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Abstract—Adverse intrauterine conditions can program hypertension. Because one of the underlying mechanisms is thought to be cardiac autonomic balance, we investigated the association between prepregnancy body mass index (BMI) and blood pressure and indicators of the autonomic balance in the child at age 5 to 6 years. Also investigated was whether these associations were mediated by standardized birth weight and child BMI. Pregnant women (n=3074) participating in the Amsterdam Born Children and their Development study completed a questionnaire at gestational week 14. At age 5 to 6 years, offspring's sympathetic drive (pre-ejection period), parasympathetic drive (respiratory sinus arrhythmia), and heart rate were measured by electrocardiography and impedance cardiography at rest. Blood pressure was assessed simultaneously. After adjusting for possible maternal/offspring confounders, prepregnancy BMI was positively linearly associated with diastolic blood pressure (β=0.11 mm Hg; 95% confidence interval, 0.05–0.17), systolic blood pressure (β=0.14 mm Hg; 95% confidence interval, 0.07–0.21), but not with heart rate, sympathetic or parasympathetic drive. After adding birth weight and child BMI to the model, the independent effect size of prepregnancy body mass index on systolic blood pressure (β=0.07 mm Hg; 95% confidence interval, 0.00–0.14) and diastolic blood pressure (β=0.07 mm Hg; 95% confidence interval, 0.01–0.13) decreased by ≈50%. Birth weight did not mediate these relationships, but was independently and negatively associated with blood pressure. Child BMI was positively associated with blood pressure and partly mediated the association between prepregnancy BMI and blood pressure. In conclusion, higher prepregnancy BMI is associated with higher blood pressure in the child (aged 5–6 years) but does not seem to be attributable to early alterations in resting cardiac autonomic balance. Child BMI, but not birth weight, mediated the association between prepregnancy BMI and blood pressure. **(*Hypertension*. 2013;62:641-647.)** • **Online Data Supplement**

Key Words: autonomic nervous system ■ fetal development

With the drastic increase in the prevalence of obesity, there is an exponential increase in the prevalence of obesity among women in the reproductive age group. Currently, in the United States, nearly two thirds of the women of reproductive age are overweight or obese.[1] This causes an increased risk for pregnancy complications.[2]

Besides short-term pregnancy complications, maternal obesity can also have serious consequences for their offspring's health later in life. There is increasing evidence that maternal metabolism and intrauterine conditions can program the development and growth of their children.[3–5] Although the exact mechanisms remain unclear, animal studies have shown that maternal obesity can program the child for obesity and related cardiometabolic disorders such as hypertension.[6–8]

One of the pathways through which maternal obesity could program their offspring for hypertension is that maternal overweight/obesity may cause a shift in the offspring's cardiac autonomic balance toward more sympathetic activation. This seems plausible as one of the pathways via which blood pressure is regulated is by autonomic control.[9,10] A rat study on the effect of maternal obesity on blood pressure, and blood pressure regulatory pathways in juvenile and adult offspring, showed that hypertension in the offspring of obese rats may arise from persistent sympathoexcitatory hyper-responsiveness acquired in the early stages of development.[11]

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Although the relationship between maternal obesity and blood pressure in the child has been studied,[12–14] little is known about the association between maternal obesity, child blood pressure, and the excitation of the autonomic nervous system. One study investigating this association in 41 fetuses found that maternal prepregnancy body mass index (pBMI) was positively associated with cardiac sympathetic activation during labor.[15] However, in the latter study, blood pressure was not assessed, and (to our knowledge) the consequences after birth have not yet been examined.

Therefore, the present study investigates the association between pBMI and blood pressure in the child at age 5 to 6 years. We hypothesized that elevated sympathetic nervous system activity is programmed in utero as an underlying mechanism; therefore, we investigated the association between pBMI and the offspring's heart rate (HR), and sympathetic and parasympathetic drive. Second, we assessed whether birth weight (BW) mediated this association because BW lies within the pathways via which maternal pBMI could program the fetus for hypertension either by decreased BW, attributable to, for instance, placental insufficiency or increased maternal plasma leptin levels,[16,17] or by increased BW through increased glucose and fatty acid exposure.[6,7,18] Third, we investigated whether child BMI could be a mediating pathway reflecting familial environmental factors that could result in higher offspring blood pressure.

