Maternal and Child Health Journal (2022) 26:1328–1338
https://doi.org/10.1007/s10995-021-03331-z

Cognitive and Motor Development in 3- to 6-Year-Old Children Born to Mothers with Hyperglycaemia First Detected in Pregnancy in an Urban African Population

L. M. Soepnel[1,2] · V. Nicolaou[2] · C. E. Draper[2] · N. S. Levitt[3] · K. Klipstein-Grobusch[1,4] · S. A. Norris[2,5]

Accepted: 25 November 2021 / Published online: 8 January 2022

Abstract

Objectives Hyperglycaemia first detected in pregnancy (HFDP), on the rise in urban sub-Saharan Africa (SSA), may negatively impact foetal neurodevelopment, with potential long-term cognitive consequences for the child. Data on this association from SSA is lacking, and we aimed to investigate the association in 3- to 6-year-old children in Soweto, South Africa.

Methods In this comparative study, we compared cognitive skills measured with the Herbst Early Childhood Development Criteria test in 95 children born to mothers with HFDP and 99 participants unexposed to maternal HFDP. Fine and gross motor skills were secondary outcomes. Ordinal regression analysis with known confounders was performed for children born at-term.

Results Of children exposed to HFDP born at-term, 24.3% scored 'high' and 25.7% scored 'low' in the cognitive subsection of the test, as opposed to 37.7% and 12.9% in the HFDP-unexposed group, respectively. In ordinal regression, exposed participants had a significantly lower odds of scoring in a higher cognitive category when adjusting for maternal confounders and socio-economic status (OR 0.33, 95% CI 0.15–0.74, p = 0.007). No difference was found in gross motor development between the two groups; differences in fine motor development were attenuated after adjustment for maternal pregnancy factors and household socioeconomic status (OR 0.62, 95% CI 0.28–1.37, p = 0.239).

Conclusions for Practice Exposure to HFDP was negatively associated with cognitive development at preschool age. Optimising maternal (preconception) health and early childhood cognitive stimulation could help more children reach their developmental potential.

Keywords Hyperglycaemia in pregnancy · Gestational diabetes · Cognitive development · Early childhood development · Sub-Saharan Africa

Significance Statement

What is already known? Hyperglycaemia first detected in pregnancy (HFDP) may negatively impact offspring cognitive and motor development. Alongside the global rise in obesity and non-communicable diseases, the rate of HFDP is increasing in urban sub-Saharan Africa, amidst existing risk factors for poor cognitive development.

What this study adds? Exposure to HFDP was associated with poorer cognitive score, even after adjustment for confounders. Preschool attendance, socioeconomic household score, and maternal HIV status were predictors of cognitive

✉ L. M. Soepnel
Larske.soepnel@gmail.com

1 Julius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Stratenum 6.131, P.O Box 85500, 3508 GA Utrecht, The Netherlands

2 SAMRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

3 Chronic Disease Initiative for Africa, Department of Medicine, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa

4 Division of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa

5 Global Health Research Institute, School of Human Development and Health, University of Southampton, Southampton, UK

performance. This highlights maternal (preconception) health and early childhood stimulation as two avenues for improving childhood development in sub-Saharan Africa.

Introduction

Worldwide, an estimated 219 to 279 million children do not reach their developmental potential, and a large proportion of these children are in sub-Saharan Africa (SSA) (Grantham-McGregor et al., 2007). Cognitive setbacks at preschool age (3–6 years) can have lasting consequences, from poorer school performance to lower future incomes (Black et al., 2017). To date, however, evidence from sub-Saharan Africa is limited, indicated by a recent scoping review noting that only 30% of sub-Saharan African countries were represented by available studies on factors impacting childhood cognitive and motor development (French et al., 2020). Risk factors for poorer cognitive development often co-occur, and include childhood malnutrition, disease exposure, lack of cognitive stimulation, and other early environmental exposures, including exposures during pregnancy (Walker et al., 2007).

Due to epidemiological and nutritional transitions, low- and middle-income countries (LMICs) with such risk factors for poorer child development are also increasingly contending with maternal metabolic conditions, such as hyperglycaemia first detected in pregnancy (HFDP) (Macaulay et al., 2018; Steyn & Mchiza, 2014). HFDP includes both the milder gestational diabetes and more severe 'overt' diabetes first detected in pregnancy, but not diabetes diagnosed prior to pregnancy (pre-gestational diabetes) (World Health Organisation, 2013). The consequences of HFDP are increasingly recognised to extend past the immediate pregnancy period for both women and their children (Koning et al., 2016).

Exposure to HFDP has been suggested to adversely impact childhood cognitive and motor development, through altered brain structure and/or function due to neuroinflammation, altered cell differentiation, and epigenetic modifications (Márquez-Valadez et al., 2018). Additionally, neonatal complications associated with HFDP, such as hypoglycaemia, can play a role (Adane et al., 2018). However, existing epidemiological studies of this association in high-income countries (HICs) have found contradictory evidence (Clausen et al., 2013; Fraser et al., 2012; Silverman et al., 1998), and the heterogeneity of study designs and findings was confirmed in two recent systematic reviews on cognitive and psychomotor development, although both authors suggest that larger studies tended to show a more significant effect of hyperglycaemia on cognitive development (Adane et al., 2016; Robles et al., 2015). In addition, studies with younger participants showed a stronger association with cognitive development, which might imply that mediating environmental factors, such as cognitive stimulation, have the potential to alleviate early life vulnerabilities (Adane et al., 2016; Dionne et al., 2008).

Despite the growing prevalence of HFDP in urban SSA, we did not identify any existing studies investigating the association with early childhood cognitive development in Africa, at any age. Lower socioeconomic status has been found to compound the effect of hyperglycaemia on neurodevelopment in preschool children (Nomura et al., 2012), and urban SSA is affected by additional risk factors for poor cognitive development, including childhood stunting and socioeconomic inequalities (Ford & Stein, 2016), so the largely inconclusive findings from HICs may also not accurately represent the issue in SSA and LMICs elsewhere.

