Original Article

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The impact of maternal hyperglycaemia first detected in pregnancy on offspring blood pressure in Soweto, South Africa

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Background: The long-term consequences for offspring born to mothers with hyperglycaemia first detected in pregnancy (HFDP) are not yet well understood and its influence on childhood blood pressure has not previously been assessed in sub-Saharan Africa.

Objective: The objective of this study was to evaluate the association between maternal HFDP and offspring blood pressure in 3 to 6-year-old children in Soweto, South Africa.

Methods: Oscillometric blood pressure was measured in 189 children born to mothers with and without HFDP diagnosed by 75 g 2-h oral glucose tolerance test. The 2017 AAP Guidelines for Childhood Hypertension were used as reference standard, and the term 'elevated blood pressure' referred to blood pressure readings above the 90th percentile for age, height and sex. The association between maternal HFDP and offspring blood pressure was analysed using multivariable linear regression.

Results: Elevated blood pressure was identified in 49.7% of children. Maternal hyperglycaemia was not associated with offspring blood pressure when adjusted for offspring age, height and sex (SBP: 0.199, $P = 0.888$; DBP: 0.185, $P = 0.837$) or after multivariable adjustment (SBP: −0.286, $P = 0.854$; DBP: 0.215, $P = 0.833$). In the full model for SBP, child BMI age z-score was a significant predictor of blood pressure at 3–6years (1.916, $P = 0.008$).

Conclusion: Although maternal HFDP was not associated with childhood blood pressure at 3–6 years, the prevalence of elevated blood pressure in this group of preschool-aged children is concerning. Future research is needed to further evaluate childhood obesity as a modifiable risk factor to reduce hypertension and cardiovascular risk in an African setting.

Keywords: blood pressure, childhood obesity, gestational diabetes mellitus, hyperglycaemia in pregnancy, paediatric hypertension, South Africa

Abbreviations: AAP, American Academy of Pediatrics; ANOVA, analysis of variance; CHBAH, Chris Hani Baragwaneth Academic Hospital; GDM, gestational diabetes mellitus; HAPO, hyperglycemia and Adverse Pregnancy Outcome (study); HFDP, hyperglycemia first detected in pregnancy; IADPSG, International Association of Diabetes and Pregnancy Study Groups; LMIC, low and middle-income countries; OGTT, oral glucose tolerance test; SES, socioeconomic status; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus

INTRODUCTION

Gestational diabetes mellitus (GDM) is a condition of glucose intolerance with first onset during pregnancy and is associated with increased risk of cardiovascular disease and various metabolic conditions for both mother and child [1]. In recent years, GDM has increasingly become a global burden, as approximately 16.2% of all live births in 2017 were hyperglycaemic pregnancies [2]. In 2009, the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) study suggested that even blood glucose levels below GDM diagnostic criteria used at the time can be linked to adverse neonatal outcomes [3]. This gave rise to the term hyperglycaemia first detected in pregnancy (HFDP), to include lower degrees of glucose intolerance in pregnancy, according to the International Association of the Diabetes and Pregnancy Study Groups (IADPSG) diagnostic criteria. The long-term consequences for offspring born to mothers with HFDP are not yet well understood, especially in low and middle-income countries (LMIC).

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In South Africa, the occurrence of paediatric hypertension is increasing and of concern. A retrospective study indicated that in 1995, the prevalence of high blood pressure among 5-year-old children was estimated at 32.2% [4], while in 2020, the reported prevalence of high blood pressure among primary school-aged children was 42.8% [5]. Moreover, it has been estimated that 60% of South African children with high blood pressure maintain this status into adolescence and beyond [6], contributing to the highest prevalence of hypertension (78%) in people aged 50 years or older globally [7]. Paediatric hypertension can partially be attributed to genetic factors; however, the recent increase in paediatric hypertension is also thought to stem from in-utero environments and early-life factors [4], including maternal parity, maternal blood pressure, male sex, preterm birth, small for gestational age at birth and increased weight in childhood [1,4,8–10].

Previous research conducted in high income countries established a link between maternal hyperglycaemia in pregnancy and offspring blood pressure [9–12]; however, the exact physiological mechanisms through which the interaction occurs are largely still unknown. This has led to some controversy surrounding results, especially when associations between maternal HFDP and offspring blood pressure can be attributed to important confounders [1,13], such as childhood adiposity. Research into the effect of maternal HFDP and offspring blood pressure in preschool-age children is sparse, despite findings that suggest that elevated blood pressure in adolescents can be tracked from childhood [6]. The consequences of increasing levels of maternal HFDP, and the impact of introducing lower IADPSG criteria, need to be better understood so that intergenerational cycles of risk can be prevented. To the best of our knowledge, these associations have not yet been investigated in South Africa. Thus, the objective of this study is to evaluate the association between HFDP and offspring blood pressure in 3 to 6-year-old children in Soweto, South Africa.

MATERIALS AND METHODS

Study population and design

The setting of the study was the Chris Hani Baragwaneth Academic Hospital (CHBAH) located in urban Soweto, South Africa. The study utilized a cross-sectional analysis, in which maternal hyperglycaemic status during pregnancy was identified retrospectively using hospital records and offspring blood pressure was measured 3 –6 following delivery. The study population consisted of children born to mothers in the Soweto-area for whom the hyperglycaemic status during pregnancy was known.