Methods

Study Population

The present study is part of the Amsterdam Born Children and their Development (ABCD) study, a large community-based birth cohort.[19] The study protocol was approved by the Medical Ethics Committees of the Amsterdam hospitals involved and the Registration Committee of Amsterdam. All participants provided written informed consent. Details of the study design are described elsewhere.[20]

In short, between January 2003 and March 2004, all pregnant women living in Amsterdam were invited to participate in the ABCD study by their obstetric care provider at their first antenatal care visit. After inclusion, women were asked to fill out a questionnaire that covered sociodemographic characteristics, medical history, height, weight, and lifestyle. In the questionnaire, permission was requested for follow-up. When the children turned 5 years, the mothers received another questionnaire, including an informed consent sheet for the health check at 5 years. For the current study, only mothers with singletons who participated in the health check, and children without congenital malformations of the nervous system, cardiovascular system, chromosomal deviations, and multiple malformations were included (Figure S1 in the online-only Data Supplement).

Independent Variables

Prepregnancy Body Mass

pBMI was based on height and weight as reported in the pregnancy questionnaire. Missing values were imputed for maternal height (1.9% missing) and prepregnancy weight (7.7% missing) by a random imputation procedure using linear regression analysis and other variables known to be associated with maternal height and weight, respectively.[21]

Birth Weight

Children's BW, parity (primiparous: yes/no), gestational age (≈90% by echo), and sex were available from the Youth Health Care Registration. BW was standardized for sex, gestational age, and parity (standardized [std] BW) using reference values from the Dutch Perinatal Registration (www.perinatreg.nl)[22] to have a proxy for intrauterine growth.

Dependent Variables

Blood Pressure, HR, Parasympathetic, and Sympathetic Activation

Blood pressure, HR, pre-ejection period (PEP; a derivate of sympathetic nervous system activity),[23] and respiratory sinus arrhythmia (RSA; a derivative of parasympathetic nervous system activity)[24] were measured during the health check performed at age 5 to 6 years.[20]

To assess PEP and RSA, the VU University-Ambulatory Monitoring System (VU-AMS, Amsterdam, The Netherlands) was used.[23] Reliability and validity and recording methodology aspects of this device have been described previously.[23] Measurement of blood pressure, HR, PEP, and RSA was as follows: first, the electrodes for the 3-lead ECG and the 4-lead impedance cardiogram were attached; then the child lay in supine position. After 1 minute of rest in which a test blood pressure was measured (Omron Healthcare Inc, Bannockburn, IL), 6 minutes of VU-AMS recording took place from which HR, PEP, and RSA in lying position were assessed. This was followed by another 2 minutes of lying supine in which blood pressure was measured twice. Then the child was seated at a table and acclimatized for 1 minute, followed by 4 minutes of sitting at rest during which VU-AMS recording took place again. Subsequently, blood pressure was measured twice. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were calculated by taking the mean values of the repeated measurements. Blood pressure was measured with the Omron 750 IT (Omron Healthcare Inc, Bannockburn, IL) with its small cuff (arm circumference, 17–22 cm) that is validated in children.[25]

RSA was defined as the peak valley estimation.[24] This was obtained automatically by subtracting the mean shortest interbeat interval during HR acceleration in the inspirational phase from the mean longest interbeat interval during deceleration in the expirational phase. PEP was defined as the time interval between the onset of ventricular depolarization (the Q-wave onset in the ECG) and the opening of the aortic valves (B-point in impedance cardiogram).[23] This was scored manually in large-scale ensemble averages of the impedance cardiograms.[26]

Potential Confounders and Effect Modifiers

Maternal age, ethnicity, educational level, and smoking were available from the pregnancy questionnaire. Ethnicity was defined by maternal country of birth and the country of birth of her mother. Five ethnic categories were formed: Dutch, Turkish, Moroccan, Western African, and others. Years of education after primary school were considered as a proxy for socioeconomic status. Smoking during pregnancy was dichotomized (yes/no). Information on hypertension (no/pre-existent/pregnancy induced) was available by combining data from the pregnancy questionnaire and The Netherlands Perinatal Registry. The categories were classified in accordance with the guidelines of the International Society for the Study of Hypertension in Pregnancy (www.isshp.com).

Child BMI

During the health check measurements, the children wore their underwear only. Height was determined to the nearest mm with a Leicester portable height measure (Seca, Hamburg, Germany) and weight to the nearest 100 g using a weighing scale (Marsden MS-4102, Oxfordshire, UK).

