Childhood Hypertension

Maternal Diabetes Mellitus as a Risk Factor for High Blood Pressure in Late Childhood
A Prospective Birth Cohort Study

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Abstract—Intrauterine fetal conditions can have lifelong cardiovascular effects. The impact of maternal diabetes mellitus on children's cardiovascular profile is not well established. The goal of this study was to explore the association between maternal diabetes mellitus and offspring's blood pressure (BP) ≤10 years of age. Generation XXI is a prospective birth cohort, which enrolled 8301 mother-offspring pairs, including 586 (7.1%) children of diabetic mothers. The associations between maternal diabetes mellitus and BP at 4, 7, and 10 years of age was modeled using linear regression. A mixed-effects model was built to assess differences in BP variation over time. Path analysis was used to quantify effects of potential mediators. Maternal diabetes mellitus was associated with higher BP in offspring at the age of 10 (systolic: β, 1.48; 95% CI, 0.36–2.59; and diastolic: β, 0.86; 95% CI, 0.05–1.71). This association was independent of maternal perinatal characteristics, and it was mediated by child's body mass index and, to a lesser extent, by gestational age, type of birth, and birth weight (indirect effect proportion, 73%). No significant differences in BP were found at 4 and 7 years of age. Longitudinal analysis showed an accelerated systolic BP increase on maternal diabetes mellitus group (β, 1.16; 95% CI, 0.03–2.28). These finding were especially relevant in males, suggesting sex differences in the mechanisms of BP prenatal programing. Our results provide further evidence that maternal diabetes mellitus is associated with high BP late in childhood, demonstrating a significant role of child's body mass in the pathway of this association. (***Hypertension***. 2019;73:e1-e7. DOI: 10.1161/HYPERTENSIONAHA.118.11761.) ● Online Data Supplement

Key Words: blood pressure ■ body mass index ■ child ■ gestational diabetes ■ hypertension ■ pregnancy ■ prospective studies

In utero programing caused by prenatal exposure to specific risk factors may determine cardiovascular diseases later in adulthood.[1] The impact of this entangled milieu on cardiovascular structure and function is already tangible in the human fetus.[2] In diabetes mellitus during pregnancy, the intrauterine exposure to a hyperglycemic environment is known to have a substantial impact on fetal cardiovascular development, increasing the incidence of structural heart defects[3] and inducing myocardial hypertrophy and cardiac dysfunction.[4,5] In addition to these immediate effects, maternal diabetes mellitus is also a strong predictor for the prevalence of cardiometabolic risk factors in adolescence and adulthood.[6–8]

Although the association between hypertension in adults and previous exposure to diabetes mellitus in utero is recognized, the association between maternal diabetes mellitus and high blood pressure (BP) in childhood is not well established.[9] Differences in children's age at the time of outcome assessment might account for the reported discrepancies, as the cardiometabolic effects of prenatal exposure to diabetes mellitus

may only become apparent in late childhood or even in adolescence.[6,8] Larger sample size studies assessing age-related changes in BP across childhood would help to get further insight into early-life programing of high BP.

We sought to test the hypothesis that exposure to a hyperglycemic environment in utero is associated to higher BP in late childhood. Thus, we evaluated the association between maternal diabetes mellitus and offspring BP trajectories from age of 4 to 10 years. Additionally, we measured the impact of maternal diabetes mellitus on offspring's BP and BP percentiles during childhood at the age of 4, 7, and 10 years, taking into consideration possible sex differences.

Methods

Our article adheres to the American Heart Association journal implementation of the Transparency and Openness Promotion Guidelines. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be sent to the Instituto de Saúde Pública da Universidade do Porto, Porto, Portugal.

