 1.82)*	0.98 (0.17 to 1.79)*
Pregnancy outcome			
Std BW			
GECKO Drenthe study		−5.55 (−9.26 to −1.85)†	−5.07 (−8.81 to −1.33)†
ABCD study		−8.40 (−11.33 to −5.48)‡	−8.24 (−11.19 to −5.28)‡
Total sample		−7.28 (−9.58 to −4.98)‡	−6.93 (−9.25 to −4.61)‡
Gestational age			
GECKO Drenthe study		−0.27 (−0.56 to 0.01)	−0.25 (−0.54 to 0.04)
ABCD study		−0.25 (−0.46 to −0.04)*	−0.24 (−0.46 to −0.03)*
Total sample		−0.26 (−0.43 to −0.09)†	−0.25 (−0.42 to −0.08)†
Postnatal factors			
Breastfeeding (reference: no breastfeeding or <1 mo)			
Breastfeeding (1–2.9 mo)			
GECKO Drenthe study			−1.29 (−2.59 to 0.02)
ABCD study			−0.72 (−1.89 to 0.45)
Total sample			−0.96 (−1.82 to −0.09)*
Breastfeeding (3–5.9 mo)			
GECKO Drenthe study			−0.11 (−1.37 to 1.14)
ABCD study			−0.04 (−1.05 to 0.97)
Total sample			−0.06 (−0.84 to 0.72)
Breastfeeding (≥6 mo)			
GECKO Drenthe study			−0.20 (−1.37 to 0.97)
ABCD study			−0.40 (−1.38 to 0.59)
Total sample			−0.32 (−1.07 to 0.43)
Early BMI gain			
GECKO Drenthe study			0.70 (0.15 to 1.26)*
ABCD study			0.16 (−0.25 to 0.58)
Total sample			0.41 (0.08 to 0.74)*

Model 1: sex, age, height, child BMI, maternal education, maternal smoking during pregnancy, maternal prepregnancy BMI, and maternal hypertension. Model 2: model 1+Std BW (birth weight standardized for sex and gestational age) and gestational age (weeks). Model 3: model 2+breastfeeding and early BMI gain. ABCD indicates Amsterdam Born Children and Their Development; BMI, body mass index; GECKO, Groningen Expert Center for Kids With Obesity; SBP, systolic blood pressure; and Std BW, standardized birth weight.

*$P<0.05$.
†$P<0.01$.
‡$P<0.001$.

Table 3. Results of Hierarchical Multiple Regression Analyses With Childhood DBP at the Age of 6 Years as Outcome in Individual Cohorts and Total Sample