Improved understanding of this association at preschool age, a period of rapid neurodevelopment that affects the child's later performance (Lake & Chan, 2015), can help inform life-course strategies for improving child development. Our main objective was therefore to assess the association between exposure to maternal HFDP and early childhood cognitive development in 3- to 6-year old children in Soweto, South Africa. Fine and motor skill development were assessed as secondary outcomes.

Methods

Design and Setting

We conducted a comparative study from March to November 2019 at Chris Hani Baragwanath Academic Hospital (CHBAH), a large tertiary hospital servicing the urban region of Soweto, which is populated by around 1.3 million people living in both formal and informal housing. In Soweto, an estimated 42% of households are categorised as low-income, and only around 3% as high-income (Statistics South Africa, 2016). Around 38.3% of the adult population has attained a high school degree (Statistics South Africa, 2016).

Participants were 3- to 6-year-old children born to mothers managed for HFDP at a specialized endocrine clinic at CHBAH between 2014 and 2016 (HFDP-exposed group); or to mothers who attended antenatal care visits at CHBAH but tested negative for hyperglycaemia in a research setting between 2014 and 2016 (HFDP-unexposed group) (Macaulay et al., 2018). Mothers of both groups attended antenatal care at CHBAH. Participants were identified from CHBAH hospital and research records and were recruited starting from March 2019, 3 to 6 years after the index pregnancy.

HFDP, comprised of both gestational diabetes mellitus (GDM) and diabetes diagnosed in pregnancy (DIP),

was diagnosed using the 75-g 2-h oral glucose tolerance test (OGTT) with International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria (World Health Organisation, 2013), as follows: a fasting plasma glucose ≥ 5.1 mmol/L, 1-h plasma glucose ≥ 10 mmol/L, and/or 2-h plasma glucose ≥ 8.5 mmol/L, random plasma glucose ≥ 11.1 mmol/l, and/or HbA1c ≥ 6.5%.

Children were excluded in case of inability to trace their parent/guardian, inability to attend the data collection appointment (for example, due to relocation), presence of a major congenital disorder such as Down Syndrome, ages < 3 years or > 6 years old, mother's diagnosis of hyperglycaemia or diabetes other than HFDP (pre-gestational type 1 or type 2 diabetes, steroid-induced, or other pancreatic diabetes), or incomplete cognitive, fine, and gross motor sections of the assessment.

Ethical approval for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (reference number: M180317), and the study was therefore performed in accordance with the 1964 Declaration of Helsinki and its amendments. Written informed consent was obtained from the participants' parent or guardian prior to participation in the study. Any details that might disclose the identity of the participants were omitted.

Outcomes

The primary outcome of this study was cognitive development, measured using the Herbst Early Childhood Development Criteria test. Secondary outcomes were fine and gross motor skill development.

Cognitive and Motor Assessment

The Herbst Early Childhood Development Criteria test (Herbst & Huysamen, 2000) was used to assess cognitive and motor skill development. Developed in South Africa to assess cognitive and motor tasks that represent important aspects of school readiness in 3- to 6-year-old children from varying socioeconomic backgrounds, the Herbst test is specifically geared towards a culturally unbiased evaluation of cognitive and motor skill development. The test consists of 10 cognitive subsections, one fine motor subsection (including, for example, colouring within lines, cutting out a circular shape), and one gross motor subsection (including, for example, walking on heels and tiptoes, catching and throwing a ball). The complete assessment takes around 1 h to complete. Results are evaluated against age-adjusted norms based on a South African reference population of 40–72 month old children. The scales were previously found to be reliable and valid in terms of concurrent validity (correlating results to the similar Gesell Preschool Test), and correlational and experimental construct validity, as reported in more detail by Herbst and Huysamen (2000). In evaluating the test–retest reliability, the coefficients of stability were 0.93 for the cognitive and 0.85 for the motor section (Herbst & Huysamen, 2000). An alpha coefficient between 0.81 and 0.84 was previously reported (Draper et al., 2012). The tester (LS) was trained by an experienced administrator of the Herbst test (CD) and assisted by a research assistant fluent in the home language of the participant. If the participant requested the presence of the mother in the testing room, the mother was asked to join but to refrain from participating (e.g. prompting the child). The participants received a light meal and refreshment prior to the testing.

Collection of Data on Additional Variables

Information on participants' age and sex were recorded and the mother of each child completed a validated questionnaire with the help of a research assistant, providing information on: preschool attendance; presence of breastfeeding; hospitalizations in the first two years of life; maternal highest level of education; socioeconomic score based on household assets; maternal smoking and alcohol consumption during pregnancy; and maternal HIV infection.

Anthropometric measures of the child included height, measured using a Holtain mounted stadiometer (Crymych, UK), and weight, measured using an electronic SECA scale (Hamburg, Germany). Both weight and height were measured three times, recorded to the nearest 0.1 kg or cm, respectively, and the average of the three measurements was used.

For the HFDP exposed group, information on the index pregnancy, including their OGTT results, obstetric complications, birth weight, gestational age at delivery, and early neonatal complications, was obtained from hospital files from the gestational endocrine clinic. For the HFDP-unexposed group, OGTT results collected in research setting (Macaulay et al., 2018) and the child's Road to Health Card, a patient-held medical record used to monitor health from birth, were used to extract the same information. Prematurity was defined as delivery prior to 37 completed weeks gestational age. Low birth weight (LBW) was defined as birth weight < 2500 g; macrosomia was defined as birth weight > 4000 g. Early neonatal complications included prematurity, low birth weight, macrosomia, respiratory distress syndrome, ICU admission, jaundice, seizures, and hypoglycaemia.

Data Management

Data was collected and managed electronically using REDCap (Vanderbilt University, Nashville, USA) (Harris et al., 2009). HFDP-exposure was treated as a dichotomous variable (maternal HFDP diagnosis yes/no). The cognitive and

motor skill scores from the Herbst test were converted into an age-adjusted z-score using the Herbst test norm data, rounding up to 40 months for children aged 36–39.9 months, categorizing the results into very low/low (≤ − 1SD), normal (0SD), or high/very high (≥ + 1SD). BMI was calculated as the average weight divided by average height, squared (kg/m^2). Height and BMI were converted into z-scores using the WHO growth standards and references, and stunting was defined as being below − 2 from the standard median (World Health Organization, 2006). Birth weight was converted into a z-score adjusted for gestational age using the Intergrowth 21 standards (Chatfield et al., 2013). A continuous household socioeconomic status score was determined by summing the participant's current household assets. Maternal education level was categorised into having primary/secondary education vs further education (professional training or university).

