

Obesity and adiposity of 3- to 6-year-old children born to mothers with hyperglycaemia first detected in pregnancy in an urban South African setting

Larske M. Soepnel, Veronique Nicolaou, Christine Slater, Glory Chidumwa, Naomi S. Levitt, Kerstin Klipstein-Grobusch & Shane A. Norris

To cite this article: Larske M. Soepnel, Veronique Nicolaou, Christine Slater, Glory Chidumwa, Naomi S. Levitt, Kerstin Klipstein-Grobusch & Shane A. Norris (2021) Obesity and adiposity of 3- to 6-year-old children born to mothers with hyperglycaemia first detected in pregnancy in an urban South African setting, *Annals of Human Biology*, 48:2, 81-92, DOI: [10.1080/03014460.2021.1918245](https://doi.org/10.1080/03014460.2021.1918245)

To link to this article: <https://doi.org/10.1080/03014460.2021.1918245>



© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group



View supplementary material [↗](#)



Published online: 06 May 2021.



Submit your article to this journal [↗](#)



Article views: 959



View related articles [↗](#)



View Crossmark data [↗](#)

RESEARCH PAPER

OPEN ACCESS



Obesity and adiposity of 3- to 6-year-old children born to mothers with hyperglycaemia first detected in pregnancy in an urban South African setting

Larske M. Soepnel^{a,b} , Veronique Nicolaou^a, Christine Slater^c, Glory Chidumwa^d , Naomi S. Levitt^e , Kerstin Klipstein-Grobusch^{b,d}  and Shane A. Norris^{a,f} 

^aSAMRC/Wits Developmental Pathways for Health Research Unit, Department of Paediatrics, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ^bJulius Global Health, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; ^cIndependent Consultant, Maryport, UK; ^dDivision of Epidemiology and Biostatistics, School of Public Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa; ^eDepartment of Medicine, Chronic Disease Initiative for Africa, Faculty of Health Sciences, University of Cape Town, Cape Town, South Africa; ^fGlobal Health Research Institute, School of Human Development and Health, University of Southampton, Southampton, UK

ABSTRACT

Background: Understanding the association between maternal metabolic conditions in pregnancy and the risk of childhood overweight, a growing concern in sub-Saharan Africa (SSA), helps to identify opportunities for childhood obesity prevention.

Aim: To assess the association between hyperglycaemia first detected in pregnancy (HFDP) (gestational diabetes mellitus [GDM] and diabetes in pregnancy [DIP]) and child obesity and adiposity in pre-school-aged children in South Africa, independently of maternal BMI.

Subjects and methods: Measurement of anthropometry and fat mass index (FMI) by the deuterium dilution method was done for 102 3–6-year-old children born to mothers with HFDP and 102 HFDP-unexposed children. Hierarchical regression analysis and generalised structural equation modelling (GSEM) were performed.

Results: The prevalence of overweight/obesity was 10.5% and 11.1% in children exposed to GDM and DIP, respectively, and 3.9% in the HFDP-unexposed group. Log-transformed FMI was significantly higher in the DIP-exposed group ($\beta = 0.166$, 95% CI = 0.014–0.217 $p = .026$), but not when adjusting for maternal pregnancy BMI ($\beta = 0.226$, 95% CI = 0.003–0.015, $p = .004$). GSEM showed significant total effects of maternal BMI and birth weight on FMI/BMI.

Conclusions: Maternal pregnancy BMI seems to play a greater role in the development of childhood adiposity than maternal hyperglycaemia, requiring further research and identifying maternal BMI as a relevant prevention target in our setting.

ARTICLE HISTORY

Received 29 December 2020
Revised 7 March 2021
Accepted 6 April 2021

KEYWORDS

Gestational hyperglycaemia; childhood obesity; childhood adiposity; South Africa; maternal BMI


Introduction

Nutritional changes and the increase of sedentary “modern” urban lifestyles are driving the obesity epidemic in low- and middle-income countries (LMICs) (Wells et al. 2020). Globally, an estimated 40 million children under the age of 5 were impacted by overweight/obesity in 2018, with the majority living in LMICs (Black et al. 2013; UNICEF, WHO, World Bank Group 2018). Aside from the negative physical and socio-emotional consequences of childhood obesity, it is also associated with a higher risk of persistent adulthood obesity, cardiovascular disease, and type 2 diabetes (Lakshman et al. 2012). While overweight/obesity determined by BMI is the most widely recognised surrogate measure for childhood adiposity, measures that distinguish between fat and lean mass provide additional information predictive of future disease risk (Samadi et al. 2013). The search for early life obesity prevention strategies has prompted investigations into

pregnancy exposures that contribute to childhood overweight and adiposity (Gillman and Ludwig 2013).