The exposed group was chosen first and consisted of children whose mothers attended the Gestational Endocrine Clinic of CHBAH between 2014 and 2016 for the management of hyperglycaemia detected in pregnancy. The majority of these women underwent testing for HFDP on the basis of selective risk-factor based screening, while a subgroup was referred to CHBAH's Gestational Endocrine Clinic as a result of universal screening being performed by a research study [14]. The HFDP-unexposed group consisted of children whose mothers underwent screening for HFDP during their pregnancy as part of the universal screening study [14] and tested negative for HFDP. The enrolment of children to the HFDP-unexposed group was done on the basis of birth year similar to the exposed group, ensuring a relatively equal distribution of age between HFDP-exposed and unexposed. A description of this study population has been published elsewhere [14].

Between March and October of 2019, blood pressure was measured in 3 to 6-year-old children born to mothers with and without HFDP. To be eligible for the study, participants had to be 3—6 years of age; have the ability to return to the unit for the blood pressure measurement appointment; and have the ability for their mother/guardian to give informed consent and fill in the questionnaires. Children were excluded from the study if they had a diagnosis of a major congenital disorder or congenital cardiovascular malformations; a childhood diagnosis of Type 1 diabetes mellitus (T1DM) or Type 2 diabetes mellitus (T2DM); if their mother had been diagnosed with pancreatic diabetes, steroid-induced diabetes, or pre-gestational diabetes (T1DM or T2DM); if a child's mother/guardian was unable to be contacted after three attempts; or if they were a twin. A flowchart of the participant selection process is shown in Fig. 1.

Maternal hyperglycaemic status

The hyperglycaemic status of the mothers was identified retrospectively using the 2010 IADPSG criteria for hyperglycaemia in pregnancy at the time of diagnosis [2]. Following a 75-g 2-h oral glucose tolerance test (OGTT), pregnant women were classified as HFDP if one or more of the following criteria were fulfilled: a fasting plasma glucose level at least 5.1 mmol/l, a 1-h plasma glucose level at least 10 mmol/l or a 2-h plasma glucose level at least 8.5 mmol/l.

The term 'HFDP' is used to encompass the varying degrees of glucose intolerance experienced by some women in pregnancy and can be further differentiated into cases of GDM and more severe cases of hyperglycaemia, the latter of which are likely undetected cases of pre-gestational diabetes. More severe cases of hyperglycaemia can be identified using fasting plasma glucose levels at least 7.0 mmol/l or 2-h plasma glucose levels at least 11.1 mmol/l [2]. However, as the sample size was too small to conduct sub-group analyses using these further differentiated groups, exposure was only evaluated as maternal HFDP diagnosis in this study. The diagnosis of maternal hyperglycaemic status as used in the present study is illustrated in Fig. 2.

Offspring blood pressure

Evaluating blood pressure measurements in children is difficult due to inter-individual variability among children, especially in ages 3—6 where growth and development occur at different stages [15]. Therefore, blood pressure measurements were obtained through a standardized procedure using an automated oscillometric blood pressure monitor (Dinamap, Hatfield, UK). Prior to obtaining blood pressure measurements, children's mid-upper arm circumference was measured to ensure that the appropriate paediatric cuff size was used. Trained research staff took three blood pressure measurements, 1 min apart, while the child had been seated for at least 5 min in the presence of their