Determinants	β (95% CI), mm Hg		
	Model 1	Model 2	Model 3
Prenatal factors			
Maternal smoking during pregnancy			
GECKO Drenthe study	0.34 (−0.82 to 1.50)	0.23 (−0.95 to 1.41)	0.32 (−0.87 to 1.50)
ABCD study	−0.09 (−1.15 to 0.98)	−0.35 (−1.42 to 0.71)	−0.29 (−1.35 to 0.78)
Total sample	0.19 (−0.59 to 0.97)	−0.04 (−0.82 to 0.75)	0.03 (−0.76 to 0.82)
Maternal prepregnancy BMI			
GECKO Drenthe study	0.12 (0.03 to 0.21)*	0.12 (0.03 to 0.21)†	0.12 (0.03 to 0.21)*
ABCD study	0.07 (−0.02 to 0.15)	0.09 (0.00 to 0.18)*	0.08 (0.00 to 0.17)
Total sample	0.1 (0.04 to 0.16)†	0.11 (0.05 to 0.17)‡	0.11 (0.04 to 0.17)‡
Maternal hypertension			
GECKO Drenthe study	0.47 (−0.81 to 1.75)	0.41 (−0.87 to 1.70)	0.37 (−0.92 to 1.66)
ABCD study	1.03 (0.20 to 1.86)*	0.86 (0.03 to 1.69)*	0.84 (0.01 to 1.67)*
Total sample	0.8 (0.09 to 1.51)*	0.69 (−0.02 to 1.40)	0.67 (−0.04 to 1.38)
Pregnancy outcome			
Std BW			
GECKO Drenthe study		−1.57 (−4.92 to 1.78)	−1.45 (−4.83 to 1.93)
ABCD study		−5.23 (−7.74 to −2.72)‡	−5.11 (−7.64 to −2.58)‡
Total sample		−3.79 (−5.82 to −1.76)‡	−3.65 (−5.7 to −1.61)‡
Gestational age			
GECKO Drenthe study		−0.04 (−0.30 to 0.23)	−0.02 (−0.28 to 0.24)
ABCD study		0.01 (−0.17 to 0.19)	0.00 (−0.18 to 0.18)
Total sample		0.00 (−0.15 to 0.15)	0.00 (−0.15 to 0.15)
Postnatal factors			
Breastfeeding (reference: no breastfeeding or <1 mo)			
Breastfeeding (1–2.9 mo)			
GECKO Drenthe study			−1.05 (−2.23 to 0.12)
ABCD study			0.10 (−0.91 to 1.10)
Total sample			−0.42 (−1.18 to 0.35)
Breastfeeding (3–5.9 mo)			
GECKO Drenthe study			−0.50 (−1.63 to 0.64)
ABCD study			−0.33 (−1.19 to 0.54)
Total sample			−0.42 (−1.1 to 0.27)
Breastfeeding (≥6 mo)			
GECKO Drenthe study			0.32 (−0.74 to 1.38)
ABCD study			0.41 (−0.44 to 1.26)
Total sample			0.36 (−0.30 to 1.02)
Early BMI gain			
GECKO Drenthe study			0.54 (0.04 to 1.03)*
ABCD study			0.23 (−0.13 to 0.59)
Total sample			0.37 (0.07 to 0.66)*

Model 1: sex, age, height, child BMI, maternal education, maternal smoking during pregnancy, maternal prepregnancy BMI, and maternal hypertension. Model 2: model 1+Std BW (birth weight standardized for sex and gestational age) and gestational age (weeks). Model 3: model 2+breastfeeding and early BMI gain. ABCD indicates Amsterdam Born Children and Their Development; BMI, body mass index; DBP, diastolic blood pressure; GECKO, Groningen Expert Center for Kids With Obesity; and Std BW, standardized birth weight.