In urban sub-Saharan Africa (SSA), the global obesity epidemic is also heavily impacting women of reproductive age, as exemplified by the overweight/obesity prevalence of around 62% in South African women aged 20–34 years (Black et al. 2013; Onubi et al. 2016; South African National Department of Health et al. 2019). As a result, a rising number of pregnancies is complicated by obesity-associated conditions, on top of existing communicable disease, maternal health, and (childhood) malnutrition challenges (Steyn and Mchiza 2014; Kruger 2018). One such increasingly prevalent condition is hyperglycaemia first detected in pregnancy (HFDP), which consists of less severe gestational diabetes mellitus (GDM) and “overt” diabetes first diagnosed in pregnancy (DIP), according to the 2013 WHO criteria (World Health Organization [WHO] 2013). GDM alone has been

CONTACT Larske M. Soepnel  larske.soeepnel@gmail.com  SAMRC/Wits Developmental Pathways for Health Research Unit, Faculty of Health Sciences, University of the Witwatersrand, Private Bag 3, Wits, 2050 Johannesburg, South Africa

 Supplemental data for this article is available online at <https://doi.org/10.1080/03014460.2021.1918245>

© 2021 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way.

found to impact up to 9.3% of pregnancies in urban SSA (Oppong et al. 2015; Macaulay, Munthali, et al. 2018; Macaulay, Ngoben, et al. 2018).

These conditions in pregnancy are thought to confer risk for childhood obesity and overweight through early developmental programming in response to altered intrauterine conditions, exacerbating the problem of childhood adiposity in the next generation (Catalano 2010). Maternal pre-pregnancy obesity itself was found to increase the odds of childhood obesity by 264% in a recent meta-analysis (Heslehurst et al. 2019). In addition, evidence from middle and high-income countries has indicated that maternal HFDP might be an independent risk for childhood obesity (Zhao et al. 2016; Zhu et al. 2016; Logan et al. 2017). However, contrasting findings have also arisen, possibly due to the use of varying diagnostic criteria, follow-up times, and measures of childhood adiposity (Pettitt et al. 2010; Pham et al. 2013; Bider-Canfield et al. 2017). Most recently, evidence from a follow-up study of the Hyperglycaemia and Adverse Pregnancy Outcome (HAPO) study in 4832 children aged 10–14 years showed an independent association between a continuum of (untreated) maternal blood glucose levels and childhood adiposity (Lowe et al. 2018, 2019). Despite the alarming rate of maternal obesity and the increase in hyperglycaemia in pregnancy in urban SSA, this association remains to be thoroughly explored in an African setting at any age. Pre-school age is of interest in this relationship since SSA has a significant prevalence of pre-school overweight/obesity (Gebremedhin 2015) and interventions at this age have been found to be more effective than in later childhood (Goldfield et al. 2012; Draper et al. 2017).

Considering the growing number of children born to mothers with HFDP, the increasingly obesogenic environments children are exposed to in urban SSA and LMICs elsewhere, and the serious long-term consequences of childhood obesity, it is essential to build evidence to guide childhood obesity prevention efforts in SSA. We therefore aimed to assess the association between HFDP and childhood obesity and adiposity, hypothesising that exposure is positively associated with these outcomes in pre-school aged children from Soweto, South Africa, independently of maternal BMI. Additionally, as a secondary objective, we explored the direct and indirect effects of maternal BMI on childhood obesity and adiposity within the context of HFDP.