Study Design and Sample

This study was embedded in Generation XXI study—a prospective population-based birth cohort that recruited 8647 children from all public maternity units of Porto, Portugal, during 2005 to 2006. A detailed description of the cohort methodology was reported previously.[10] In total, 8301 mothers had available information about diabetes mellitus during pregnancy and gave birth to singleton live-born children. Of those, 586 (7.1%) were children of diabetic mothers. At the age of 4, 7, and 10 years, participants were reevaluated, and BP measurements were available for 54.5%, 67.1%, and 61.8% of the participants (exposed/unexposed ratio: 298/4223, 392/5178, and 365/4760), respectively. A comparison of the characteristics for mother-child pairs enrolled versus dropped out at the age of 4, 7, and 10 years is presented in Table S1 in the online-only Data Supplement.

Data Collection and Variable Definition

Maternal Characteristics

Maternal history and pregnancy data were obtained within 72 hours of delivery by face-to-face interview using structured questionnaires, complemented with clinical records.

Maternal diabetes mellitus was defined as gestational diabetes mellitus during the current pregnancy or previous type 1 or 2 diabetes mellitus. Gestational diabetes mellitus was considered present when reported on obstetric records as a diagnosis during pregnancy. History of type 1 or type 2 diabetes mellitus was self-reported. Maternal age and gestational hypertensive disorders, including preeclampsia and eclampsia, were retrieved from medical records. Maternal data on prepregnancy and predelivery weight, history of previous arterial hypertension, education level, and smoking habits during pregnancy (ever smoker or never smoker) were self-reported.

Maternal height was measured by interviewers using a portable stadiometer and, when not possible, was obtained from the national identity card. Prepregnancy body mass index (BMI; weight [in kg] divided by height [in meters] squared) and maternal relative weight gain during gestation (difference between predelivery weight and prepregnancy weight divided by prepregnancy weight) were calculated.

Offspring Characteristics

Gestational age, birth weight, and length were retrieved from clinical records. Gestational age was estimated by first trimester ultrasound or, in alternative, estimated based on the last menstrual period.

At each time point—4, 7, and 10 years—the participants were reevaluated at the study site. Children's weight was measured in light clothing to the nearest 0.1 kg using a digital scale (Seca), and height was determined in the upright position to the nearest 0.1 cm with a wall stadiometer (Seca). BMI was calculated as described previously. Systolic (SBP) and diastolic BP (DBP) were measured twice, after at least a 5-minute rest, using the appropriate cuff size for the upper arm circumference and an aneroid sphygmomanometer (Erka Vario Desk Model). When the difference between the 2 determinations was >5 mm Hg for SBP or DBP, a third measurement was taken, and the mean of the 2 closest values was considered. SBP and DBP percentiles were computed according to subject's sex, age, and height Z score following the recommendations of the American Academy of Pediatrics.[11] Hypertension was defined as SBP or DBP or both at or above the 95th percentile for sex, age, and height.[11] Pubertal stage at the age of 10 years was assessed by physical examination according to Tanner criteria (standards for pubic hair and genitalia growth in boys; standards for breast and pubic hair development in girls).[12] Children were classified as either prepubertal (Tanner stage I) or pubertal (Tanner stages II–V). Menarche status was self-reported.

Ethics

All phases of the study complied with the ethical principles for medical research involving human subjects expressed in the Declaration of Helsinki. The study was approved by the Ethics Committee of São João Hospital, Porto, and Faculty of Medicine of the University of Porto and by the National Data Protection Commission. Written informed consent was obtained from caretakers on behalf of the children enrolled in our study, and the children provided verbal assent to participate.

Statistical Analysis

Categorical and continuous variables are presented as count (valid percentage, excluding missing values) and mean (SD) or median (interquartile range) according to their distribution. Student t test was used for 2-group comparisons and χ^2 test for proportions comparisons.