*P<0.05.
†P<0.01.
‡P<0.001

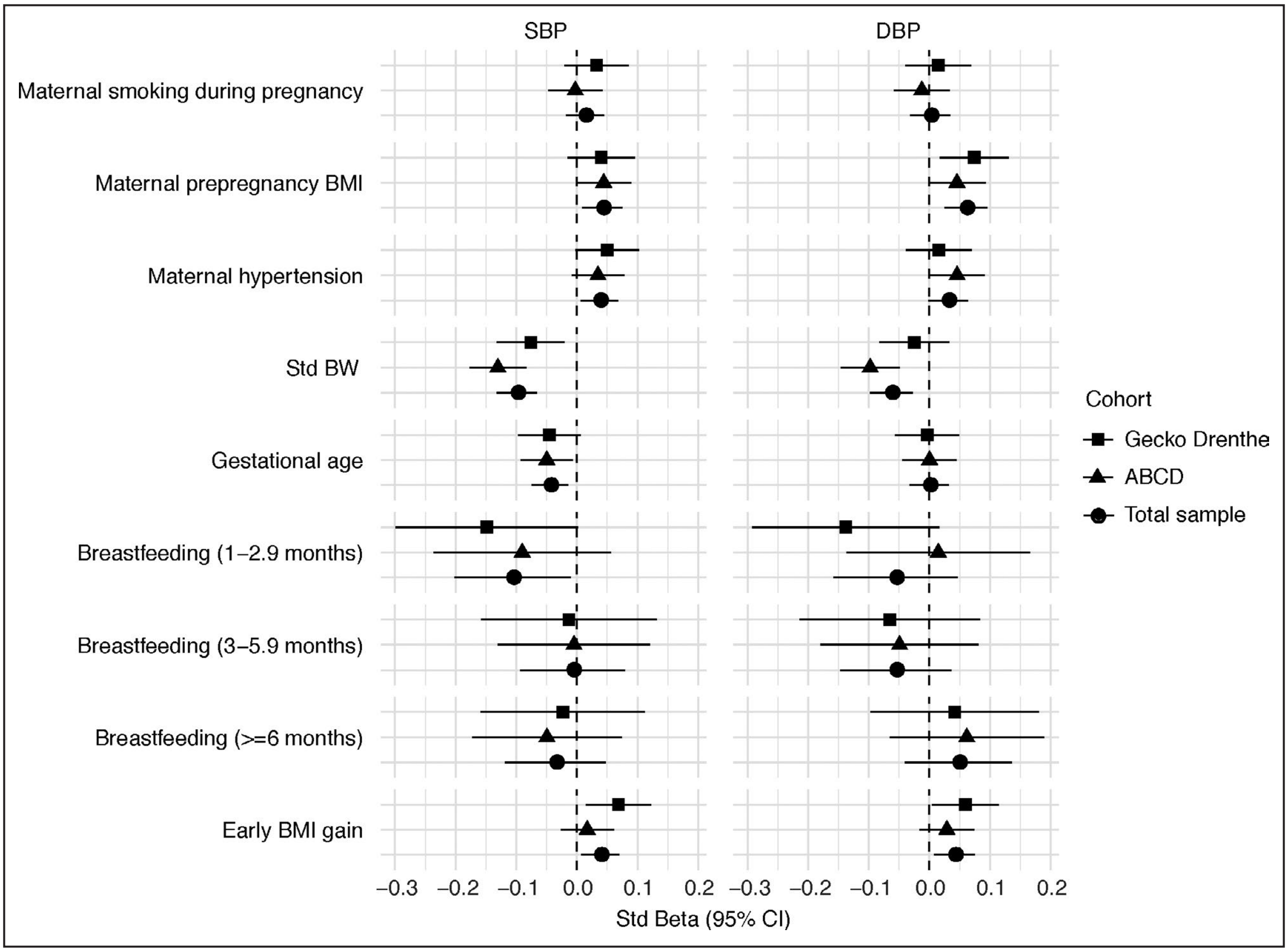

Figure. Standardized effect size of early determinants on childhood blood pressure at the age of 6 years.
ABCD indicates Amsterdam Born Children and Their Development; BMI, body mass index; DBP, diastolic blood pressure; GECKO, Groningen Expert Center for Kids With Obesity; SBP, systolic blood pressure; Std β, standardized β coefficient; and Std BW, standardized birth weight.

age of 6 years. These effects were statistically significant after adjustment for covariates, including the child's own BMI at the age of 6 years. Inclusion of birth weight and gestational age in the model partly explained the effect of maternal hypertension on blood pressure.

Prenatal Factors

Consistent with the literature,[5,32,33] we found that maternal prepregnancy BMI was positively associated with blood pressure in the offspring. The association was also observed in a previous study in the ABCD study,[28] but effect sizes differed from those in the current study. This is probably because of our selection of Dutch ABCD study children only to make it more comparable to the GECKO Drenthe study cohort. Some studies suggested this association could largely be explained by the link between maternal and offspring adiposity.[34,35] However, even after adjusting for age, sex, height, and BMI at 6 years, maternal education, pregnancy outcomes, and infant growth, the association remained significant, indicating that there may be direct effects of maternal prepregnancy BMI on childhood blood pressure through intrauterine mechanisms.[5]

In addition, maternal hypertension during pregnancy was found to be associated with childhood blood pressure, which is in line with other epidemiological studies.[36–38] One study from a prospective cohort in the Netherlands reported similar effects of maternal and paternal blood pressure on blood pressure in the child, which suggests that the association of maternal hypertension with childhood blood pressure may, at least partly, be explained by shared environmental or genetic factors between mothers and offspring.[38] Poor intrauterine development of the fetus may also explain part of the association as the effect of maternal hypertension on blood pressure did attenuate after adjustment for birth weight and gestational age in our study.[39] Alternatively, maternal hypertension during pregnancy may have a direct impact on fetal vascular development that may subsequently influence childhood blood pressure.[37]