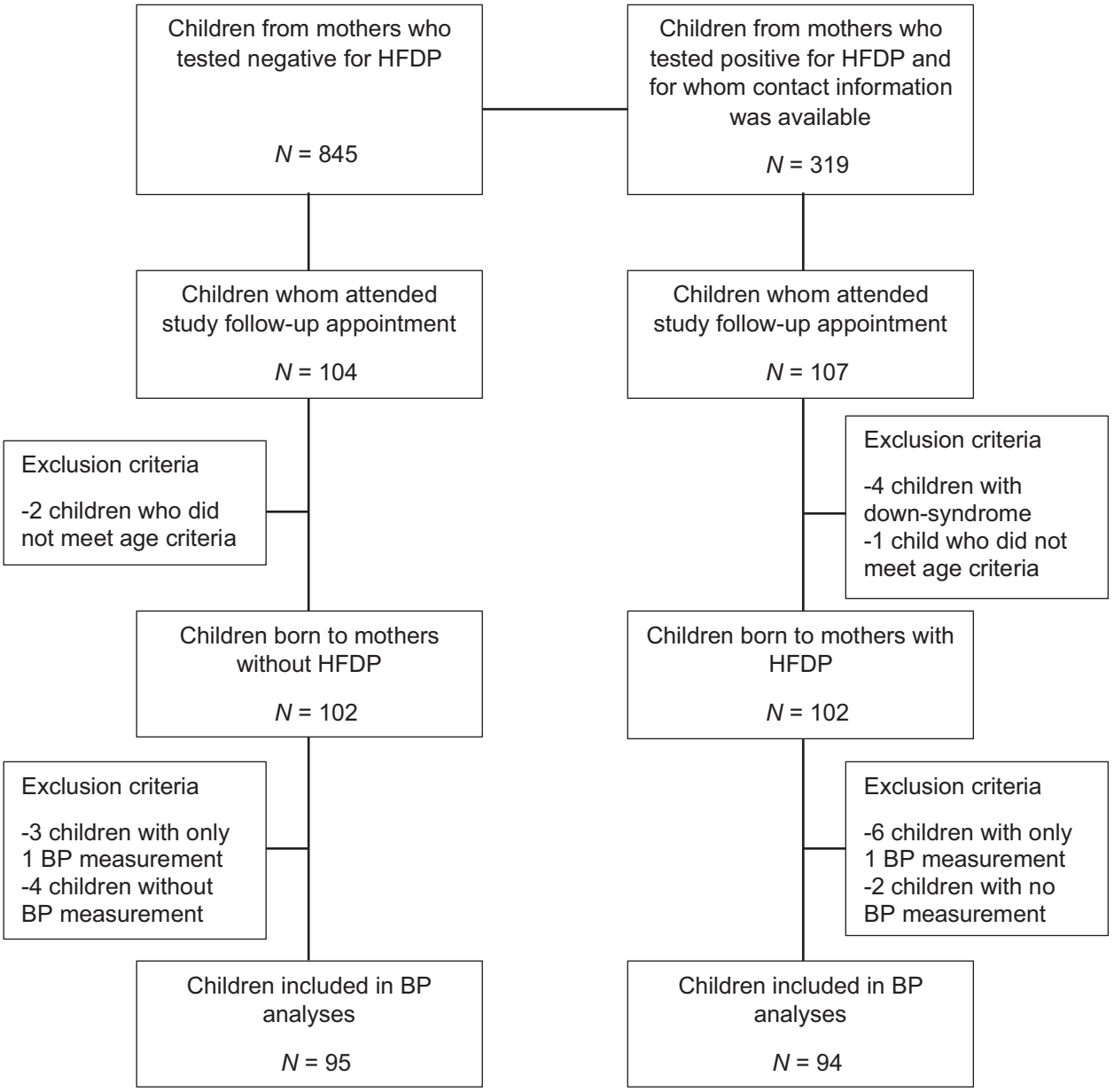

FIGURE 1 Flowchart of participant selection. HFDP, hyperglycaemia first detected in pregnancy.

mother/guardian. To help the child relax for an accurate reading, there were child-friendlyposters, opportunities for drawing and a stuffed toy in the room that they could play with prior to starting the blood pressure protocol. In addition, the mother/guardian's blood pressure was taken first, involving the child by allowing them to press the button, if they wish. The first blood pressure measurement was excluded from analysis to reduce potential white-coat effect [measurement 1 was significantly higher than measurements 2 and 3 ($P < 0.0001$) as determined through a repeated measures one-way ANOVA test]. Participants with only one blood pressure measurement were, thus, excluded from analysis for this reason ($n = 9$). In children with two blood measurements, only the second blood pressure measurement was used (n = 2), and in children with three blood pressure measurements, an average was taken of the second and third measurement. Blood pressure measurements were unable to be obtained from six participants included in the study due to excessive movement, participants becoming distressed or asking for the measurement to be discontinued.

Offspring blood pressure was recorded as a continuous variable, and subsequently age, sex and height-specific blood pressure categories were obtained for each participant according to the 2017 American Academy of Pediatrics (AAP) Hypertension Guidelines [16] using the online calculator developed in partnership with the AAP [17,18]. In the present study, the term 'elevated blood pressure' is used to refer to blood pressure measurements above the 90th percentile for age, height and sex, and children were