Table 1 details classic regression and path analyses elements. Child's SBP and DBP were modeled as a continuous variable both in unadjusted and adjusted models. SBP percentile was modeled as a continuous variable and is presented in unadjusted and adjusted models in the online-only Data Supplement. These analyses were performed for the total cohort and after stratification by sex. A more in-depth characterization of maternal diabetes mellitus effect on SBP was performed at a 10-year time point: structural equation modeling was used considering maternal diabetes mellitus as the exposure, SBP as the outcome, and child's BMI and birth characteristics (gestational age, type of birth, and birth weight) as potential mediators (path model 1; causal diagram represented in Figure 1). SBP was chosen, in lieu of DBP, because it is a better predictor of adult hypertension and adverse cardiovascular outcomes.[13] Child's birth weight was coded as an indicator variable taking into account the U-shaped relationship between birth weight and maternal diabetes mellitus. Birth weight was categorized as small for gestational age (birth weight below the 10th percentile for the gestational age) and large for gestational age (birth weight above the 90th percentile for the gestational age). Full information maximum likelihood estimation was used to account for missing data.[14] Direct effects (by in utero programing), indirect effects (through mediators), and total effects of diabetes mellitus were calculated. The relevance of potential mediator factors was calculated as the proportion of the total effect explained by the indirect effect. The analysis was repeated after stratification by sex. A similar path analysis was conducted for SBP percentile at 10 years of age, and this is presented in the online-only Data Supplement. To adjust for pubertal development, pubertal stage and menarche status were included as covariates in a different path model analysis (path model 2).

Table 1. Statistical Model Description

Model	Dependent Variables	Independent Variables
Unadjusted model		
Univariate linear regression	SBP, DBP, or SBP percentile at 4, 7, or 10 y	Maternal diabetes mellitus
Adjusted model		
Multivariate linear regression	SBP, DBP, or SBP percentile at 4, 7, or 10 y	Maternal diabetes mellitus, maternal age, maternal prepregnancy BMI, maternal education level, maternal smoking habits, gestational hypertensive disorders, and prepregnancy history of hypertension
Path model 1		
Structural equation modeling	SBP or SBP percentile at 10 y	Covariates: similar to adjusted model variables
		Potential mediators: child's BMI at 10 y and birth characteristics (gestational age, type of birth, and birth weight)
Path model 2, adjusted for pubertal development		
Structural equation modeling	SBP or SBP percentile at 10 y	Similar to path model 1 plus pubertal stage and menarche status as covariates

BMI indicates body mass index; DBP, diastolic blood pressure; and SBP, systolic blood pressure.
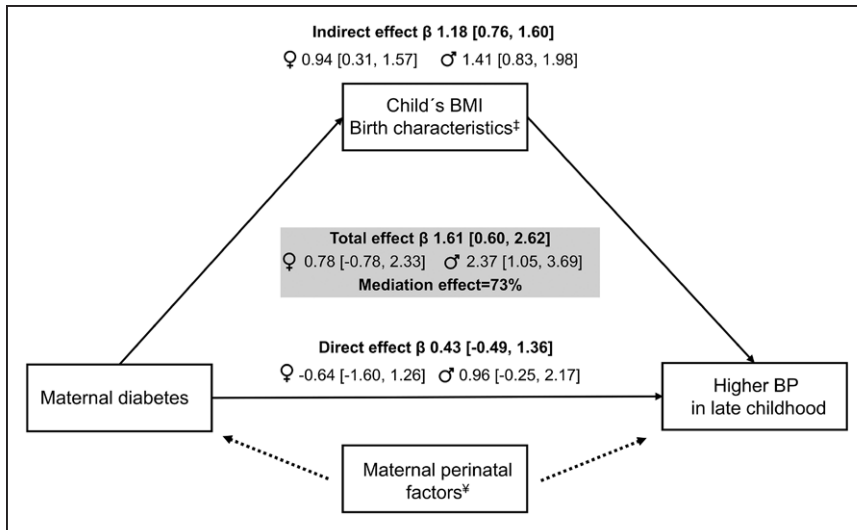
Figure 1. Path diagram for mediation analysis for systolic blood pressure (BP; path model 1). Data presented as adjusted β and 95% CI. First row presents values for the whole cohort; second row: ♀ represents females; ♂, males; ¥, maternal age at delivery, prepregnancy body mass index (BMI), education level, smoking habits, gestational hypertensive disorders, and prepregnancy history of hypertension. ‡Gestational age, type of birth, and birth weight.