Subjects and methods

Study population and hyperglycaemia first detected in pregnancy

Between March and November 2019, we conducted a study of 3–6-year-old children. The exposed and HFDP-unexposed group were defined on the basis of maternal exposure to HFDP, as follows: children were born to mothers who were diagnosed with HFDP (GDM or DIP) at Chris Hani Baragwanath Academic Hospital (CHBAH) (exposed) vs. to mothers who attended antenatal care at the same hospital but tested negative for HFDP (HFDP-unexposed), between February 2014 and January 2017 (see Figure 1 for study flow diagram). CHBAH is a tertiary hospital with around 1400–1600 deliveries per month, servicing the urban region

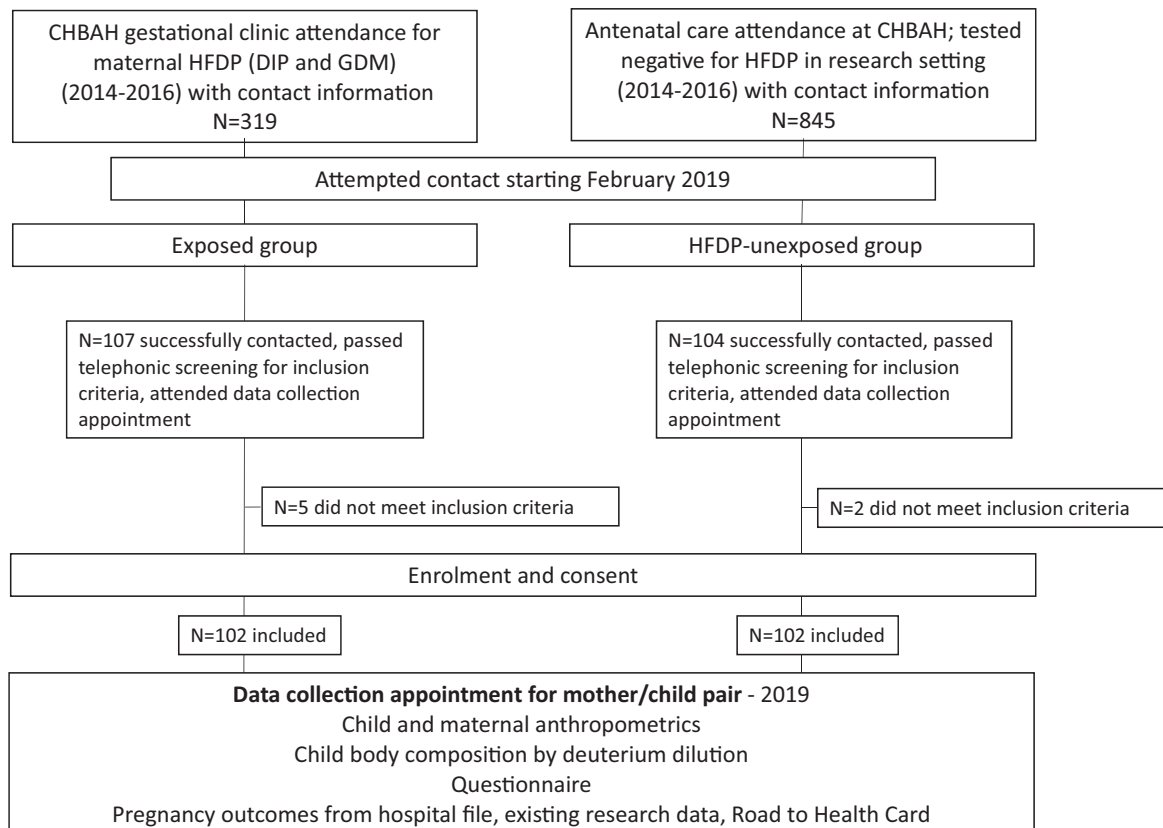


Figure 1. Flow chart depicting study design.

Table 1. Definitions of HFDP, birth outcomes, and anthropometric characteristics at age 3–6 years.