Our finding of no association between maternal smoking and elevated blood pressure in offspring was consistent with some previous studies.[40,41] A study in a large British children cohort found that maternal smoking in pregnancy was not associated with blood pressure at 7 years after adjusting for variables related to socioeconomic position.[40] Although Wen et al observed association between heavy maternal smoking (20 cigarettes per day) during pregnancy and SBP, the association attenuated to null after adjustment for changes in BMI from birth to 7 years of age.[35] It is also possible that the effect size of maternal smoking during pregnancy is not large enough to be detected by our sample size. For example, our sample size had only 34% power at a probability level of 0.05 to detect an effect size of maternal smoking of 0.81 mm Hg on SBP for model 1 in the total sample. Therefore, we find no support for the effect of maternal smoking during pregnancy on blood pressure in offspring, and further studies with larger sample size may help to clarify this association.

Birth Weight and Gestational Age

Our results supported the association between low birth weight and elevated blood pressure. Although a study based on The US Collaborative Perinatal Project reported a positive association between birth weight and blood pressure at 7 years of age, the most likely reason is that it did not include current size (or BMI) in the model.[10] In the present study, we found a negative association after adjustment for current BMI and prenatal factors. This is in line with a systematic review of 80 studies from many populations, which demonstrated that in children, adolescents, and adults, there is an inverse relationship between birth weight and SBP after adjustment for current weight.[7] Our study also found an negative association between gestational age and SBP. This is consistent with previous studies.[16,42] For instance, Gopinath et al showed that both gestational age and birth weight were inversely associated with blood pressure among 6-year-old children.[42]

However, low birth weight may be caused by poor intrauterine growth or preterm birth, but most of the previous studies did not clearly distinguish between the effects of the length of gestational age and intrauterine growth.[12,43] To address this, we standardized birth weight for sex and gestational age to create a proxy for intrauterine growth independent of gestational age, then found that both gestational age and intrauterine growth were associated with childhood blood pressure with std BW having a relatively larger effect than gestational age. Kahn et al also used birth weight for gestational age as a measure of fetal growth and found inverse but not statistically significant relationships between birth weight for gestational age and blood pressure in adults. The insignificant results were likely because of the small sample size of only 393 US adults in this study.[44]

Several studies have been conducted to explore the underlying mechanisms. A study among Swedish twins found that genetic factors and shared familiar environment do not confound the association between birth weight and hypertension.[45] However, a recent genome-wide association study meta-analysis showed that the inverse birth weight–blood pressure association is attributable to genetic effects, including both indirect maternal and direct fetal genetic effects.[46] In addition, a systematic review suggested that low birth weight attributable to poor fetal growth or preterm birth may lead to irreversible structural and functional changes in the vascular tree (eg, endothelial function and microvascular density), and thereby increase blood pressure later in life.[47] Alternatively, reduced numbers of nephrons or changes in the endocrine system have been proposed as the explanation of the association between low birth weight and elevated blood pressure.[48,49] It has further been suggested that the relationship between birth weight and SBP becomes stronger with increasing age, indicating that there may be amplification of the pathogenic mechanisms with age.[50]

Postnatal Factors and Childhood Blood Pressure

Compared with no or limited duration of breastfeeding (<1 month), breastfeeding for 1 to 2.9 months was significantly associated with lower SBP in our study. This is in agreement with findings from a meta-analysis in 2005, which showed that initiation of breastfeeding was associated with 1.4 mm Hg lower SBP in later life.[8] However, our findings do not support a graded, dose-response association between duration of breastfeeding and childhood blood pressure. This is consistent with the PROBIT (Promotion of Breastfeeding Intervention Trial), a large randomized controlled trial of breastfeeding promotion, which showed that an intervention that increases the duration and degree of breastfeeding did not reduce blood pressure at the ages of 6 and 16 years.[51,52]