Linear mixed-effects models were fitted to determine whether the pattern of change in SBP and DBP differs between the 2 exposure groups: with or without maternal diabetes mellitus. This modeling approach was chosen because it accounts for intrasubject correlation of repeated measures and partially incomplete number of observations on each subject on each occasion. The model included an effect of group (maternal diabetes mellitus status), an effect of time (treated as a categorical variable), and an interaction between group and time. The SBP and DBP trajectories model for the examined period of time can be described by the equation

$$BP_{ij} = \beta_0 + \beta_1 diabetes_{ij} + \beta_2 time7_{ij} + \beta_3 time10_{ij} + \beta_4 diabetes_{ij}$$
$$\times time7_{ij} + \beta_5 diabetes_{ij} \times time10_{ij} + e_{ij}$$

Where $_i$ accounts for the individual and $_j$ for measurement time. An unadjusted model was initially fitted, only including maternal diabetes mellitus category as the exposure. An additional model was built accounting for children's BMI as a time-varying confounder.

A P value <0.05 was considered significant for classical tests of hypothesis. For regression analysis and structural equation modeling, statistical significance was assumed when the 95% CI of the coefficient (β) estimation did not include the value of 0. Statistical analyses were run on Stata version, 14.1 (StataCorp, College Station, TX).

Results

The prevalence of diabetes mellitus during pregnancy in the cohort was 7.1%, comprising 6.5% (n=541) of mothers with gestational diabetes mellitus and 0.5% (n=45) with previous type 1 or 2 diabetes mellitus.

Baseline characteristics of mother-child pairs by maternal diabetes mellitus status are detailed in Table 2. Mothers with diabetes mellitus during pregnancy were significantly older at delivery, had a higher BMI, and lower relative weight gain during pregnancy. Diabetic mothers gave birth to babies at lower gestational age and more frequently by cesarean section. No significant differences were found in child's sex, birth weights, or lengths. Pubertal stage and menarche status were similar regarding maternal diabetes mellitus status.

At the age of 10 years, children exposed to maternal diabetes mellitus presented higher SBP (111.30±9.77 versus 109.59±9.31 mm Hg; *P*<0.001) and DBP (70.22±7.16 versus 69.26±6.91 mm Hg; *P*=0.011). Hypertension prevalence did not differ between groups. At the 3 time points evaluated,

children of diabetic mothers had a significantly higher BMI (Table 3).

Table 4 presents results of the unadjusted and adjusted linear regression models for SBP and DBP for the total cohort. There were no significant associations between maternal diabetes mellitus and SBD and DBP at the age of 4 and 7 years. In contrast, at the age of 10 years, maternal diabetes mellitus was associated with higher offspring SBP and DBP, even after adjusting for potential maternal perinatal confounders. Similar results were observed for SBP percentile analysis, presented in Table S2. When stratifying by sex, the differences observed at the age of 10 years remained significant only in males, both for SBP and SBP percentile, as demonstrated in Table 4 and Table S2, respectively. At the age of 4 and 7 years, no significant differences were found between groups in the sex-stratified analysis (data not shown), except for SBP in males at the age of 7 years (adjusted model: β, 1.39; 95% CI, 0.05–2.72).