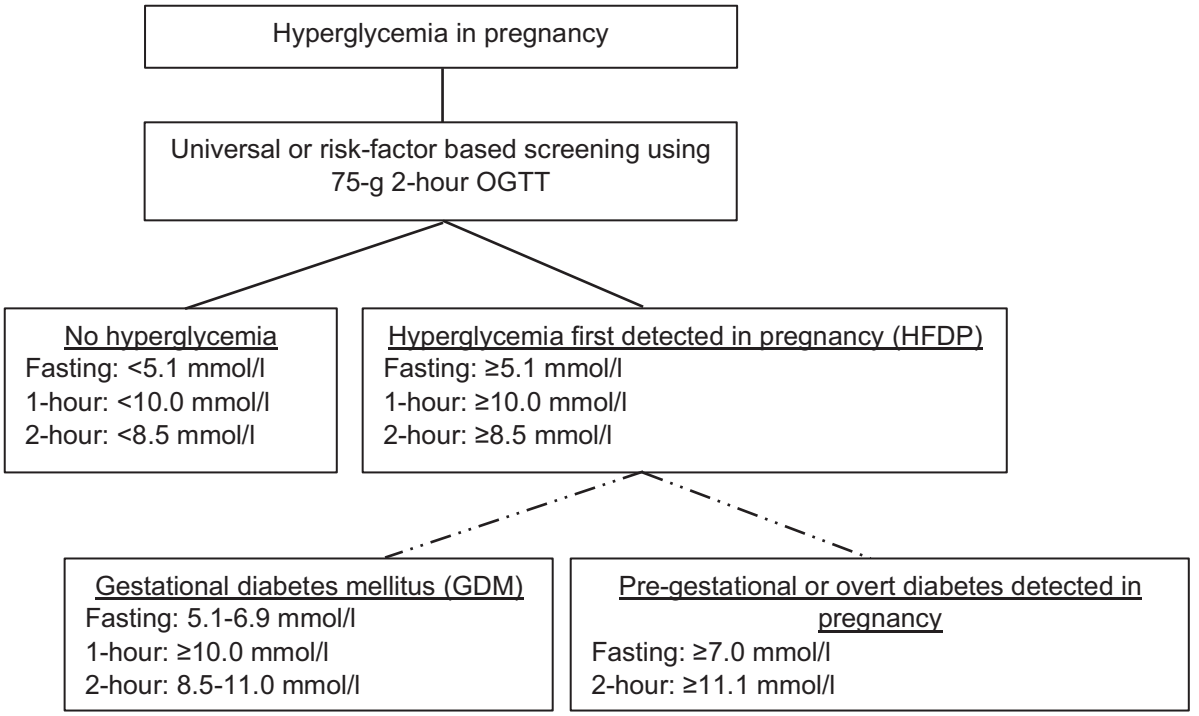

FIGURE 2 Diagnosis of maternal hyperglycaemic status using 2010 International Association of the Diabetes and Pregnancy Study Groups criteria. OGTT, oral glucose tolerance test.

additionally categorized as being '>90th percentile but <95th percentile' or '>95th percentile'. Clinical terminology as defined in the 2017 AAP guidelines (such as Stage 1 or Stage 2 hypertension) was avoided, as the classification reported in this study is not equivalent to a clinical diagnosis, for which blood pressure measurements have to be obtained on three separate occasions and confirmed using the auscultatory method [16].

Data sources for other covariates

Data for the covariates included in the study were sourced from maternal medical records from the Gestational Endocrine Clinic at CHBAH, patient-held 'Road to Health' cards used to monitor childhood health in South Africa, an existing research dataset for the HFDP-unexposed group [14] and/or collected during this study's blood pressure measurement visit. Some early life factors and maternal obstetric factors, including mode of delivery, preterm birth (< 37 completed weeks), birthweight, macrosomia, maternal age at delivery, parity and pregnancy BMI were obtained from existing medical records. Pregnancy BMI was obtained during the mother's first visit at the gestational Endocrine Clinic at CHBAH. Small and large for gestational age were calculated using the 10th and 90th percentile for birthweight, respectively, using the Intergrowth 21 standards [19], which were also used to determine birthweight zscore adjusted for gestational age.

At the time of the blood pressure measurement visit, the participant's mothers/guardians were asked to complete questionnaires for maternal and offspring characteristics at 3—6 years, including maternal: education, marital status, smoking status, HIV status and hypertension status during the index pregnancy; and offspring: age, ethnicity and household socioeconomic status (SES). In the present study, childrenwere nottested forHIV, butnone of the childrenhad known HIV or were taking anti-HIV medication (which is known to increase blood pressure) [20]. The household SES was based on a standardized household asset score that was calculated by adding the number of household items found in their home from a set list of items. The household asset score was comprised of the presence of electricity, refrigerator, stove, vacuum cleaner, washing machine, television, cable television, DVD player, automobile, landline telephone, cell phone, computer and internet access. Anthropometric data were also obtained during this study's blood pressure measurement visit by a trained nurse or research assistant according to WHO standardized procedures [21]. Height was measured to the nearest 0.1 cm, using a fixed and mounted Holtain stadiometer (Crymuch, UK) and weight was measured to the nearest 0.1 kg, using a SECA digital scale (Hamburg, Germany). The average of three measurements was used for both height and weight, and the mean height and weight per participant were used to calculate BMI. BMI age z-scores were calculated according to WHO growth standards [22]. Maternal height, weight and blood pressure measurements were also obtained during this study's blood pressure measurement visit and were used to determine current maternal BMI and hypertensive status.

Statistical analysis

Data were entered into the electronic database REDCap (Vanderbilt University, Nashville, Tennessee, USA) upon collection, and managed in Excel (Microsoft, Redmond, Washington, USA) prior to data analysis using SPSS (IBM, Chicago, Illinois, USA). Continuous variables are presented as mean (standard deviation) or median (interquartile range), whereas categorical variables are presented as

number and percentage per category. Differences in blood pressure values between the HFDP-exposed and unexposed groups were tested using a Student's t-test or Mann–Whitney *U* test, and differences in blood pressure categories were tested using a chi-squared test. Fischer's exact test was used if more than 20% of cells have expected frequencies less than 5.

The association between maternal HFDP and offspring SBP and DBP was analysed using multivariable linear regression. Model building was determined *a priori* on the basis of existing literature (a theoretical framework for the covariates included in the model can be found in Supplemental Digital Content 1, http://links.lww.com/HJH/B883). Model 1 contained only the variable for HFDP; model 2 contained HFDP, and introduced offspring factors related to blood pressure, namely sex, age and height; model 3 introduced the following maternal obstetric factors: parity at the time of index pregnancy, HIV status at the time of index pregnancy, hypertension in pregnancy and pregnancy BMI; model 4 additionally introduced the following neonatal factors: mode of delivery, born preterm and birthweight z-score; and model 5 introduced the following remaining factors at 3–6 years following birth: child BMI age z-score, exposure to maternal smoke, household SES and current maternal hypertensive status. After checking for its impact on the model, the variable for hypertension in pregnancy was removed from model 5 so that current maternal hypertensive status could be introduced without raising issues of multicollinearity. Theoretically, the variable for current maternal hypertension combines the risk from hypertension in pregnancy with environmental risks shared between mother and child in early life.