Maternal diagnosis	
HFDP	Diagnosed using a 2-h 75-g OGTT and IADPSG criteria, distinguishing between GDM and overt diabetes in pregnancy (DIP).
GDM	One of the following: fasting plasma glucose ≥ 5.1 mmol/L, 1-h plasma glucose ≥ 10 mmol/L, two-hour plasma glucose ≥ 8.5 mmol/L
DIP	One of the following: fasting plasma glucose ≥ 7.0 mmol/L, 2-h plasma glucose ≥ 11.1 mmol/L, random plasma glucose ≥ 11.1 mmol/L, HbA1c $\geq 6.5\%$
Birth outcomes	
Prematurity	Delivery <37 completed weeks gestational age
Low birth weight (LBW)	Birth weight <2500 g
Macrosomia	Birth weight ≥ 4000 g
Large for gestational age	Birth weight >90th percentile, by Intergrowth-21 standards
Anthropometric characteristics at age 3–6 years	
Body mass index (BMI)	Weight (kg) divided by height (m) squared
Obesity	According to WHO definition: For children <5 years BMI z-score higher than 3SD from the mean; for children >5 years BMI z-score higher than 2SD from the mean.
Overweight	According to WHO definition: For children <5 years BMI z-score +2SD to 3SD from the mean; for children >5 years BMI z-score +1SD to 2SD from the mean.
At risk for overweight	According to WHO child growth standards: For children <5 years BMI z-score +1SD to 2SD from the mean.
Stunting	Height lower than –2SD from the mean, according to WHO child growth standards per age.
Fat mass index (FMI)	Estimated fat mass (kg) (by deuterium dilution method) divided by height (m) squared.

of Soweto, where the population consists primarily of Black South Africans (Statistics South Africa 2016).

The mothers of the exposed group attended a gestational endocrine clinic at CHBAH for HFDP while pregnant with the participating child. Clinical characteristics and pregnancy outcomes of this group have previously been published (Soepnel et al. 2019). Diagnostic testing was based on selective screening of risk factors for GDM, except for some women universally screened in a research context (Macaulay, Munthali, et al. 2018; Macaulay, Ngobeni, et al. 2018). Women were diagnosed using a 75-g 2-h oral glucose tolerance test (OGTT) with IADPSG criteria (Table 1).

The HFDP-unexposed group was selected from children born to mothers who attended CHBAH's antenatal clinic during the index pregnancy and tested negative for HFDP in a research setting, using the same diagnostic criteria as the clinic. Further information around diagnosis and participant characteristics has been previously published (Macaulay, Munthali, et al. 2018; Macaulay, Ngobeni, et al. 2018). Mother/child pairs qualifying as the HFDP-unexposed group were contacted in a random order and invited to attend the data collection appointment until the number of mother/child pairs per the child's birth year in the HFDP-unexposed group was the same as in the exposed group.

Exclusion criteria included inability to contact the mother/guardian or attend the data collection appointment (e.g. due to relocation), being one of two twins, diagnosis of major congenital disorders or diabetes mellitus, maternal or child death since pregnancy, maternal diagnosis of pre-gestational diabetes, and age <2.8 years or >6 years old.

The study was approved by the Human Research Ethics Committee of the University of the Witwatersrand (M180317). Written consent was obtained from parents before participation in the study.

Sample size calculation

Sample size calculation for means was performed in STATA version 13 (STATA Corp, College Station, TX). For 80% power

at 0.05 significance, the required minimum sample size was 130 participants per group to detect a difference in BMI z-score of 0.35 between the HFDP-unexposed and exposed group, based on existing evidence (ranging from 0.22 to 0.6 with varying study designs (Zhao et al. 2016; Zhu et al. 2016; Lowe et al. 2018; Gu et al. 2019), calculated using population standard deviations (SDs) of 0.93 (5-year-old) and 1.07 (3-year-old) based on a cohort of Sowetan children (Richter et al. 2007). This would also be sufficient to detect a difference in FMI of 0.4 kg/m² with a SD of 1 ($n = 100$ per group).

Outcomes

Primary outcomes were overweight (BMI) and adiposity (fat mass index [FMI]). Secondary outcomes were linear growth (height) and stunting (Table 1).

Anthropometric measurements and determining fat mass

Anthropometric measurements were done by a trained research assistant or nurse according to standardised procedures, after removing shoes and any outerwear. The mean of three measurements was used for analyses of weight, height, waist circumference, and mid-upper arm circumference (MUAC). Weight was assessed using a SECA digital scale (Hamburg, Germany), and height was measured using a fixed, mounted Holtain stadiometer (Crymych, UK). The mean weight and height per participant were used to calculate BMI (kg/m²). Waist circumference was measured excluding clothing using a measuring tape placed halfway between the lower rib and the iliac crest. MUAC was measured halfway between the acromion and the olecranon process. The inter-observer coefficient of variance (CV) for anthropometric measures was <3%. Technical error measurement was <0.7 cm, except for waist circumference where a technical error measurement of <1.5 cm was considered acceptable.