A mediation analysis is depicted in Figure 1 (path model 1), comprising estimated direct, indirect, and total effects for the total cohort and stratified by sex. In the total cohort, at 10 years of age, when sequentially adding child's BMI and birth characteristics as mediators, the SBP in maternal diabetes mellitus group increased from 1.19 (95% CI, 0.18–2.19) to 1.59 (95% CI, 0.58–2.60) and 1.61 mm Hg (95% CI, 0.60–2.62), respectively (total effect). When included to the path alone, child's BMI mediated 67% of the association between maternal diabetes mellitus and child's SBP at 10 years of age (indirect effect). Adding birth characteristics to the path model, the indirect effect proportion increased to 73%. In both cases, the direct effect of maternal diabetes mellitus on child's SBP at 10 years of age was not statistically significant (β, 0.52; 95% CI, −0.40 to 1.45; and β, 0.43; 95% CI, −0.49 to 1.36, respectively). After stratification by sex, the total effect of maternal diabetes mellitus on SBP at the age of 10 years remained statistically significant in males but not in females (males: β, 2.37; 95% CI, 1.05–3.69; females: β, 0.78; 95% CI, −0.78 to 2.33). In males, child's BMI and birth characteristics together mediated 59% of the association between maternal diabetes mellitus and boy's SBP at 10 years of age (indirect

Table 2. Baseline Characteristics of Study Participants by Maternal Diabetes Mellitus Status

Variables	Unexposed (n=7715)	Exposed (n=586)	*P* Value
Maternal characteristics			
Age at child's birth, y	28.71±5.57 [7712]	32.16±5.42 [586]	<0.001
Prepregnancy BMI, kg/m²	22.86 (20.94–25.64) [7443]	24.91 (22.27–28.88) [567]	<0.001
Relative gestational weight gain, %	23.23±10.53 [7136]	18.75±11.52 [528]	<0.001
Prepregnancy history of hypertension, n (%)	116 (1.6%) [7404]	31 (5.5%) [563]	<0.001
Gestational hypertensive disorders, n (%)	235 (3%) [7715]	49 (8.4%) [586]	<0.001
Smokers during pregnancy, n (%)	1807 (23.8%) [7608]	119 (20.6%) [579]	0.080
Maternal educational level at birth, n (%)			
Primary education	5159 (77.1%) [6694]	416 (84.7%) [491]	<0.001
Secondary education	1244 (18.6%) [6694]	55 (11.2%) [491]	
Higher education	291 (4.3%) [6694]	20 (4.1%) [491]	
Previous type 1 or 2 diabetes mellitus, n (%)	…	45 (8%) [563]	
Child's characteristics			
Male, n (%)	3920 (50.8%) [7715]	319 (54.4%) [586]	0.090
Gestational age, wk	38.67±1.72 [7696]	38.26±1.86 [586]	<0.001
Cesarean section, n (%)	2640 (35.6%) [7416]	267 (47.3%) [564]	<0.001
Birth weight, g	3183±493 [7714]	3215±541 [586]	0.14
Birth length, cm	49 (47.5–50) [7674]	49 (47.5–50) [573]	0.70
Prepubertal stage, n (%)	2123 (47.7%) [4452]	148 (43.8%) [338]	0.17
Menarche (girls), n (%)	74 (3.2%) [2293]	9 (5.7%) [159]	0.10

Data presented as mean±SD, median (interquartile range), n (valid percentage), and [total N] for each variable. BMI indicates body mass index.

effect). A repeated analysis for SBP percentiles is illustrated in Figure S1, with comparable results.

When exploring the effect of sexual maturity on the association between maternal diabetes mellitus and child's SBP or SBP percentile at the age of 10 years (path model 2), the inclusion of pubertal stage and menarche status as covariates did not significantly change the mediation analysis results, as demonstrated in Figures S2 and S3.

Figure 2 displays the modeled BP growth trajectories from 4 to 10 years of children by maternal diabetes mellitus status. Linear slope for SBP growth from 4 to 10 years was steeper for those exposed to maternal diabetes mellitus (β_5, 1.16; 95% CI, 0.03–2.28). However, after controlling for children's BMI, the effect of maternal diabetes mellitus on SBP trajectory was no longer present (β_5, 0.35; 95% CI, −0.74 to 1.45). DBP linear slope from this age range did not differ by maternal diabetes mellitus status (β_5, 0.66; 95% CI, −0.39 to 1.71). A repeated analysis stratified by sex did not show differences between groups in the slope in either strata.