Statistics

ANOVA with post hoc Tukey test was used to assess differences between maternal pBMI categories for continuous variables, and the χ^2 test for categorical variables. An independent Student *t* test was used to compare the study population with the women lost to follow-up for continuous variables and the χ^2 test for categorical variables. Departure from linearity within the regression models was tested with a likelihood ratio test using splines (R version 2.14.2); no proof was found for departure from linearity. Linear regression models assuming normally distributed errors were used to investigate the association between maternal pBMI and SBP, DBP, HR, RSA, and PEP. In the

basic model, adjustments were made only for the child's sex, height, and age at the time of outcome measurement (model 1). Interactions between sex and other variables were investigated. Subsequently, we adjusted for maternal characteristics that could confound the association (model 2) knowing ethnicity, gestational age, maternal age, maternal education, maternal height, hypertension during pregnancy, parity, and smoking. In model 3, std BW was added to investigate the role of intrauterine growth in the postulated associations. In the final model (model 4), we added the child's BMI at age 5 to 6 years. Analyses were performed for all outcome measures in both lying and sitting positions. Because analyses of the outcome measures in both positions resulted in the same conclusions, only the results in lying position are reported; the rationale for this is that blood pressure measurements were more stable in lying position.

Results

Maternal and Child Characteristics

The present study included 3074 mothers with their singletons (Figure S1). Compared with the women lost to follow-up, the included women had a lower pBMI (23.0±3.8 versus 23.2±4.1 kg/m^2; P<0.01), were more often Dutch origin (P<0.01), and had a higher education level, that is, 9.7±3.7 versus 8.0±4.2 years of education after primary school, respectively (P<0.01; see Table S1).

Table 1 presents the maternal/child characteristics by pBMI category. Obesity (BMI≥30) was prevalent in 5.2% of the mothers, and 16.2% were overweight (BMI, 25–29.9). Women in higher pBMI categories were more often of non-Dutch origin, had a higher prevalence of pregnancy or preexisting hypertension, were more likely to be multiparous, and their educational level was lower. Furthermore, children of women with a higher pBMI had a higher BW and a higher BMI at age 5 to 6 years.

Table 2 reports the outcome measures by pBMI category. Offspring of women in the higher pBMI categories had significantly higher DBP/SBP values. There was a trend toward a higher HR in the lowest pBMI category (P=0.052). No differences in RSA and PEP were found between the pBMI categories.

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Table 3 shows the linear associations between pBMI and the child's SBP, DBP, HR, RSA, and PEP. We did not find significant interactions between sex and pBMI on any outcome variables (P>0.40), indicating similar associations for boys and girls. Both SBP and DBP were positively associated with pBMI when adjusted for offspring sex, age at time of outcome measurement, and child's height. After adjusting for possible maternal confounders, the association between SBP, DBP, and pBMI was reduced. When adding std BW to the model, the associations between pBMI and SBP and DBP remained

Table 1. Maternal (N=3074) and Child Characteristics by Maternal Prepregnancy Body Mass Index

Characteristics	pBMI<18.5 n=143 (4.7%)	pBMI=18.5–24.9 n=2271 (73.9%)	pBMI=25–29.9 n=499 (16.2%)	pBMI≥30 n=161 (5.2%)	*P* Value
Maternal					
Age, y	30.3±5.0	32.06±4.5	31.4±5.1	31.6±5.1	<0.001
Ethnicity, %					<0.001
Dutch	48.3	65.8	51.1	43.4	
Turkish	3.5	3.0	3.8	5.0	
Moroccan	5.6	3.9	13.4	14.3	
Western African	6.3	3.9	9.2	10.6	
Others	35.7	23.4	22.4	26.1	
Education after primary school, y	9.28±3.9	10.1±3.5	8.5±4.0	7.5±3.9	<0.001
Primiparous, % yes	61.5	57.6	47.5	41.0	<0.001
Hypertension					<0.001
Preexisting hypertension, % yes	0	2.3	5.8	11.8	
Pregnancy hypertension, % yes	2.1	8.0	11.0	11.8	
Nonsmoking, % yes	90.9	91.3	90.2	90.1	0.86
Child					
Sex, % boys	55.9	49.5	50.9	50.9	0.48
Gestational age, d	277±13	279±12	279±12	278±15	0.07
Birth weight, g	3222±498	3478±535	3538±552	3528±658	<0.001
Standardized birth weight	0.95±0.12	1.01±0.12	1.02±0.13	1.03±0.14	<0.001
Age, y	5.69±0.47	5.73±0.50	5.77±0.50	5.83±0.53	<0.05
BMI, kg/m^2	14.9±1.3	15.4±1.4	16.0±1.6	16.4±2.1	<0.001

ANOVA with post hoc Tukey test was used to assess differences between maternal pBMI categories for continuous variables, and the χ^2 test for categorical variables. BMI indicates body mass index; and pBMI, maternal prepregnancy body mass index.