RESULTS

Maternal and offspring characteristics

A total of 204 children were included in the study, of which 102 (50.0%) were born to mothers with HFDP (Table 1). HFDP-exposed children had a higher rate of preterm birth (< 37 weeks) compared with children not exposed to HFDP (21.6 vs. 12.7%). Children born to mothers with HFDP had a higher mean birthweight *z*-scores than children born to mothers without HFDP (0.29 vs. −0.14), and thus were also more likely to be born large for gestational age (21.2 vs. 10.8%). At 3–6 years of age, the median BMI age z-score for

TABLE 1. Maternal and offspring characteristics

Category	Covariates	Total	n	HFDP	n	HFDP-unexposed	n
	Sample size totals		204		102		102
Neonatal factors	Mode of delivery, caesarean	128 (63.7%)	201	68 (68.7%)	99	60 (58.8%)	102
	Preterm (<37 weeks)	35 (17.2%)	204	22 (21.6%)	102	13 (12.7%)	102
	Birthweight (gestational age z-score)	0.07 (1.15)	201	0.29 (1.11)	99	—0.14 (1.16)	102
	Small for gestational age, < 10th percentile	26 (12.9%)	201	8 (8.1%)	99	18 (17.6%)	102
	Large for gestational age, >90th percentile	32 (15.9%)	201	21 (21.2%)	99	11 (10.8%)	102
	Macrosomia	10 (4.9%)	201	5 (5.1%)	99	5 (4.9%)	102
Offspring characteristics at 3–6 years	Age (years)[a]	3.47 (1.06)	204	3.45 (1.08)	102	3.48 (1.03)	102
	Sex, male	105 (51.5%)	204	56 (54.9%)	102	49 (48.0%)	102
	Ethnicity		204		102		102
	Black	197 (96.5%)		97 (95.1%)		100 (98.0%)	
	Coloured	5 (2.5%)		3 (2.9%)		2 (2.0%)	
	Indian	2 (1.0%)		2 (2.0%)		0 (0.0%)	
	Socioeconomic status	8.33 (2.15)	204	8.02 (2.20)	102	8.64 (2.06)	102
	BMI/age z-score[a]	0.34 (1.34)	204	0.40 (1.22)	102	0.22 (1.37)	102
	Exposure to maternal smoke	20 (9.8%)	204	11 (10.8%)	102	9 (88.2%)	102
Maternal obstetric factors	Age at time of delivery	31.75 (5.87)	204	33.00 (5.61)	102	30.49 (5.89)	102
	Pregnancy BMI[a]	32.32 (9.81)	196	35.05 (9.28)	94	29.43 (8.30)	102
	Parity at time of pregnancy[a]	1.00 (1.00)	204	1.00 (1.00)	102	1.00 (2.00)	102
	HIV in pregnancy	37 (18.1%)	204	17 (16.7%)	102	20 (19.6%)	102
	Hypertension in pregnancy	49 (23.9%)	204	27 (26.5%)	102	22 (21.6%)	102
	Pregnancy-induced hypertension	19 (9.3%)	204	10 (9.8%)	102	9 (8.8%)	102
	Smoking during pregnancy	6 (3.0%)	203	3 (3.0%)	101	3 (2.9%)	102
Maternal factors 3–6 years after delivery	Current hypertension	61 (30.3%)	201	37 (37.0%)	100	24 (23.8%)	101
	Current BMI[a]	31.37 (9.51)	193	33.15 (9.43)	95	29.38 (9.44)	98
	Educational level		202		101		101
	None/primary school	2 (1.0%)		2 (2.0%)		0 (0.0%)	
	Secondary school	139 (68.8%)		66 (65.3%)		73 (72.2%)	
	Professional or technical training	55 (27.2%)		31 (30.7%)		24 (23.8%)	
	University	6 (3.0%)		2 (2.0%)		4 (4.0%)	
	Marital status		204		102		102
	Single	142 (69.5%)		59 (57.8%)		83 (81.3%)	
	Married	55 (27.0%)		38 (37.3%)		17 (16.7%)	
	Divorced	2 (1.0%)		1 (1.0%)		1 (1.0%)	
	Other (partner)	5 (2.5%)		4 (3.9%)		1 (1.0%)	

Covariates are presented as mean (SD) or [a]median (IQR) or number (%) per category.

TABLE 2. Differences in blood pressure between HFDP-exposed and HFDP-unexposed children

Outcome	Total	HFDP	HFDP-unexposed	P
Sample size	189	94	95	
SBP	100.63 (9.47)	100.76 (9.82)	100.52 (9.15)	0.862
DBP[a]	57.50 (7.00)	57.25 (6.13)	58.00 (9.00)	0.960
Blood pressure category				0.974
Normotensive	95 (50.3%)	47 (50.0%)	48 (50.5%)	
>90th-95th percentile	33 (17.5%)	17 (18.1%)	16 (16.8%)	
>95th percentile	61 (32.3%)	30 (31.9%)	31 (32.6%)	
Elevated (>90th percentile)	94 (49.7%)	47 (50.0%)	47 (49.4)	

Blood pressure values shown as mean (SD) or [a]median (IQR), and hypertensive status shown as n (%). HFDP, hyperglycaemia first detected in pregnancy.
[a]Mann∼Whitney U test performed.

participants was 0.34, indicating a slightly higher BMI age z-score than what is reported by WHO reference standards [22]. However, the distribution of BMI age z-score was comparable between HFDP-exposed and unexposed children (0.40 vs. 0.22). Other important childhood variables, including age (3.45 vs. 3.48 years) and ethnicity were similar as well (95.1% black African vs. 98.0% black African). Lastly, the SES of children born to mothers with HFDP was lower than those born to mothers without HFDP (8.03 vs. 8.63). There were no significant differences between children included in the analyses and those excluded in the analyses, as a result of missing or having only one blood pressure measurement, in terms of age, sex, ethnicity or maternal hyperglycaemic status.