Sample Size

The Herbst test has not been previously used to measure cognitive and motor outcomes in the context of a hyperglycaemic pregnancy. However, based on results from a previous intervention study using the Herbst test (Draper et al., 2012), we determined that with an HFDP-unexposed group mean cognitive score of 37 ± 4, having 100 participants in each group would require a minimum difference of − 1.59 (or, when rounded up, − 2), to detect a significant difference between two groups, which was smaller than the difference found by Draper et al. (2012).

Statistical Analysis

Data analysis was performed using STATA 13 (College Station, USA) (StataCorp, 2013). For baseline characteristics of children and their mothers, a skewness-kurtosis test was performed to test for normality. Continuous variables were described using mean and standard deviation or median and interquartile range, whereas categorical variables were described as a number and percentage. For testing of significant differences between groups per continuous outcome variable, a student's t-test or Mann–Whitney U test was used, depending on normality. Significance was assumed at a two-sided p-value of < 0.05.

Participants with missing exposure data or incomplete cognitive, fine, or gross motor subsections of the Herbst test were excluded, using a complete-case analysis. For analysis of the norm-adjusted categorical cognitive and motor outcomes, children born prematurely (before 37 weeks completed gestation, n = 34) were excluded to minimize the impact of prematurity, associated with poorer early development (Bhutta et al., 2002), on the relationship between HFDP and cognitive and motor performance. A sub-analysis of the premature vs at-term baseline characteristics and outcomes was performed.

Ordinal regression analysis was performed for norm-adjusted categorical cognitive and motor outcomes. For each model, the proportional odd's assumption was tested using a likelihood ratio test, and only interpreted if this assumption was met. Age was included in the models to additionally adjust scores for age-related differences in children < 40 months old. Models were built according to the conceptual pathways illustrated in Fig. 1, as follows: M1: exposure to HFDP; M2: M1 + age, sex, preschool attendance, not being the first-born child; M3: M2 + maternal and household factors: maternal age and BMI at pregnancy OGTT, maternal HIV infection in pregnancy, alcohol use in pregnancy maternal education, and household socioeconomic score; Additional models: M3 + potential early life intermediates (individually and simultaneously): low birth weight, having any neonatal complication; breastfeeding, hospitalisation < 2 years old, and child stunting and BMI-age z-score.

Results

Of 211 recruited participants, 9 did not meet the inclusion criteria, and 8 children did not complete any part of the Herbst test, resulting in a total of 194 participants. Additionally, three of these participants only completed the cognitive and fine motor subsection, while one participant only completed the motor subsections of the Herbst test. The standardized Cronbach-alpha coefficient for the raw subsection scores of the cognitive assessment was 0.90.

Participants exposed to HFDP had lower reported rates of (exclusive) breastfeeding (Table 1). More children in the exposed group attended preschool (82 (86.3%) vs 79 (79.8%)), although the median duration of preschool attendance was slightly lower in this group (17.6 IQR 9.2–30.1 vs 21.8 IQR 12.5–33.8). The proportion of children that were their mother's first-born was similar between the HFDP-exposed and unexposed groups, at 27 (27.3%) and 25 (26.3%), respectively.

Women with HFDP were older, had higher BMI in pregnancy, and had lower household socioeconomic status score compared to the HFDP-unexposed group, but HIV infection rates were similar between the groups. In pregnancy, 35 (18.0%) of women were HIV-positive, with 29 (85.3%) diagnosed prior to the index pregnancy, and 31 (91%) on fixed-dose combination treatment (Table 1).

Children born prematurely, who were excluded for analysis of categorical z-score outcomes (n = 34), did not have any significant differences in baseline characteristics compared to at-term participants, except having a higher rate of