Table 2. Offspring Blood Pressure, Heart Rate, and Activation of the Autonomic Nervous System by Maternal Prepregnancy Body Mass Index

Parameters	Overall N=3074 100%	pBMI<18.5 n=143 4.7%	pBMI=18.5–24.9 n=2271 73.9%	pBMI=25–29.9 n=499 16.2%	pBMI≥30 n=161 5.2%	*P* Value
DBP, mm Hg	57.29±6.09	56.35±5.34	56.98±5.89	58.31±6.62	59.44±7.02	<0.001
SBP, mm Hg	99.45±7.38	97.36±6.40	99.22±7.19	100.46±8.02	101.56±8.12	<0.001
HR, bpm	85.38±9.91	87.03±11.06	85.10±9.62	85.98±10.69	85.95±9.98	0.052
RSA, ms	124.45±58.67	118.61±59.34	124.03±58.17	125.66±58.80	131.77±64.42	0.25
PEP, ms	71.5±9.0	70.5±8.4	71.6±8.0	71.3±9.1	72.2±8.5	0.10

ANOVA with post hoc Tukey test was used to assess differences between maternal pBMI categories. DBP indicates diastolic blood pressure; HR, heart rate; pBMI, maternal prepregnancy body mass index (kg/m^2); PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; and SBP, systolic blood pressure.

similar. Std BW was inversely associated with SBP and DBP. Finally, when adding child BMI to the model, the independent effect size of pBMI on SBP/DBP decreased by ≈50%. However, the impact of pBMI remained significant for DBP, and a trend existed for SBP (*P*=0.056).

No associations between pBMI, HR, and PEP were found. RSA was positively associated with pBMI in the crude model only. After adjusting for possible confounders, this association was reduced and was no longer significant. Child BMI was positively associated with PEP and negatively associated with HR.

In absolute numbers, per unit maternal pBMI (model 2), there was an increase in SBP of 0.14 mm Hg and an increase in DBP of 0.11 mm Hg. Because we used std BW in the model, the decrease in SBP of 3.83 mm Hg should be interpreted as a decrease per unit BW (from 1 to 2). For example, for std BW, the decrease in SBP and DBP from the 2.5th percentile (std BW of 0.77) to the 97.5th percentile (std BW of 1.26) would be 1.87

Table 3. Linear Multivariable Associations Between Maternal Prepregnancy Body Mass Index and Systolic Blood Pressure, Diastolic Blood Pressure, Heart Rate, Respiratory Sinus Arrhythmia, and Pre-Ejection Period

Dependent Variables	Model	BETA pBMI (CI)	BETA BW (CI)	BETA Child BMI (CI)
SBP, mm Hg	M1	0.19 (0.12 to 0.26)*		
	M2	0.14 (0.07 to 0.21)*		
	M3	0.16 (0.09 to 0.23)*	−3.83 (−5.94 to −1.72)*	
	M4	0.07 (0.00 to 0.14)	−5.82 (−7.87 to −3.76)*	1.30 (1.12 to 1.48)*
DBP, mm Hg	M1	0.18 (0.12 to 0.23)*		
	M2	0.11 (0.05 to 0.17)*		
	M3	0.13 (0.07 to 0.19)*	−3.81 (−5.56 to −2.05)*	
	M4	0.07 (0.01 to 0.13)*	−5.02 (−6.76 to −3.28)*	0.79 (0.64 to 0.93)*
HR, bpm	M1	0.09 (−0.01 to 0.17)		
	M2	0.06 (−0.03 to 0.16)		
	M3	0.06 (−0.03 to 0.16)	−0.57 (−3.44 to 2.30)	
	M4	0.09 (−0.01 to 0.19)	−0.04 (−2.94 to 2.85)	−0.34 (−0.59 to −0.10)*
RSA, ms	M1	0.56 (0.01 to 1.12)*		
	M2	0.38 (−0.21 to 0.97)		
	M3	0.47 (−0.13 to 1.06)	−13.38 (−31.09 to 4.33)	
	M4	0.40 (−0.21 to 1.00)	−14.95 (−32.81 to 2.91)	1.04 (−0.50 to 2.57)
PEP, ms	M1	0.02 (−0.07 to 0.10)		
	M2	0.04 (−0.05 to 0.12)		
	M3	0.03 (−0.06 to 0.12)	1.82 (−0.85 to 4.50)	
	M4	0.00 (−0.09 to 0.09)	1.16 (−1.53 to 3.86)	0.44 (0.21 to 0.67)*