Mothers with HFDP were older (33 vs. 30.49 years) and had a higher pregnancy BMI (35.05 vs. 29.43 kg/m^2) and current BMI (33.15 vs. 29.38 kg/m^2) compared with mothers without HFDP. Mothers with HFDP also presented with a higher rate of chronic hypertension 3–6 years following the index pregnancy (37.0 vs. 23.8%). No other relevant differences were observed.

Offspring blood pressure

There were no significant differences in SBP ($P = 0.862$) or DBP values (P = 0.960) between the HFDP-exposed and unexposed group, nor were there significant differences in blood pressure categories across percentile groups ($P = 0.915$), as summarized in Table 2. However, nearly half (49.7%) of the paediatric study population had elevated blood pressure levels (>90th percentile) and 32.3% of children had blood pressure levels suspected above the 95th percentile [18].

The association between maternal HFDP and offspring blood pressure (Table 3) was analysed for each of the five models. The association between maternal HFDP and offspring SBP was not significant in model 1 with only HFDP [β: 0.240, 95% CI: (−2.546 to 3.025), $P = 0.865$], model 2 with HFDP adjusted for offspring sex, age and height [0.199 (−2.584 to 2.982), $P = 0.888$], model 3 wherein maternal obstetric factors were introduced [−0.525 (−3.640 to 2.589), $P = 0.740$], model 4 wherein neonatal factors were introduced [−0.500 (−3.663 to 2.664), $P = 0.756$], nor in model 5 wherein HFDP was adjusted for all other covariates [−0.286 (−3.357 to 2.785), $P = 0.854$]. In the full model 5, offspring BMI age z-score [1.916 (0.501–3.330, P = 0.008] was significantly associated with offspring SBP, while offspring SES [0.669 (−0.002 to 1.340), P = 0.051] approached significance.

Similar to SBP, the association between maternal HFDP and offspring DBP was not significant in model 1 with HFDP only [0.255 (−1.502 to 2.012), $P = 0.775$], model 2 with HFDP adjusted for offspring age, sex and height [0.185 (−1.587 to 1.957), $P = 0.837$], model 3 wherein maternal obstetric factors were introduced [−0.321 (−1.669 to 2.312), $P = 0.750$], model 4 wherein neonatal factors were introduced [−0.315 (−1.692 to 2.323), $P = 0.757$], nor model 5 wherein HFDP was adjusted for all other covariates [0.215 (−1.789 to 2.220), $P = 0.833$]. None of the other covariates were significantly associated with offspring DBP.

The fit of model 5 with the variable for maternal hypertension in pregnancy was similar to the fit of model 5 with the variable for current hypertensive status ($R^2 = 0.122$ vs. $R^2 = 0.120$). Similarly, replacing current maternal hypertensive status with a variable for maternal blood pressure in its continuous form had no effect on the association between maternal HFDP and offspring blood pressure, or any other predictors of offspring blood pressure.

DISCUSSION

Our results indicate that there was no significant association between maternal HFDP and offspring blood pressure in this study population. Despite this, BMI age z-score in offspring was found to be a significant predictor of SBP in offspring. To the best of our knowledge, this is the first study to evaluate the association between maternal HFDP and offspring blood pressure in sub-Saharan Africa, despite the high prevalence of both health conditions in this setting.

Findings from previous research investigating the association between maternal hyperglycaemia in pregnancy and offspring blood pressure are controversial. Some studies reported higher mean blood pressure in children born to mothers with GDM [9–12], while other studies reported null findings [1,13]. The inconsistency in results could be influenced by varying diagnostic criteria used to detect hyperglycaemia in pregnancy [1]. Studies that observed a significant association between maternal hyperglycaemia and offspring blood pressure used a two-step GDM screening procedure combining a non-fasting glucose challenge test, which, if high, was followed by a 2-h 75 g [12] or 3-h 100-g OGTT [10]. The present study used a single-step HFDP screening, and our results are consistent with other studies that used a single-step screening [1,13,23]. In addition, the reference standards used to identify maternal hyperglycaemia may also contribute to the inconsistency in results. The 1999 WHO criteria for diabetes uses more