Discussion

Small but consistent deviations in childhood BP may represent one of the most important predictors of cardiovascular risk in later life.[13,15,16] In this large population-based birth cohort, we found that maternal diabetes mellitus is associated with increased BP and SBP percentile in the offspring at the age of 10 years. This association is independent of maternal perinatal characteristics, and it is significantly mediated by the effects of maternal diabetes mellitus on child's BMI, gestational age, type of birth, and birth weight. The predominant effect of maternal diabetes mellitus in male offspring suggests sex differences in the complex mechanisms of BP prenatal programing.

Examining the impact of maternal diabetes mellitus on childhood BP trajectories, an accelerated SBP growth is seen on maternal diabetes mellitus group. Looking at each time point individually, in contrast to the age of 10 years, at the age of 4 and 7 years, no differences were found between groups in SBP or DBP for the whole cohort. Altogether, our observations shed light on the apparent conflicting results of previous studies examining BP in the offspring of diabetic mothers.[9,17] Our data evidence an effect of maternal diabetes mellitus in the offspring only in late childhood, after an apparent quiescent subclinical period.

Several biological pathways link intrauterine hyperglycemia to offspring BP. Studies on offspring of diabetic rats show that nephron number is reduced,[18] and angiotensin-converting enzyme activity is enhanced in the cardiovascular system,[19] predisposing to hypertension and kidney diseases in postnatal life.[20] In parallel, an intrauterine hyperglycemic environment disturbs angiogenesis and fetal vascular development. That is evident both in animal studies, demonstrating an impairment of fetal endothelial cell functions[21] and abnormal signaling of vascular growth factors,[22] but also in humans

Table 3. Children's BMI and Blood Pressure in the Different Time Points by Maternal Diabetes Mellitus Status

Variables	Unexposed (n=7715)	Exposed (n=586)	P Value
BMI, kg/m²			
At 4 y	16.29±1.78 [5259]	16.64±1.89 [405]	<0.001
At 7 y	17.05±2.50 [5192]	17.56±2.83 [395]	<0.001
At 10 y	18.78±3.38 [4769]	19.73±3.64 [366]	<0.001
SBP, mm Hg			
At 4 y	98.25±8.37 [4223]	98.60±8.49 [298]	0.47
At 7 y	105.47±8.84 [5178]	106.16±9.18 [392]	0.14
At 10 y	109.59±9.31 [4760]	111.30±9.77 [365]	<0.001
DBP, mm Hg			
At 4 y	57.73±8.10 [4223]	58.01±8.18 [298]	0.56
At 7 y	69.99±7.58 [5178]	70.50±7.33 [392]	0.20
At 10 y	69.26±6.91 [4760]	70.22±7.16 [365]	0.011
Hypertension, n (%)			
At 4 y	360 (8.6%) [4205]	31 (10.5%) [296]	0.26
At 7 y	1220 (23.6%) [5174]	100 (25.5%) [392]	0.39
At 10 y	693 (14.6%) [4759]	57 (15.6%) [365]	0.58

Data presented as mean±SD, n (valid percentage), and [total N] for each variable. BMI indicates body mass index; DBP, diastolic blood pressure; and SBP, systolic blood pressure.

studies showing that children of diabetic mothers have significant upregulation of endothelial cell adhesion molecules.[23]

Besides this direct effect of maternal diabetes mellitus on childhood BP, our path analysis suggests that most of the association is mediated by child's BMI and, to a lesser extent, gestational age, type of birth, and birth weight. Epidemiological data linking obesity to elevated BP is remarkably consistent across different cohorts and populations, including pediatric studies.[24,25] The underlying mechanisms are probably related to a persistent sympathetic overactivation, increased renal sodium retention secondary to insulin resistance/hyperinsulinemia, and obesity-mediated inflammation.[26] It is unfortunately difficult to untwine metabolic syndrome components

from each other. Maternal diabetes mellitus is itself strongly associated with higher BMI in the offspring, and this is present in the causal pathway between maternal diabetes mellitus and childhood BP.[6–8,17]