M1: adjusted for offspring sex, age at time of outcome measurement and child's height.
M2: Model 1 + adjusted for ethnicity, gestational age, maternal age, maternal education, maternal height, hypertension during pregnancy, parity, and smoking.
M3: Model 2 + standardized birth weight.
M3: BW: the standardized birth weight effect in model 3.
M4: Model 3 + child's BMI.
M4: BMI child: the effect of the child's BMI in model 4.
BETA BMI indicates effect size per unit increase in body mass index; BETA BW, effect size per unit increase in standardized birth weight; BETA Child BMI, effect size per unit increase in child body mass index; BW, standardized birth weight; DBP, diastolic blood pressure; HR, heart rate; pBMI, maternal prepregnancy body mass index; PEP, pre-ejection period; RSA, respiratory sinus arrhythmia; and SBP, systolic blood pressure.
*P<0.05.

mm Hg for SBP and 1.86 mm Hg for DBP. In the same model (model 3) for pBMI, the increase in SBP and DBP from the 2.5th percentile (pBMI of 17.96 kg/m^2) to the 97.5th percentile (pBMI of 33.25 kg/m^2) would be 2.44 mm Hg for SBP and 1.99 mm Hg for DBP. When adding child BMI to model 4, the impact of pBMI decreased to 1.07 mm Hg for both SBP and DBP. Child BMI had the highest absolute impact on blood pressure: the change in blood pressure from the 2.5th percentile (child BMI of 13.24 kg/m^2) to the 97.5th percentile (child BMI of 19.22 kg/m^2) was 7.77 mm Hg for SBP and 4.72 mm Hg for DBP.

Figure S2 shows the relation between SBP, DBP, std BW, and pBMI; std BW was divided into quintiles. Irrespective of BW, blood pressure increased with every pBMI category. We found no synergistic effect of pBMI and BW on blood pressure (P for interaction >0.45), However, pBMI and BW showed additive effects such that children with a low BW, from a mother with high pBMI, had the highest blood pressure.

Discussion

This study shows that a higher pBMI was associated with higher blood pressure in the child at age 5 to 6 years, but this was not the result of early alterations in resting cardiac autonomic balance because pBMI was not related to HR, PEP, and RSA. Low BW was also associated with higher blood pressures. Child BMI, but not standardized BW, mediated the association between pBMI and blood pressure.

Our finding that pBMI is positively associated with offspring blood pressure is in line with other epidemiological studies.[12–14] Therefore, a high maternal pBMI is a risk factor for higher blood pressure in the offspring in later in life. Although we hypothesized that an elevated sympathetic nervous system activity programmed in utero was an underlying mechanism, no association was found between pBMI and sympathetic/parasympathetic drive. An earlier study showed an association between pBMI and fetal sympathetic activation,[15] but these results were not confirmed in our study population. However, the latter study assessed sympathetic activation in fetuses during labor using a fetal ECG, whereas we measured older children with the VU-AMS device, that is, we measured cardiac autonomic balance at rest only, and did not investigate sympathetic hyper-responsiveness. The differences in outcome between these studies might be attributable to the differences in age and study protocols. To our knowledge, no other human studies have reported on the association between pBMI and activation of the autonomic nervous system at rest; this topic warrants further investigation.

Similar to others, we found that BW was inversely related to blood pressure[27–30]; no evidence was found for a U-shaped curve. Although Filler et al[12] found a positive relation between high BW and high blood pressure, we could not confirm these findings; however, they did not use age, sex, and height standardization of blood pressure, and included hospitalized patients. In the present study, BW did not mediate the relation between pBMI and blood pressure but was independently and negatively associated with blood pressure. Thus, low BW is an independent risk factor for higher blood pressure later in life. Furthermore, our results indicate that high pBMI in combination with low BW led to the highest blood pressure in the child. Common genes related to both high blood pressure and growth retardation might explain this additive effect.[31] On the other hand, the theory of predictive adaptive response may also be applicable. Placenta vascular dysfunction, which is more prevalent in obese pregnancies, could lead to nutrient and oxygen restriction to which the fetus adapts.[32] After birth in an environment with abundance of food, these adaptations could have detrimental consequences for blood pressure regulation.[33]