TABLE 3. The association between maternal HFDP and offspring blood pressure

		SBP			DBP		
Model	Covariate	Coefficient	P	95% CI	Coefficient	*P*	95% CI
1	Model with HFDP only						
	Maternal HFDP	*0.240*	*0.865*	*[−2.546, 3.025]*	*0.255*	*0.775*	*[−1.502, 2.012]*
2	HFDP + offspring sex, age and height						
	Maternal HFDP	*0.199*	*0.888*	*[−2.584, 2.982]*	*0.185*	*0.837*	*[−1.587, 1.957]*
	Child sex, male	0.532	0.714	[−2.323, 3.386]	0.909	0.325	[−0.909, 2.726]
	Child age	0.152	0.930	[−3.253, 3.556]	0.042	0.969	[−2.125, 2.210]
	Child height	0.214	0.213	[−0.124, 0.553]	0.040	0.717	[−0.176, 0.255]
3	HFDP + offspring sex, age and height + maternal obstetric factors						
	Maternal HFDP	*−0.525*	*0.740*	*[−3.640, 2.589]*	*0.321*	*0.750*	*[−1.669, 2.312]*
	Child sex, male	0.745	0.611	[−2.144, 3.635]	0.843	0.369	[−1.003, 2.690]
	Child age	0.075	0.967	[−3.444, 3.593]	0.104	0.928	[−2.145, 2.352]
	Child height	0.199	0.254	[−0.144, 0.542]	0.046	0.676	[−0.173, 0.266]
	Maternal parity at time of index pregnancy	−0.472	0.055	[−2.019, 1.074]	0.400	0.425	[−0.588, 1.389]
	Maternal HIV during pregnancy	0.860	0.658	[−2.971, 4.691]	0.089	0.943	[−2.359, 2.537]
	Maternal pregnancy BMI	0.164	0.142	[−0.055, 0.384]	−0.053	0.458	[−0.193, 0.088]
	Maternal hypertension in pregnancy	−1.039	0.554	[−4.500, 2.422]	0.214	0.849	[−1.997, 2.426]
4	HFDP + offspring sex, age and height + maternal obstetric factors + neonatal factors						
	Maternal HFDP	*−0.500*	*0.756*	*[−3.663, 2.664]*	*0.315*	*0.757*	*[−1.692, 2.323]*
	Child sex, male	0.741	0.616	[−2.171, 3.653]	0.878	0.350	[−0.970, 2.725]
	Child age	0.516	0.786	[−3.236, 4.269]	0.731	0.545	[−1.650, 3.112]
	Child height	0.150	0.425	[−0.221, 0.521]	−0.015	0.897	[−0.251, 0.220]
	Maternal parity at time of index pregnancy	−0.524	0.515	[−2.112, 1.063]	0.329	0.520	[−0.678, 1.337]
	Maternal HIV during pregnancy	0.931	0.642	[−3.018, 4.880]	0.493	0.698	[−2.013, 2.998]
	Maternal pregnancy BMI	0.149	0.199	[−0.079, 0.377]	−0.049	0.506	[−0.193, 0.096]
	Maternal hypertension in pregnancy	−0.712	0.696	[−4.296, 2.873]	0.593	0.608	[−1.682, 2.867]
	Mode of delivery, caesarean	−0.011	0.994	[−3.060, 3.037]	− 1.331	0.176	[−3.265, 0.604]
	Child born preterm	−1.026	0.599	[−4.876, 2.824]	−0.451	0.716	[−2.894, 1.992]
	Child birthweight *z*-score	0.449	0.518	[−0.920, 1.817]	0.488	0.269	[−0.380, 1.356]
5	Model with HFDP, adjusted for all other covariates						
	Maternal HFDP	*−0.286*	*0.854*	*[−3.357, 2.785]*	*0.215*	*0.833*	*[−1.789, 2.220]*
	Child sex, male	1.133	0.432	[−1.707, 3.974]	0.941	0.318	[−0.913, 2.795]
	Child age	1.530	0.395	[−0.013, 5.073]	0.841	0.474	[−1.471, 3.153]
	Child height	0.073	0.689	[−0.286, 0.432]	−0.017	0.889	[−0.251, 0.218]
	Maternal parity at time of index pregnancy	−0.205	0.796	[−1.773, 1.363]	0.435	0.403	[−0.589, 1.458]
	Maternal HIV during pregnancy	1.668	0.319	[−2.162, 5.498]	0.610	0.631	[−1.890, 3.110]
	Maternal pregnancy BMI	0.043	0.715	[−0.188, 0.273]	−0.073	0.340	[−0.224, 0.078]
	Mode of delivery, caesarean	−0.447	0.765	[−3.397, 2.503]	− 1.441	0.141	[−3.367, 0.484]
	Child born preterm	−0.381	0.842	[−4.137, 3.375]	−0.081	0.948	[−2.533, 2.371]
	Child birthweight *z*-score	0.401	0.562	[−0.961, 1.764]	0.408	0.366	[−0.481, 1.297]
	Child BMI age *z*-score	1.916	0.008	[0.501, 3.330]	0.576	0.219	[−0.347, 1.500]
	Child exposure to maternal smoke	3.691	0.119	[−0.957, 8.340]	2.651	0.086	[−0.383, 5.685]
	Child socioeconomic status	0.669	0.051	[−0.002, 1.340]	0.064	0.775	[−0.374, 0.501]
	Maternal hypertension status	1.820	0.275	[−1.458, 5.097]	0.836	0.441	[−1.303, 2.976]

Coefficients are unstandardized. $N = 189$. For SBP: model 1: constant = 100.515, R-squared = 0.000; model 2: constant = 78.847, R-squared = 0.028; model 3: constant = 76.205, R-squared = 0.041; model 4: constant = 79.944, R-squared = 0.045; model 5: constant = 79.029, R-squared = 0.122. For DBP: Model 1: constant = 58.489, R-squared = 0.000; model 2: constant = 54.043, R-squared = 0.010; model 3: constant = 54.284, R-squared = 0.016; model 4: constant = 58.667, R-squared = 0.034; model 5: constant = 57.898, R-squared = 0.061. HFDP, hyperglycaemia first detected in pregnancy.

stringent diagnostic criteria compared with the 2010 IADPSG criteria, so women diagnosed with stricter criteria likely have more severe hyperglycaemia and may also be more likely to show an association between exposure and outcome. The present study used the lower IADPSG cutoffs to identify maternal HFDP due to evidence for an impact of lower levels of maternal hyperglycaemia on offspring development [3,24]. The impact of varying degrees of hyperglycaemia in pregnancy requires further research in our setting.