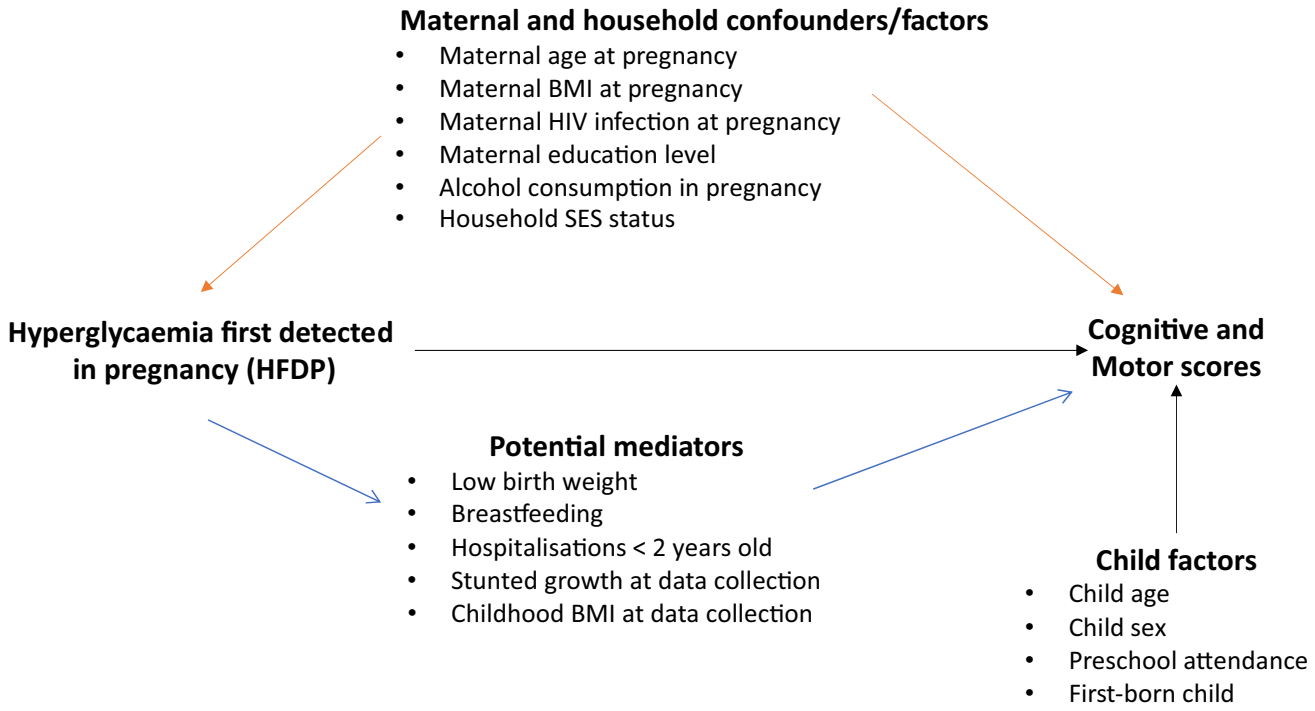

Fig. 1 Conceptual pathways between a priori determined variables included in ordinal regression analysis, including the exposure variable, outcome variables, potential confounders and mediators, and childhood factors requiring adjustment

low birth weight. Participants born prematurely and at-term did not have significantly different median cognitive (23 IQR:17–33 vs. 22.5 IQR:19–32, p = 0.979), fine (6 IQR:5–8 for both, p = 0.731), and gross motor scores (10 IQR:9–12 for both, p = 0.761).

Cognitive and Motor Assessment

Overall raw cognitive scores and most subtest percentiles were higher in the HFDP-unexposed group than in the HFDP-exposed group, but this difference was only significant for one cognitive subtest ("Directions and similarities") (Table 1). The raw fine motor score, but not gross motor score, was significantly higher in the HFDP-unexposed group participants.

Figure 2 illustrates that the proportion of participants born at-term that scored 'low' according to age-adjusted z-scores was higher in the group exposed to HFDP for cognitive, fine motor, and gross motor skills, and a higher percentage of HFDP-unexposed participants scored 'high'. The difference between groups was larger for cognitive and fine motor than for gross motor scores.

The ordinal regression results indicate that participants exposed to HFDP had a significantly lower odds of scoring in a higher cognitive category, even when adjusting for age, sex, preschool-attendance, and being first-born (OR 0.37, 95% CI 0.19–0.71, p = 0.003) (Table 2A), and when adjusting for potential maternal confounders. Maternal HIV in pregnancy (OR 0.39, 95% CI 0.16–0.98, p = 0.045) and household socioeconomic status score (OR 1.18, 95% CI 1.01–1.38, p = 0.034) were significant in the fully-adjusted model. Since only 2 cases of maternal alcohol use in pregnancy were reported, this variable was not included in analysis. When adding potential mediators to the model, none were significant associated with cognitive skills (Online Resource 1, Table S1), and they did not notably attenuate the relationship between HFDP and cognitive score, even when all included in the model simultaneously (OR HFDP = 0.36, 95% CI 0.16–0.82, p = 0.014) (Online Resource 1, Table S2).

Ordinal regression for fine motor results showed significantly lower odds of scoring in a higher z-score category in children exposed to HFDP, but this association was not significant when correcting for maternal factors in Model 3 (OR 0.62, 95% CI 0.28–1.37, p = 0.239; Table 2B). Of these maternal factors, household socioeconomic status was significantly associated with the outcome (OR 1.33, 95% CI 1.10–1.22, p = 0.001). In the model including all potential mediators, two significantly impacted the fine motor category: low birth weight (OR 0.19, 95% CI 0.05–0.73, p = 0.015) and childhood BMI (OR 0.66, 95% CI 0.45–0.97, p = 0.033). However, these did not largely change the effect size or significance level of HFDP-exposure (Online Resource 1, Table S4). No significant association was found

Table 1 Baseline characteristics and cognitive and motor score outcome of participants in the HFDP-exposed and unexposed groups

	N	HFDP-unexposed	n	HFDP-exposed
Number	–	99	–	95
Age, years (median, IQR)	99	3.5 (3.1–4.1)	95	3.5 (3.1–4.1)
Male (n, %)	99	48 (48.5)	95	49 (51.6)
Early childhood				
Received breastfeeding (n, %)	99	81 (81.8)	95	68 (71.6)
Months breastfeeding (median, IQR)	81	15 (6–24)	65	15 (5–24)
Exclusive breastfeeding (n,%)	99	76 (76.8)	95	57 (60.0)*
Hospitalized in first 2 years (n, %)	99	19 (19.2)	95	14 (14.7)
BMI at data collection	99	15.6 (14.9–17.0)	95	16.0 (15.2–16.9)
Stunted at data collection (n, %)	99	9 (9.1)	95	13 (13.7)
Attending preschool (n, %)	99	79 (79.8)	95	82 (86.3)
Obstetric factors				
OGTT (mean, SD)				
Fasting	99	4.0 (0.53)	88	6.7 (1.9)*
2-h	99	5.4 (1.2)	88	10.5 (3.6)*
Maternal age at OGTT (mean, SD)	99	30.0 (5.8)	95	32.3 (5.5)*
Maternal BMI	99	29.6 (24.8–33.0)	88	35.4 (30.8–40.2)*
HIV infection in pregnancy (n,%)	99	19 (19.2)	95	16 (16.8)
Caesarean section (n, %)	99	60 (60.6)	92	65 (70.7)
Birth weight, g (mean, SD)	99	3027 (640)	92	3032 (640)
Macrosomia (n, %)	99	5 (5.1)	92	4 (4.4)
LBW (n, %)	99	16 (16.2)	92	16 (17.4)
Prematurity (n, %)	99	13 (13.1)	95	21 (22.1)
Maternal and household characteristics				
Highest education	98		95	
1 none/primary school		0 (0)		3 (3.2)
3 secondary school		70 (71.4)		61 (64.2)
4 professional training/university		28 (28.6)		31 (32.6)
Household SES score (mean, SD)	99	8.6 (2.1)		8.0 (2.2)*
Mother is primary caregiver (n, %)	99	93 (93.9)	95	90 (94.7)
Cognitive and motor score outcome				
Cognitive score (median, IQR) (max 79)	98	24.5 (19–34)	95	22 (18–32)
Percentile cognitive subtests				
Incomplete man		69 (50–82)		69 (50–82)
Visual-motor integration		75 (56–99)		75 (56–92)
Block building		47 (19–81)		47 (19–78)
Stick figures		85.5 (56–94)		78 (56–88)
Direction and similarities		88 (62–94)		76 (50–88)*
Form concept		58 (56–81)		58 (56–81)
Colour concept		94 (89–100)		94 (84–99)
Counting concepts		53 (25–82)		44 (25–82)
Picture puzzle		78 (56–100)		72 (56–100)
Picture perception		88 (87–88)		88 (71–88)
Fine motor score (median, IQR) (max 12)	99	7 (6–8)	95	6 (5–7)*
Gross motor score (median, IQR) (max 17)	97	10 (9–13)	94	10 (9–12)