Similar to others, we found that childhood growth (measured by BMI gain) from 2 to 6 years of age was positively associated with SBP and DBP at 6 years of age.[7,17,53–55] For example, a study on 10 495 children found the detrimental effect of faster weight gain from birth to 3 months, 3 months to 1 year, and 1 to 5 years on blood pressure at the age of 6.5 years.[53] Although Taine et al[56] found an interaction between birth weight categories and postnatal weight growth velocity in their relations with blood pressure, we did not find this interaction in our study. However, they only found the interaction for weight growth velocity from 1 to 4 months but not at older ages. In the present study, childhood growth from 2 to 6 years of age was used. Thus, there is no interaction between birth weight and childhood growth from 2 to 6 years of age or the interaction is not large enough to be detected by our sample size. It has been suggested that rapid childhood growth is associated with future obesity and therefore with increased blood pressure in later life.[57] But in this study, we found that the effect of BMI gain was statistically significant after adjustment for the actual child's BMI at the age of 6 years, which indicates that other mechanisms are involved (eg, through kidney development).[54]

Strengths and Limitations

There are some limitations to our study. First, as in most cohort studies, selective loss to follow-up occurred in our study (Table S2). In GECKO Drenthe study, the current samples had older and slightly more highly educated mothers. Nonetheless, prenatal factors and pregnancy outcomes did not differ between participating and excluded children. Second, we were not able to explore the effect of heavy maternal smoking because of the lack of detailed measurements for the number of cigarettes smoked per day. Third, we could not separately investigate the influence of gestational diabetes mellitus because the numbers were too small. However, after excluding those with gestational diabetes mellitus, the results were similar. Fourth, we observed a high prevalence of hypertension in GECKO Drenthe study. This is largely because of use of the most recent hypertension guideline. We defined hypertension based on the 95th percentile of reference values from the American Academy of Pediatrics 2017 guideline, because it allows better identification of youth with high risk for cardiovascular disease.[58] The American Academy of Pediatrics 2017 references do not include children with overweight and obesity, so they represent normative blood pressure values for normal weight children. This causes hypertension reference values to be several mm Hg lower than those in previous guidelines (eg, Fourth Report[59]) using the whole population. Recent evidence suggests that use of the 2017 American Academy of Pediatrics guideline will result in an overall increase in prevalence of hypertension, particularly in youth who are obese, who have taller stature, or who have other cardiovascular risk factors.[60] If we would have used the 2004 Fourth Report to define hypertension, the prevalence of hypertension would have been 11.4% in GECKO Drenthe study and 4.3% in ABCD study. The main reason for the large difference in mean blood pressure values and hypertension prevalences between GECKO Drenthe study and ABCD study is that GECKO Drenthe study participants were generally more unhealthy than those from the ABCD study cohort. Compared with ABCD study, children in GECKO Drenthe study had higher childhood BMIs and higher prevalence of overweight/obesity (14.1% versus 6.6%). In addition, GECKO Drenthe study had higher maternal prepregnancy BMIs and lower maternal education. GECKO Drenthe (Drenthe) and ABCD (Amsterdam) studies have different settings. Economic, social, and geographical (eg, rural versus urban) differences between Drenthe and Amsterdam may partly cause these health inequalities between the 2 cohorts. Therefore, it was expected that blood pressure was higher in GECKO Drenthe study than in ABCD study. Although the differences in mean blood pressure levels between GECKO Drenthe and ABCD studies were substantial, the observed associations between early determinants and childhood blood pressure were generally consistent between the 2 cohorts. However, we also admit that as in any observational study there may be residual confounding (eg, lifestyles of mothers) in our study, so we cannot exclude that measures of effect appear to be similar when in fact they are different but masked because of confounding.

Despite these potential limitations, our study contributes to the understanding of developmental origins of blood pressure by exploring the effects of a comprehensive set of potential determinants throughout prenatal, birth, and postnatal periods. In addition, we calculated birth weight for gestational age as a proxy for intrauterine growth, which is independent of gestational age. Therefore, we could quantify the relative contributions of length of gestation and intrauterine growth to blood pressure. Finally, we replicated our results in an independent cohort, and results in the 2 cohorts were consistent, which provides strong confirmation of our results.