The uncertainty surrounding the exact physiological mechanisms in which hyperglycaemic in-utero environments act on offspring metabolic outcomes may also contribute to the controversy surrounding results. The generally accepted theory of 'metabolic imprinting' refers to the long-term consequences for offspring that can occur as the result of changes in epigenetic programming [12,25]. Hyperglycaemic in-utero environments can cause oxidative stress that can impact foetal grown and impair placental functioning to a degree that is associated with increased cardiometabolic risk in the future [1]. However, the association between maternal hyperglycaemia in pregnancy and paediatric hypertension is expected to be influenced, at least partially, through increased childhood obesity [10]. In the present study, childhood BMI was identified as a significant predictor of childhood SBP, and removing the variable for childhood BMI from our linear models did not change the association between maternal HFDP and offspring blood pressure. This might suggest that, in our setting and at preschool age, offspring blood pressure is

largely influenced by early childhood factors, and interventions targeted at childhood obesity and other early-life factors could play an important role in breaking the cycle of risk for hypertension in South Africa. As studies have shown that maternal obesity likely impacts childhood obesity [26], interventions targeted towards preconception health and pregnancy weight management are also an important avenue to explore. Previous research has shown that offspring born from hypertensive pregnancies have an increased risk for elevated blood pressure at adolescence [27], and including a variable for hypertension in pregnancy in our models allows us to evaluate this relationship at 3–6 years of age. In the present study, hypertension in pregnancy was not significantly associated with offspring blood pressure.

The prevalence of elevated blood pressure found in this study population is concerning, as results indicate that nearly half (49.7%) of all children presented with blood pressure levels above the normotensive range. A direct comparison with the 32.2% prevalence of elevated blood pressure measured in 5-year-old children in a similar setting in 1995 by Kagura *et al.* [6] suggests an increasing trend. This rise in childhood blood pressure is supported by more recent studies performed in South Africa: Mokwatsi et al. [28] reported a 32.5% prevalence of elevated blood pressure in 6–8 year-old boys in 2015 and Matjuda et al. [5] reported a 42.8% prevalence of elevated blood pressure in 6–9 year-old children in 2020. Moreover, a recent meta-analysis has estimated that childhood hypertension has increased by 75% globally between 2000 and 2015 [29]. Therefore, although this study was not designed as a clinical prevalence study and it used blood pressure measurements from only one occasion, our findings suggest a worrying rate of paediatric elevated blood pressure that supports findings from other relevant studies.

Although paediatric hypertension is partly attributable to genetic factors, the recent increase in elevated blood pressure may be the consequence of a change in early-life environment [4]. In South Africa, rapid urbanization has led to changes in SES and has increased modifiable risk factors known to contribute to hypertension, including the double burden of malnutrition (increased consumption of energy-dense and high sodium foods with low-nutrient value), alongside sedentary behaviour, and increasing obesity [4]. In the present study, SES of the child was nearing significance in the full model, indicating that these trends are transmitted across generations and may be visible even in children between 3 and 6 years of age.

Despite the importance of our results, this study comes with several limitations that provide opportunities for future research. Previous studies that found a significant association between maternal hyperglycaemia in pregnancy and offspring blood pressure had a greater sample size that allowed for the detection of an effect size between 0.2 and 0.4 [9,10,12], while the effect size identified by this study was much lower (0.027 at 5% significance level with 80% power). We experienced difficulty tracing women from hospital records 3–6 years later. A greater sample size may have increased our ability to detect significance of this smaller effect; however, the clinical significance of such a small difference between groups is unclear. Another limitation was the inability to measure all suspected confounders and risk factors for paediatric hypertension, including maternal pre-pregnancy weight, maternal gestational weight gain and offspring weight gain through infancy, which could be done in a longitudinal prospective study. Furthermore, the AAP reference standards used to calculate hypertension percentiles may not be entirely generalizable to the Soweto-based study population. There are, however, no validated and widely accepted references for South African children that could be used otherwise. Lastly, clinical guidelines recommend blood pressure measurements to be obtained through auscultation on three separate occasions before a hypertensive diagnosis can be determined in children [16], which may be less feasible in low-resource settings in low- and middle-income countries. As such, although we are confident in our results, our findings do not reflect clinical prevalence rates. It is crucial for future research that South Africa joins ongoing work to create international blood pressure references, measurement guidelines and appropriate cut-points for defining hypertension, particularly for children [4].

In conclusion, although this study found no statistically significant association between maternal HFDP and childhood blood pressure at 3–6 years, the high prevalence of elevated blood pressure in this group of preschool-aged children is concerning and illustrates the need for improved screening and early-life interventions to detect and prevent paediatric elevated blood pressure. Interventions to reduce childhood obesity from a young age hold potential to decrease the cycle of hypertension and cardiovascular risk in an African setting.

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Conflicts of interest

The authors have no conflict of interest to declare.

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