HFDP hyperglycaemia first detected in pregnancy, *IQR* interquartile range, *OGTT* oral glucose tolerance test, *LBW* low birth weight, *SES* socioeconomic status

*Significant difference between groups ($p < 0.05$)

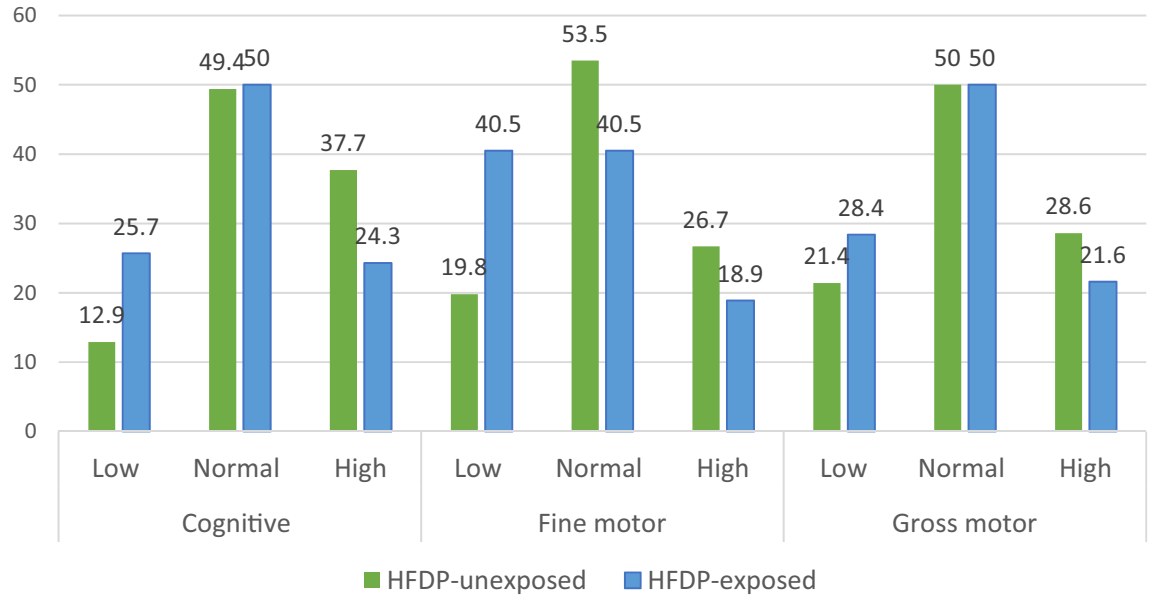

Fig. 2 Norm-based categorical results for at-term participants by exposure group for cognitive (n = 159), fine motor (n = 160) and gross motor score (n = 158) by percent (%) scoring low, normal, or high

for gross motor score category and HFDP in ordinal regression analysis (Online Resource 1, Table S5).

Discussion

In this study, preschool aged children exposed to HFDP had lower scores for cognitive and fine motor skills. The difference in cognitive skills was found to be statistically independent of maternal and pregnancy factors such as household socioeconomic status. No differences were found in gross motor skills between the two groups. To our knowledge, this study is the first to explore this relationship in Africa.

Our findings of poorer cognitive performance corroborate findings from a number of HIC studies that early neurodevelopment may be directly impacted by intrauterine exposure to maternal hyperglycaemia (Adane et al., 2016; Fraser et al., 2012; Robles et al., 2015), rather than through confounding or intermediate factors. The magnitude of the impact of HFDP is difficult to compare directly between studies due to the use of different cognitive assessment techniques and definitions of HFDP. Potential mechanisms, while far from fully understood, include the deleterious effects of increased inflammation, oxidative stress, and altered brain insulin-signalling on brain function and structure, and hyperglycaemia-induced epigenetic changes (de Sousa et al., 2018). Additionally, maternal and/or neonatal complications of HFDP (such as ketoacidosis or hypoglycaemic events) may adversely impact foetal brain development (Adane et al., 2016). HFDP-specific risks, including the level of hyperglycaemic control attained, seem to impact child neurodevelopment more than, for example, type of diabetes (pre-gestational vs detected in pregnancy) (Robles et al., 2015; Silverman et al., 1998), which needs to be further explored in our setting. Interestingly, HFDP may also have neurobehavioral consequences for offspring, such as attention-deficit disorders (Nomura et al., 2012), with one study finding an impact on inattention levels, but not cognition (Ornoy, 2005). In the present study, underlying neurobehavioral symptoms may have impacted cognitive performance, requiring further clarification.