As expected, child BMI was positively associated with blood pressure.[34] Furthermore, child BMI mediated the association between pBMI and blood pressure of the child at age 5 to 6 years; in this association, the effect size of child BMI was high (an increase of 1 unit in child BMI increased SBP by 1.30 mm Hg). Also, the independent effect size of pBMI dropped by ≈50% after the addition of child BMI to the model. Therefore, it seems that familial environmental factors (family diet, physical activity patterns) are relatively important in this association. However, animal and human studies showed that prenatal nutrition may affect dietary preferences.[8,35] Thus, besides a family pattern, a high caloric diet may also exert, in part, a programming effect. Furthermore, in the model with child BMI included, the association between pBMI and blood pressure remained significant. The increase of 1.07 mm Hg from the 2.5th to the 97.5th percentile seems a small change; however, as blood pressure tracks into adulthood, this increase could have serious consequences later.[29] For instance the Bogalusa Heart Study showed that the prevalence of clinically diagnosed hypertension was much higher in subjects whose childhood SBP was in the top quintile: 18% versus 5% compared with subjects in every other quintile.[36]

We found a significant correlation between RSA at rest and blood pressure of the child (data not shown), but not between resting PEP and blood pressure. This was against expectation because sympathetic drive is one of the pathways via which blood pressure is regulated.[9,10] However, we consider PEP to be a valid measure of sympathetic drive. This has been validated several times,[23,26] also among 5-year-old children.[37] Few studies have examined the association between the sympathetic drive and blood pressure in young children. Zhou et al[38] performed a study in 9- to 11-year-olds and found that elevated blood pressure was associated with both altered sympathetic and vagal drive, measured by HR variability indices obtained by 24-hour Holter recordings. Again, the age difference and the measurement protocol (other indices, and an overall 24-hour measurement instead of measurement at rest) might explain the differences compared with our study.

Thus, although we found an association between pBMI and child blood pressure, and a correlation between RSA and blood pressure of the child, we found no evidence that pBMI programmed the autonomic nervous system of the offspring at rest toward a more sympathetic drive or less parasympathetic drive. This would imply that at the age of 5 to 6 years other mechanisms, such as epigenetics, endothelial dysfunction, the renin-angiotensin-aldosterone system, and vascular stiffness, play a role in the relationship between pBMI and blood pressure. For example, Martyn and Greenwald[39] hypothesized that impaired elastin synthesis may be the underlying mechanism behind intrauterine growth retardation and high blood pressure later in life. Also, in a human study, pBMI was associated with methylation of a transcriptional coactivator involved in mitochondrial biogenesis and function (metabolic programming of the offspring via epigenetics).[40] Further research is needed on the underlying mechanisms by which maternal adiposity programs the blood pressure of the child.

Strengths and Limitations

This large multiethnic cohort study collected extensive data on blood pressure and the autonomic nervous system and their confounders in 5- to 6-year-olds. However, as in most cohort studies, selective loss to follow-up occurred. The women lost to follow-up had a higher pBMI than our study participants, were more often of non-Dutch origin, and had a lower education level. However, this selective loss to follow-up was unlikely to distort our results because there are no reasons why the association between pBMI and child blood pressure would differ between these 2 populations. Moreover, because our study population is a relatively healthy cohort, it is more difficult to find significant associations because the number of overweight/obese women is relatively low. Furthermore, although we measured children in lying position, with good support of the upper arm, blood pressure is highly variable in children. This means that variation in blood pressure measurements is high. However, because of our large sample size, we were able to detect relatively small effect sizes. Also, because the children were measured during rest, it might be possible that fetal programming did result in altered reactivity in the autonomic nervous system.[11] Hence, research on the topic of altered reactivity is necessary to further elucidate the effects of maternal pBMI on the offspring's autonomic nervous system. And finally, pBMI of the mothers was self-reported; it is known that self-reported height tends to be slightly overestimated and weight underestimated, resulting in an underestimation of BMI.[41] Nevertheless, such an underestimation would have occurred across almost the entire study population.

Conclusions

Higher prepregnancy BMI and lower BW are associated with higher blood pressure in the child at age 5 to 6 years. However, this does not seem to be the result of early alterations in resting cardiac autonomic balance.

Perspectives

Higher prepregnancy BMI and lower BW are associated with higher blood pressure in the child aged 5 to 6 years. Because of the tracking of childhood blood pressure into adulthood, we expect this increase in blood pressure to persist and become more distinct later in life. Therefore, the impact of this small increase at a young age might have detrimental effects on hypertension and cardiovascular disease later in life. We are aware of the need for our results to be confirmed by future research that would also address causality. However, the effects observed here already at early age, in combination with convincing animal studies and the epidemic proportion of overweight and obese women in the reproductive age, justify further study into preventive strategies to reduce prepregnancy BMI, for example, physical activity, and diet advice, already in the preconception phase, to improve offspring's health.