CONCLUSIONS

The present study suggests that higher maternal prepregnancy BMI, maternal hypertension, a relatively lower birth weight for gestational age, shorter gestational age, limited duration of breastfeeding, and faster early BMI gain are associated with elevated blood pressure at the age of 6 years, which contributes to our understanding of the developmental origins of blood pressure. It also helps to develop preventive strategies to reduce blood pressure and the risk of cardiovascular diseases later in life. For instance, overweight and obese women in the reproductive age are suggested to control their BMI to improve offspring's health. It requires further study into effective interventions to reduce prepregnancy BMI, such as dietary advice and physical activity. In addition, children with maternal hypertension and children who are born with low birth weight or preterm may need closer blood pressure monitoring to detect hypertension if it occurs, but more studies are needed to explore how to screen and manage children with higher risk of developing hypertension. Furthermore, breastfeeding has additional benefits, such as reducing a child's risk for infectious diseases and obesity,[61] and should therefore be recommended. Moreover, postnatal growth velocity should also be monitored and appropriate feeding should be recommended, which justify further studies on identifying possible critical windows of growth associated with blood pressure and establishing the optimal growth patterns.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Tables S1–S2
Figure S1

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SUPPLEMENTAL MATERIAL

Table S1. Results of hierarchical logistic analyses with childhood hypertension at age 6 as outcome in individual cohorts and total sample.

Factors	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Prenatal factors			
Maternal smoking during pregnancy			
Gecko Drenthe	1.17 (0.81, 1.67)	1.10 (0.75, 1.58)	1.10 (0.75, 1.59)
ABCD	0.94 (0.46, 1.74)	0.79 (0.39, 1.49)	0.80 (0.39, 1.52)
Total sample	1.11 (0.81, 1.51)	1.01 (0.72, 1.38)	1.01 (0.73, 1.39)
Maternal prepregnancy BMI			
Gecko Drenthe	1.03 (1.00, 1.06)*	1.03 (1.01, 1.06)*	1.03 (1.00, 1.06)*
ABCD	1.04 (0.99, 1.09)	1.05 (1.00, 1.10)*	1.05 (1.00, 1.10)*
Total sample	1.03 (1.01, 1.06)**	1.04 (1.02, 1.06)**	1.04 (1.01, 1.06)**
Maternal hypertension			
Gecko Drenthe	1.18 (0.78, 1.74)	1.12 (0.74, 1.66)	1.09 (0.72, 1.62)
ABCD	1.44 (0.89, 2.26)	1.29 (0.79, 2.04)	1.29 (0.78, 2.04)
Total sample	1.26 (0.93, 1.70)	1.18 (0.87, 1.60)	1.16 (0.85, 1.57)
Pregnancy outcome			
Std BW			
Gecko Drenthe		0.40 (0.13, 1.16)	0.46 (0.15, 1.37)
ABCD		0.07 (0.01, 0.35)**	0.09 (0.02, 0.44)**
Total sample		0.22 (0.09, 0.54)***	0.26 (0.11, 0.64)**
Gestational age			

Gecko Drenthe	0.95 (0.87, 1.03)	0.95 (0.88, 1.03)
ABCD	0.94 (0.85, 1.04)	0.94 (0.85, 1.04)
Total sample	0.94 (0.88, 1.00)	0.94 (0.88, 1.01)
Postnatal factors		
Breastfeeding (ref: no breastfeeding or < 1 month)		
Gecko Drenthe		
Breastfeeding (1-2.9 months)		0.86 (0.58, 1.26)
Breastfeeding (3-5.9 months)		0.94 (0.65, 1.36)
Breastfeeding (>=6 months)		0.84 (0.59, 1.18)
ABCD		
Breastfeeding (1-2.9 months)		1.01 (0.54, 1.87)
Breastfeeding (3-5.9 months)		0.99 (0.58, 1.72)
Breastfeeding (>=6 months)		0.85 (0.50, 1.48)
Total sample		
Breastfeeding (1-2.9 months)		0.90 (0.65, 1.24)
Breastfeeding (3-5.9 months)		0.95 (0.70, 1.28)
Breastfeeding (>=6 months)		0.85 (0.63, 1.13)
Early BMI gain		
Gecko Drenthe		1.16 (0.99, 1.37)
ABCD		1.19 (0.95, 1.49)
Total sample		1.18 (1.03, 1.34)*

OR indicates odds ratio; BMI, body mass index; std BW, standardized birth weight.