Our results highlight the impact of early childhood environmental exposures on cognitive and fine motor aspects of school readiness, including preschool attendance (Herbst & Huysamen, 2000) and household socioeconomic status (Draper et al., 2012; Nomura et al., 2012). The impact of lower socioeconomic status has been attributed to decreased exposure to task-related tools (such as scissors and pencils), and associated factors including increased psychosocial stress or compromised nutrition and health care (Kristenson et al., 2004). The importance of environmental stimulation is further emphasized by the theory, from existing literature, that poorer development in children exposed to HFDP may not persist into later childhood in the case of adequate stimulation, as has been suggested based on evidence from later childhood and early adulthood in HICs (Adane et al., 2016; Robles et al., 2015). Though reassuring, it remains unclear whether this same "catch-up" of cognitive skills would also occur spontaneously in a setting such as ours,

Table 2 Ordinal logistic regression for (a) cognitive and (b) fine motor score category (low, normal, or high) in participants born at-term; R2 = pseudo R2

	M1: crude model		M2: M1 + age, sex, preschool, first-born		M3: M2 + maternal factors	
	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value
(A) Cognitive score						
HFDP	0.49 (0.27–0.90)	0.021	0.37 (0.19–0.71)	0.003*	0.33 (0.15–0.74)	0.007*
Child age			1.11 (1.06–1.16)	< 0.001*	1.11 (1.05–1.16)	< 0.001*
Child sex			1.28 (0.68–2.40)	0.444	1.16 (0.60–2.25)	0.669
Preschool attendance			5.23 (2.08–13.18)	< 0.001*	6.53 (2.31–18.42)	< 0.001*
First-born child			0.55 (0.28–1.10)	0.091	0.49 (0.23–1.04)	0.062
Maternal and household factors						
Maternal age at pregnancy					1.05 (0.99–1.12)	0.130
Maternal BMI at pregnancy					1.01 (0.96–1.06)	0.785
Maternal HIV in pregnancy					0.39 (0.16–0.98)	0.045*
Maternal education level					0.79 (0.38–1.67)	0.541
Household socioeconomic score					1.18 (1.01–1.38)	0.034*
	N = 159; R^2 = 0.02		N = 159; R^2 = 0.15		N = 152; R^2 = 0.18	
(B) Fine motor score						
HFDP	0.46 (0.25–0.84)	0.011*	0.44 (0.23–0.85)	0.015*	0.62 (0.28–1.37)	0.239
Child age			1.14 (1.09–1.20)	< 0.001*	1.16 (1.10–1.22)	< 0.001*
Child sex			1.36 (0.73–2.52)	0.334	1.37 (0.70–2.67)	0.359
Preschool attendance			1.89 (0.79–4.52)	0.154	1.73 (0.65–5.63)	0.276
First-born child			0.88 (0.45–1.73)	0.709	0.85 (0.41–1.79)	0.674
Maternal and household factors						
Maternal age at pregnancy					1.02 (0.96–1.08)	0.592
Maternal BMI at pregnancy					0.96 (0.91–1.01)	0.146
Maternal HIV in pregnancy					0.95 (0.39–2.32)	0.910
Maternal education level					0.67 (0.32–1.40)	0.289
Household socioeconomic score					1.33 (1.13–1.57)	0.001*
	N = 160, R^2 = 0.02		N = 160, R^2 = 0.15		N = 153, R^2 = 0.20	

HFDP hyperglycaemia first detected in pregnancy

in which children are vulnerable to socioeconomic and educational inequalities, requiring longitudinal follow-up with more robust measures of environmental stimulation. The evidence on early learning skills in South Africa suggests that children who start behind, stay behind (Spaull & Kotze, 2015).

In contrast to existing research from HICs (Ornoy et al., 2001), we did not find evidence for an impact of HFDP on gross motor development at preschool age. Previous research in South African preschool aged children has shown a high level of (unstructured) physical activity (Tomaz et al., 2020). This physical activity likely contributes to good motor skill development, even in socioeconomically disadvantaged children (Cook et al., 2019; Draper et al., 2012), which may have moderated any differences between HFDP-exposed and unexposed groups in the present study. Alternatively, a more refined tool to measure gross motor skill than the succinct subsection of the Herbst test may have been necessary to detect differences in motor performance between the two groups.

Of our participants, 18% were HIV-exposed uninfected children, and this exposure was significantly associated with poorer cognitive scores. While some studies have similarly found an impact of HIV and ARV exposure on childhood development (Van Rie et al., 2008), others have found no evidence for an adverse effect (Nozyce et al., 2014), and differences may be due to other developmental risks such as increased poverty and high caregiver burden in this population, instead. Our findings could similarly be due to residual socioeconomic confounding, or reduced breastfeeding behaviours in HIV positive mothers (West et al., 2019), since breastfeeding, while not significantly associated with cognitive performance, did attenuate the association of HIV with cognitive score (attenuated OR

0.44, 95% CI 0.17–1.19, p = 0.107) (Online Resource 1, Table S1d). This finding requires further exploration in a cohort with a greater number of HIV-exposed uninfected children.

A strength of this study was using the Herbst test, which was developed to be culturally neutral and uses a South African reference population. Our ability to adjust for a variety of known confounders in regression analysis was another strength.

However, one limitation is the retrospective nature of the pregnancy and infancy data, for which we relied on hospital records and maternal recall. For example, neonatal hypoglycaemia may have been under-recorded in the medical records and therefore inadequately adjusted for as a potential mediator. Furthermore, we were not able to include data on paternal education level or intelligence and we did not have data on maternal intelligence aside from education level, preventing us from adjusting fully for genetic and family environmental factors, possibly contributing to the lower pseudo-R^2 in our final regression models. Additionally, by excluding children unable to perform or complete the assessment, we may have introduced selection bias in favour of higher-scoring children, but, since 6 of the 8 excluded children were in the HFDP-exposed group and their baseline characteristics did not differ significantly from the included children, the direction of our findings likely would not have been altered. Another limitation is the fact that the age of participants < 40 months was rounded up for the Herbst test norms, possibly affecting the reliability of the categorization into 'low', 'normal', or 'high' scores for these younger children. However, ages were similar between the exposure groups and we additionally adjusted for age in the ordinal regression models. The Herbst test also does not test all aspects of preschool cognitive development, including language development, which may limit its predictive validity. Lastly, our sample size was limited by the ability to trace participants 3–6 years after the index pregnancy, which may have resulted in larger confidence intervals for factors included in regression analysis.

In conclusion, our results suggest that at 3–6 years old, children born to mothers with HFDP score lower on cognitive development than HFDP-unexposed participants. Differences in fine motor score were largely attributable to maternal confounders and household socioeconomic status. As the prevalence of HFDP increases in urban SSA, the implications of these findings stand to impact a growing number of children. Understanding the consequences for early child development and subsequently optimising maternal (preconception) health and early childhood stimulation, for example at preschool, could help more children reach their developmental potential.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10995-021-03331-z.