Sex-specific differences in BP levels related to multiple risk factors are well known in adults but rarely described at such young ages. Our results suggest that young boys born to diabetic mothers are at a higher risk than girls of developing increased BP already at 7 and 10 years of age. The mechanisms underlying this sexual dimorphism remain poorly understood but seem to be related to differential activation of sympathetic nervous system, renin-angiotensin system, and immune system between males and females, modulated by sex hormones and the sex chromosome complement.[27,28] Additionally, animal studies showed that abnormal nephrogenesis seen as a consequence of intrarenal renin-angiotensin system disruption and oxidative stress in maternal dietary imbalance conditions are more evident in males.[29,30] Thus, males born to diabetic mothers seem to be a more vulnerable group for developing hypertension during childhood.

Pubertal stage and menarche status were not independent predictors of high BP in our cohort, likely because of the relatively young age of assessment. A number of studies suggested that early puberty is associated to obesity and adiposity, especially in girls, but evidence for an association of pubertal timing with other cardiometabolic outcomes as hypertension is markedly weaker.[31] In our study, a short lag between puberty onset and BP measurement probably precluded an adequate assessment of the impact of pubertal stage on children's BP.

Although often asymptomatic, hypertension is associated with cardiovascular target organ damage and changes in cardiac structure already seen in adolescents and young adults.[15,32,33] Even small differences in BP, such as those we have described in our cohort study, may have important population-health implications. In the adults, it has been suggested that every 2 mm Hg rise in SBP is associated with a 7% increased risk of mortality from ischemic heart disease and a 10% increased risk of mortality from stroke.[34] The recognition of an intergenerational transmission of cardiovascular outcomes can provide an excellent opportunity of achieving long-lasting benefits in offspring by possible intervening before birth and during the first years of life.[1]

Table 4. The Associations Between Maternal Diabetes Mellitus and Childhood Blood Pressure at the Age of 4, 7, and 10 y for the Whole Cohort and After Stratification by Sex at the Age of 10 y

Models	4 y Old		7 y Old		10 y Old		10 y Old Female		10 y Old Male	
	β	95% CI	β	95% CI	β	95% CI	β	95% CI	β	95% CI
SBP										
Unadjusted model	0.36	−0.63 to 1.35	0.69	−0.22 to 1.60	1.71	0.71 to 2.70	1.04	−0.50 to 2.58	2.24	0.95 to 3.54
Adjusted model	0.38	−0.70 to 1.45	0.042	−0.98 to 1.07	1.48	0.36 to 2.59	0.58	−1.15 to 2.31	2.21	0.76 to 3.66
DBP										
Unadjusted model	0.28	−0.67 to 1.24	0.51	−0.27 to 1.29	0.96	0.22 to 1.70	0.53	−0.59 to 1.63	1.25	0.26 to 2.23
Adjusted model	−0.30	−1.36 to 0.76	0.22	−0.66 to 1.09	0.88	0.05 to 1.71	0.08	−1.18 to 1.35	1.43	0.33 to 2.54