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Disclosures

None.

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Novelty and Significance

What Is New?

- Extensive study on the relation between prepregnancy body mass index (BMI) and blood pressure and the autonomic balance in the child aged 5 to 6 years.
- Also, we investigated the role of birth weight and child BMI within these associations.

What Is Relevant?

- Higher prepregnancy BMI and lower birth weight are associated with higher blood pressure in the child aged 5 to 6 years. To improve offspring's health, studies should investigate preventive strategies to reduce prepregnancy BMI in the preconception phase.

Summary

Higher prepregnancy BMI and lower birth weight are associated with higher blood pressure in the child at age 5 to 6 years. This does not seem to be the result of early alterations in resting cardiac autonomic balance.

Maternal pre-pregnancy body mass index and their children's blood pressure and resting cardiac autonomic balance at age 5-6 years

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Maternal pBMI and the programming of hypertension

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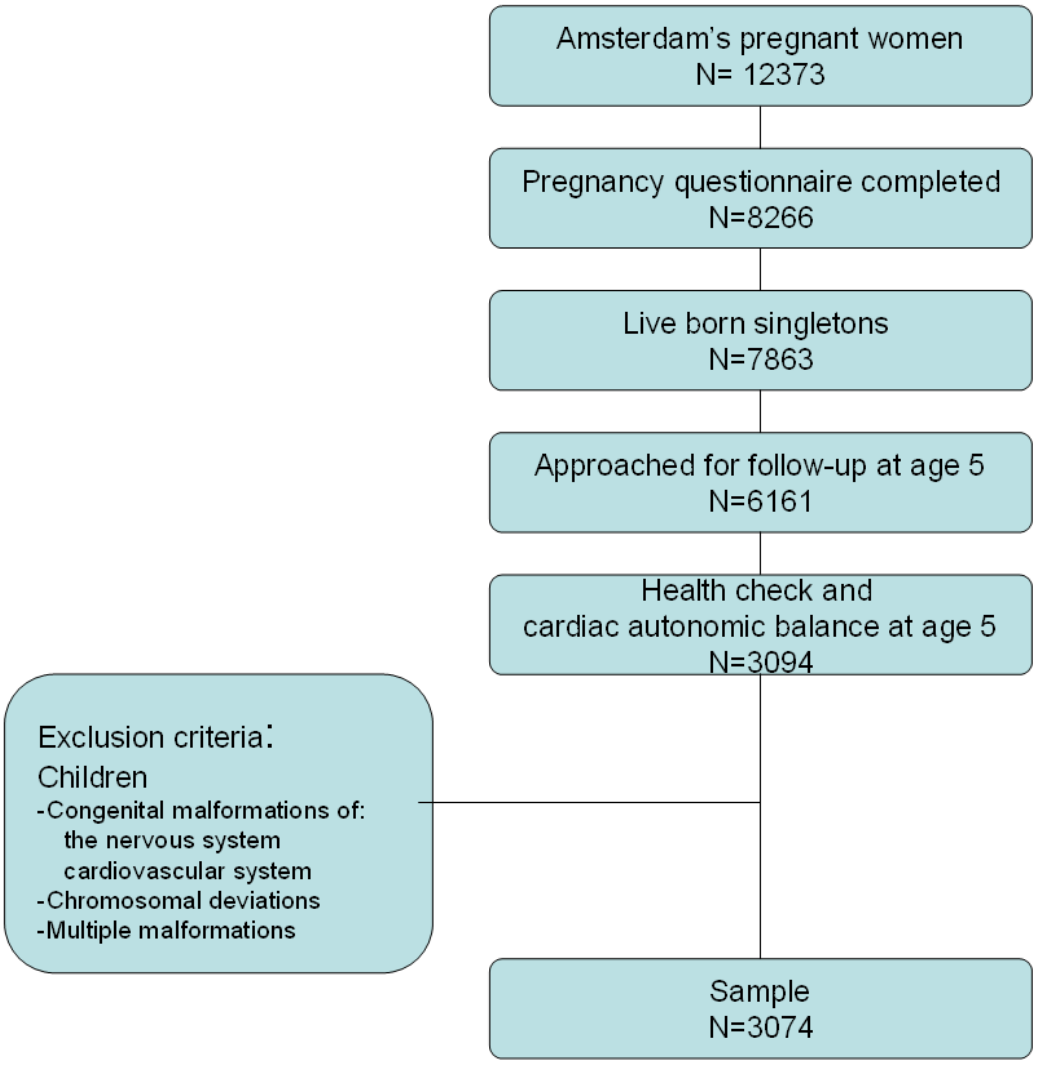
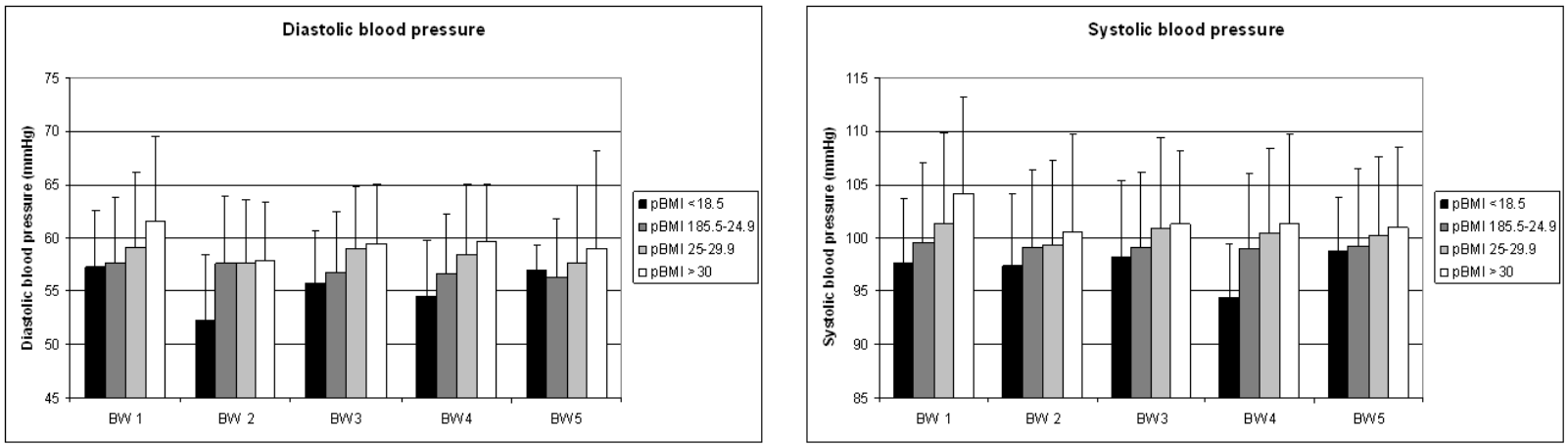
Supplementary Table. Maternal and Child characteristics of the study population and the women and children lost to follow up.