Author Contributions SAN, KKG, NSL, VN, CED and LMS contributed to research conceptualization and planning. VN and LMS contributed to the study project coordination and data collection. CD advised on the use of the Herbst test. LMS performed data analysis and wrote the initial manuscript version. All the authors contributed to interpretation of data and revising the manuscript. All authors approved the final submitted version of the manuscript.

Funding This study was supported through SAN by the South African Medical Research Council, and SAN is also supported by the DST-NRF Centre of Excellence in Human Development at the University of the Witwatersrand, Johannesburg.

Data Availability Data is available upon request to the corresponding author.

Code Availability Not applicable.

Declarations

Conflict of interest Authors have no conflict of interest to declare.

Ethical Approval Ethical approval for this study was obtained from the Human Research Ethics Committee of the University of the Witwatersrand (ref: M180317), and the study was therefore performed in accordance with the 1964 Declaration of Helsinki and its amendments.

Consent to Participate Written informed consent was obtained from the participants' parent or guardian prior to participation in the study. Any details that might disclose the identity of the participants were omitted.

Consent for Publication Not applicable.

References

Adane, A. A., Mishra, G., & Tooth, L. (2018). Maternal preconception weight trajectories, pregnancy complications and offspring's childhood physical and cognitive development. *Journal of Developmental Origins of Health and Disease, 9*(6), 653–660. https://doi.org/10.1017/S2040174418000570

Adane, A. A., Mishra, G. D., & Tooth, L. R. (2016). Diabetes in pregnancy and childhood cognitive development: A systematic review. *Review Article Pediatrics*. https://doi.org/10.1542/peds.2015-4234

Bhutta, A. T., Cleves, M. A., Casey, P. H., Cradock, M. M., & Anand, K. J. S. (2002). Cognitive and behavioral outcomes of school-aged children who were born preterm: A meta-analysis. *Journal of the American Medical Association, 288*(6), 728–737. https://doi.org/10.1001/jama.288.6.728

Black, M. M., Walker, S. P., Fernald, L. C., Andersen, C. T., DiGirolamo, A. M., Lu, C., McCoy, D. C., Bhutta, Z. A., Britto, P. R., Daelmans, B., Darmstadt, G. L., Dua, T., Gertler, P., Heymann, J., Lombardi, J., Lopez Boo, F., Lye, S. J., MacMillan, H., Perez-Escamilla, R., … Grantham-McGregor, S. (2017). Early childhood development coming of age: Science through the life course Early Childhood Development Series Steering Committee HHS Public Access. *Lancet*, *389*, 77–90. https://doi.org/10.1016/S0140-6736(16)31389-7

Chatfield, A., Caglia, J., Dhillon, S., Hirst, J., Cheikh Ismail, L., Abawi, K., Kac, G., Al Dhaheri, A., Villar, J., Kennedy, S., & Langer, A. (2013). Translating research into practice: The introduction of the INTERGROWTH-21st package of clinical standards, tools and guidelines into policies, programmes and services. *BJOG, 120*(Supplement 2), 139–142. https://doi.org/10.1111/1471-0528.12416

Clausen, T. D., Mortensen, E. L., Schmidt, L., Mathiesen, E. R., Hansen, T., Jensen, D. M., & Damm, P. (2013). Cognitive function in adult offspring of women with gestational diabetes—The role of glucose and other factors. *PLoS ONE*. https://doi.org/10.1371/journal.pone.0067107

Cook, C. J., Howard, S. J., Scerif, G., Twine, R., Kahn, K., Norris, S. A., & Draper, C. E. (2019). Associations of physical activity and gross motor skills with executive function in preschool children from low-income South African settings. *Developmental Science, 22*(5), 1–13. https://doi.org/10.1111/desc.12820

de Sousa, R. A. L., Torres, Y. S., Figueiredo, C. P., Passos, G. F., & Clarke, J. R. (2018). Consequences of gestational diabetes to the brain and behavior of the offspring. *Anais Da Academia Brasileira De Ciencias, 90*(2), 2279–2291. https://doi.org/10.1590/0001-3765201720170264

Dionne, G., Boivin, M., Séguin, J. R., Pérusse, D., & Tremblay, R. E. (2008). Gestational diabetes hinders language development in offspring. *Pediatrics, 122*(5), e1073–e1079. https://doi.org/10.1542/peds.2007-3028

Draper, C. E., Achmat, M., Forbes, J., & Lambert, E. V. (2012). Impact of a community-based programme for motor development on gross motor skills and cognitive function in preschool children from disadvantaged settings. *Early Child Development and Care, 182*(1), 137–152. https://doi.org/10.1080/03004430.2010.547250

Ford, N. D., & Stein, A. D. (2016). Risk factors affecting child cognitive development: A summary of nutrition, environment, and maternal-child interaction indicators for sub-Saharan Africa. *Journal of Developmental Origins of Health and Disease, 7*(2), 197–217. https://doi.org/10.1017/S2040174415001427

Fraser, A., Nelson, S. M., Macdonald-Wallis, C., & Lawlor, D. A. (2012). Associations of existing diabetes, gestational diabetes, and glycosuria with offspring IQ and educational attainment: The Avon longitudinal study of parents and children. *Experimental Diabetes Research, 2012*, 1–7. https://doi.org/10.1155/2012/963735

French, B., Outhwaite, L. A., Langley-Evans, S. C., & Pitchford, N. J. (2020). Nutrition, growth, and other factors associated with early cognitive and motor development in Sub-Saharan Africa: A scoping review. *Journal of Human Nutrition and Dietetics, 33*(5), 644–669. https://doi.org/10.1111/JHN.12795

Grantham-McGregor, S., Cheung, Y. B., Cueto, S., Glewwe, P., Richter, L., Strupp, B., The International Child Development Steering Group. (2007). Developmental potential in the first 5 years for children in developing countries. *Lancet, 369*(9555), 60–70. https://doi.org/10.1016/S0140-6736(07)60032-4

Harris, P. A., Taylor, R., Thielke, R., Payne, J., Gonzalez, N., & Conde, J. G. (2009). Research electronic data capture (REDCap)—A metadata-driven methdology and workflow process for providing translational research informatics support. *Journal of Biomedical Informatics, 42*(2), 377–381.