Data presented as adjusted coefficient (β) and 95% CI. Adjusted model: linear regression model adjusted for maternal age at delivery, prepregnancy body mass index, education level, smoking habits, gestational hypertensive disorders, and prepregnancy history of hypertension.
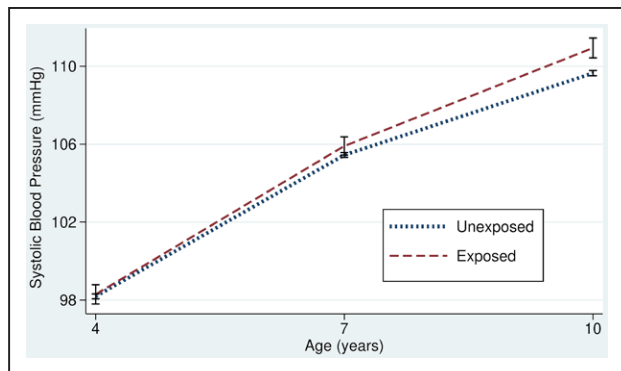
Figure 2. Offspring systolic blood pressure trajectories by maternal diabetes mellitus status from 4 to 10 y.

In fact, our work suggests that the perinatal and early childhood periods may represent windows of opportunity for targeted interventions aimed at preventing the development of high BP manifesting in late childhood. Interventions to decrease child's obesity and overweight during childhood may have the potential to diminish the cardiovascular disease burden associated with maternal diabetes mellitus exposure. Therefore, understanding to what extent could the adverse effects of maternal diabetes mellitus be mitigated by an appropriate management of children's BMI in this high-risk group is of paramount clinical importance and should be a matter for further works.

Strengths and Limitations

One of the main strengths of our study is the longitudinal nature of the data, allowing us to explore age's effect on BP and, using mixed-effects linear models, to describe BP trajectories in offspring of diabetic mothers. Additionally, cohort size allowed us to study the to date largest number of diabetic mother-offspring pairs from early life until childhood.[9]

A limitation of the present study is that we did not address the direct impact of metabolic control of diabetes mellitus during pregnancy on offspring outcomes or the effect of therapeutic options. Additionally, mother lipid profile was not analytically characterized in this cohort. Prospective follow-up of our population is now underway as it will be interesting to study more long-term effects of maternal diabetes mellitus exposure, including after puberty, when differences are likely to be more pronounced.[6,8] Although higher BP is positively associated with parameters of arterial stiffness,[35,36] ideally, BP assessment would be enhanced by a 24-hour ambulatory BP monitoring and pulse wave velocity analysis for a more detailed study of BP profile and direct evaluation of arterial stiffness. Finally, consistent with all general population birth cohorts, our study is affected by cohort attrition and missing data. Full information maximum likelihood approach was used to compensate for missing data in the matrix sampling. The process works by estimating a likelihood function for each individual based on the variables that are present so that all the available data are used.

Perspectives

Our results provide further evidence that maternal diabetes mellitus is associated with high BP late in childhood, demonstrating a significant role of child's BMI and, to a lesser extent, gestational age, type of birth, and birth weight in mediating this association. The predominant effect of maternal diabetes mellitus in male offspring suggests sex differences in the complex mechanisms of BP programing, which are independent of sexual maturity. Further studies are needed to understand whether the identification of these vulnerable risk groups and the knowledge of mediation effects could permit more effective risk reduction via earlier, age-appropriate prevention, and intervention strategies.

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Novelty and Significance

What Is New?

- Longitudinal analysis showed an accelerated systolic blood pressure (BP) growth on maternal diabetes mellitus offspring in the first decade of life.
- Child's body mass index mediates the association between maternal diabetes mellitus and childhood BP.
- Males born to diabetic mothers are more prone for developing hypertension during childhood.

What Is Relevant?

- This is the largest prospective birth cohort study assessing cardiovascular outcomes in children of diabetic mothers.
- Our findings suggest that exposure to maternal diabetes mellitus in utero accelerates BP growth in childhood and, therefore, might be an important risk factor for cardiovascular health of offspring.

- It takes almost a decade to observe the effect of maternal diabetes mellitus exposure on offspring BP, and it seems to be sooner in boys.

Summary

Our results provide further evidence that maternal diabetes mellitus is associated with high BP late in childhood, demonstrating a significant role of child's body mass index and, to a lesser extent, gestational age, type of birth, and birth weight in mediating this association.