Characteristics	Study population n=3074		Lost to follow up population n= 4716*		
	Mean	SD	Mean	SD	*P*
Maternal					
Age (years)	31.8	4.6	30.0	5.5	< 0.01
pBMI (kg/m2)	23.0	3.8	23.2	4.1	< 0.01
Ethnicity (%)					
Dutch	61.5		40.7		
Turkish	3.3		6.5		
Moroccan	6.1		11.2		
Western African	2.4		5.0		
Others	26.8		36.6		< 0.01
Education after primary school (years)	9.7	3.7	8.0	4.2	< 0.01
Primiparous (% yes)	55.2		55.0		
Hypertension					< 0.01
Pre-existing hypertension (% yes)	3.3		4.3		
Pregnancy hypertension (% yes)	8.4		6.8		
Smoking					< 0.01
Non-smoking (% yes)	8.6		9.7		
Child: measurement at birth					
Sex (% boys)	50.1		50.6		0.70
Gestational age (days)	279	12	278	14	< 0.01
Birth weight (g)	3478	547	3407	578	< 0.01
Standardized birth weight	1.01	0.13	1.00	0.13	< 0.01

pBMI; maternal pre-pregnancy body mass index, *; women that gave birth to a live singleton were used for this analysis, women who met the exclusion criteria were left out of the analysis.



Supplementary Figure 1. Flow diagram of the inclusion of the study population.



A

B

Supplementary Figure 2. Maternal pre-pregnancy body mass index, birth weight and blood pressure at age 5-6 years.
A. Maternal pre-pregnancy body mass index (pBMI), birth weight (BW) and diastolic blood pressure.
B. Maternal pre-pregnancy body mass index (pBMI), birth weight (BW) and systolic blood pressure
BW; standardized birth weight in quintiles.