Model 1: sex, age, height, child BMI, maternal education, maternal smoking during pregnancy, maternal prepregnancy BMI, maternal hypertension

Model 2: Model 1+std BW (birth weight standardized for sex, gestational age), gestational age (weeks)

Model 3: Model 2+breastfeeding, early BMI gain

*$P<0.05$, ** $P<0.01$, ***$P<0.001$

Table S2. Maternal and child characteristics of the studied population and those excluded for the study in Dutch ethnicity.

	GECKO Drenthe			ABCD		
	Study population	Excluded children	*p*	Study population	Excluded children	*p*
Number	1613	822		2052	2108	
Sex (%)						
Boys	814 (50.5)	379 (49.7)	0.774	1041 (50.7)	1038 (49.5)	0.446
Girls	799 (49.5)	383 (50.3)		1011 (49.3)	1059 (50.5)	
Mother BMI (median [IQR])	23.74 [21.45, 26.75]	23.96 [21.74, 27.12]	0.115	22.03 [20.42, 24.10]	21.63 [20.20, 23.67]	0.001
Maternal BMI category (%)						
Low (< 18 kg/m2)	18 (1.1)	8 (1.0)	0.827	39 (1.9)	56 (2.7)	0.059
Normal (< 25 kg/m2)	965 (61.4)	482 (60.4)		1642 (80.0)	1716 (81.4)	
High (> 25 kg/m2)	588 (37.4)	308 (38.6)		371 (18.1)	336 (15.9)	
Maternal smoking (%)						
No	1377 (85.4)	704 (85.6)	0.903	1869 (91.1)	1847 (87.6)	<0.001
Yes	236 (14.6)	118 (14.4)		183 (8.9)	261 (12.4)	
Maternal hypertension (%)						
No	1426 (88.4)	737 (89.7)	0.39	1670 (84.3)	1486 (81.6)	0.03
Yes	187 (11.6)	85 (10.3)		311 (15.7)	335 (18.4)	
Maternal diabetes (%)						
No	1555 (96.4)	788 (96.0)	0.683	2031 (99.0)	2085 (98.9)	0.926
Yes	58 (3.6)	33 (4.0)		12 (0.6)	12 (0.6)	

Gestational age (median [IQR])	40.00 [39.00, 40.86]	40.00 [38.86, 41.00]	0.776	40.14 [39.29, 41.00]	40.00 [39.00, 41.00]	0.003
Birth weight (mean (SD))	3558.19 (546.07)	3558.68 (553.12)	0.984	3519.01 (543.47)	3429.86 (646.65)	<0.001
Low birth weight (<2.5 kg) (%)						
Yes	48 (3.0)	20 (2.8)	0.815	69 (3.4)	105 (5.0)	0.01
No	1535 (97.0)	706 (97.2)		1979 (96.6)	1980 (95.0)	
Maternal age (mean (SD))	30.93 (4.18)	30.40 (4.57)	0.005	32.72 (3.85)	31.46 (4.57)	<0.001
Maternal education (%)						
Low/middle	993 (62.1)	540 (66.3)	0.048	496 (24.3)	223 (25.5)	0.53
High	607 (37.9)	275 (33.7)		1542 (75.7)	651 (74.5)	

Descriptives are either mean (SD) or median (interquartile range (IQR)) depending on the distribution of the variable. An independent Student's T-test was used to assess differences between boys and girls for continuous variables with normal distributions, a Wilcoxon test for non-normally distributed variables, and the $\chi 2$ test for categorical variables.

Figure S1. Flowchart of the inclusion of study population in GECKO Drenthe.