Herbst, I., & Huysamen, G. K. (2000). The construction and validation of developmental scales for environmentally disadvantaged preschool children. *South African Journal of Psychology, 30*(3), 19–24.

Koning, S. H., Hoogenberg, K., Lutgers, H. L., van den Berg, P. P., & Wolffenbuttel, B. H. R. (2016). Gestational diabetes mellitus: Current knowledge and unmet needs. *Journal of Diabetes*. https://doi.org/10.1111/1753-0407.12422

Kristenson, M., Eriksen, H. R., Sluiter, J. K., Starke, D., & Ursin, H. (2004). Psychobiological mechanisms of socioeconomic differences in health. *Social Science and Medicine, 58*(8), 1511–1522. https://doi.org/10.1016/S0277-9536(03)00353-8

Lake, A., & Chan, M. (2015). Putting science into practice for early child development. *The Lancet, 385*(9980), 1816–1817. https://doi.org/10.1016/S0140-6736(14)61680-9

Macaulay, S., Ngobeni, M., Dunger, D. B., & Norris, S. A. (2018). The prevalence of gestational diabetes mellitus amongst black South African women is a public health concern. *Diabetes Research and Clinical Practice, 139*, 278–287. https://doi.org/10.1016/j.diabres.2018.03.012

Márquez-Valadez, B., Valle-Bautista, R., García-López, G., Díaz, N. F., & Molina-Hernández, A. (2018). Maternal diabetes and fetal programming toward neurological diseases: Beyond neural tube defects. *Frontiers in Endocrinology, 9*(664), 1–10. https://doi.org/10.3389/fendo.2018.00664

Nomura, Y., Marks, D. J., Grossman, B., Yoon, M., Loudon, H., Stone, J., & Halperin, J. M. (2012). Exposure to gestational diabetes mellitus and low socioeconomic status: Effects on neurocognitive development and risk of attention-deficit/hyperactivity disorder in offspring. *Archives of Pediatrics & Adolescent Medicine, 166*(4), 337–343. https://doi.org/10.1001/archpediatrics.2011.784

Nozyce, M. L., Huo, Y., Williams, P. L., Kapetanovic, S., Hazra, R., Nichols, S., Hunter, S., Smith, R., Seage, G. R., & Sirois, P. A. (2014). Safety of in utero and neonatal antiretroviral exposure: Cognitive and academic outcomes in HIV-exposed, uninfected children 5–13 years of age. *Pediatric Infectious Disease Journal, 33*(11), 1128–1133. https://doi.org/10.1097/INF.0000000000000410

Ornoy, A. (2005). Growth and neurodevelopmental outcome of children born to mothers with pregestational and gestational diabetes. *Pediatric Endocrinology Reviews, 3*(2), 104–113.

Ornoy, A., Ratzon, N., Greenbaum, C., Wolf, A., & Dulitzky, M. (2001). School-age children born to diabetic mothers and to mothers with gestational diabetes exhibit a high rate of inattention and fine and gross motor impairment. *Journal of Pediatric Endocrinology and Metabolism, 14*(Supplement 1), 681–689. https://doi.org/10.1515/jpem.2001.14.s1.681

Robles, M. C., Campoy, C., Garcia Fernandez, L., Lopez-Pedrosa, J. M., Rueda, R., & Martin, M. J. (2015). Maternal diabetes and cognitive performance in the offspring: A systematic review and meta-analysis. *PLoS ONE, 10*(11), e0142583. https://doi.org/10.1371/journal.pone.0142583

Silverman, B. L., Rizzo, T. A., Cho, N. H., & Metzger, B. E. (1998). Long-term effects of the intrauterine environment. *Diabetes Care, 21*(Supplement 2), B142.

Spaull, N., & Kotze, J. (2015). Starting behind and staying behind in South Africa. The case of insurmountable learning deficits in mathematics. *International Journal of Educational Development, 41*, 13–24. https://doi.org/10.1016/j.ijedudev.2015.01.002

StataCorp. (2013). *Stata statistical software: Release 13 (No. 13)*. StataCorp.

Statistics South Africa. (2016). *Statistics South Africa*. Retrieved October 4, 2020 from http://www.statssa.gov.za/?page_id=4286&id=11317

Steyn, N. P., & Mchiza, Z. J. (2014). Obesity and the nutrition transition in Sub-Saharan Africa. *Annals of the New York Academy of Sciences, 1311*(1), 88–101. https://doi.org/10.1111/nyas.12433

Tomaz, S. A., Hinkley, T., Jones, R. A., Twine, R., Kahn, K., Norris, S. A., & Draper, C. E. (2020). Objectively measured physical activity in South African children attending preschool and grade R: Volume, patterns, and meeting guidelines. *Pediatric Exercise Science, 32*(3), 150–156. https://doi.org/10.1123/pes.2019-0216

Van Rie, A., Mupuala, A., & Dow, A. (2008). Impact of the HIV/AIDS epidemic on the neurodevelopment of preschool-aged children in

Kinshasa, democratic Republic of the Congo. *Pediatrics, 122*(1), e123. https://doi.org/10.1542/peds.2007-2558

Walker, S. P., Wachs, T. D., Gardner, J. M., Lozoff, B., Wasserman, G. A., Pollitt, E., Carter, J. A., International Child Development Steering Group. (2007). Child development: risk factors for adverse outcomes in developing countries. *Lancet, 369*(9556), 145–157. https://doi.org/10.1016/S0140-6736(07)60076-2

West, N. S., Schwartz, S. R., Yende, N., Schwartz, S. J., Parmley, L., Gadarowski, M. B., Mutunga, L., Bassett, J., & Van Rie, A. (2019). Infant feeding by South African mothers living with HIV: Implications for future training of health care workers and the need for consistent counseling. *International Breastfeeding Journal, 14*(1), 11. https://doi.org/10.1186/s13006-019-0205-1

World Health Organization. (2006). *The WHO child growth standards: Length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: Methods and development*. World Health Organization.

World Health Organisation. (2013). *Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy*. World Health Organization.