Childhood adiposity was assessed using the deuterium dilution method, according to International Atomic Energy Agency (IAEA) protocol adapted for 2–6-year-old children (IAEA 2010). The deuterium dilution method, a reference method for body composition assessment, measures the total body water (TBW) following a dose of deuterium oxide. The deuterium equilibrates with hydrogen in body water and evenly distributes throughout the TBW after a few hours. Since water is found exclusively in fat-free mass, the level of enrichment in the saliva allows for a deduction of the fat-free mass and, subsequently, fat mass.

The procedure involved taking a baseline saliva sample using cotton wool according to the IAEA method (IAEA 2010), followed by giving the participant an oral 20-g dose of 10% deuterium oxide diluted in water (2 g of deuterium oxide). If any of the dose was lost in this process, the procedure was aborted. Subsequent saliva samples were taken at 2.5–3 h after dosing. Food and drink were limited as follows: the last intake was at least 30 min prior to taking the baseline sample; a light meal and drink of <250 mL was offered 30–60 min after dose consumption; no additional food or drink was consumed until after the final saliva sample. Saliva samples were stored in a –20 °C freezer until deuterium enrichment analysis was performed by a qualified laboratory technician using a portable Fourier-transform infra-red spectrometer (Agilent, 4500 Series, Santa Clara, CA) (IAEA 2010). The criterion for acceptance of the deuterium analysis was a CV <2%, including the analysis of quality control standards at the start and end of the day, and saliva samples. TBW was accepted if the precision of TBW calculated separately from the first and second post-dose samples was <3%. The mean CV for deuterium analysis was 0.5% for the whole study. The mean CV for TBW was 1.1%.

Additional variables

For the exposed group, hospital files from the gestational endocrine clinic provided data regarding maternal OGTT results, BMI at the first clinic visit, maternal HIV infection, and obstetric/birth outcomes (birth weight, gestational age at delivery, and obstetric/early neonatal complications). For the HFDP-unexposed group, the same information was collected from data collected in pregnancy (Macaulay, Munthali, et al. 2018; Macaulay, Ngobeni, et al. 2018) and the child's Road to Health Card, a patient-held medical record given to every child born in South Africa to assist with childhood health monitoring. Maternal BMI was calculated at the data collection appointment using the methods described above for children.

Each mother completed a questionnaire with the help of a research assistant. This provided information on household assets at the child's primary residence (household socioeconomic score), maternal education level, maternal smoking and alcohol use in pregnancy, early life hospitalisations, breastfeeding (whether participant was breastfed, whether participant was breastfed exclusively, and the duration of any breastfeeding), and maternal HIV infection.

Data management and statistical analysis

Data was captured and managed using REDCap (Vanderbilt University, Nashville, TN; (Harris et al. 2009)), and imported into STATA version 13 (College Station, TX). Outcomes for weight-for-age, height-for-age, BMI-for-age, and MUAC-for-age were converted into standard scores (z-scores) using WHO growth standards or references (WHO 2006; de Onis et al. 2007). FMI (kg/m²) was calculated using height and body fat mass from the deuterium dilution method. Birth weight was converted into a z-score adjusted for gestational age using the Intergrowth-21 standards (Chatfield et al. 2013). Conditional weight gain was the male or female standardised residual of current weight regressed against birth weight. The participant's household assets were summed for a continuous household socioeconomic status score. Breastfeeding was categorised dichotomously as any breastfeeding vs. no breastfeeding. The occurrence of any childhood hospitalisation prior to 2 years old, maternal HIV infection during pregnancy and at the follow-up visit and use of fixed-dose-combination antiretroviral therapy (ART) at follow-up were treated as dichotomous variables. Any statistical outliers were checked for (data capturing) errors but included for analysis if no error was found. Throughout, significance was assumed at a two-sided *p* value < .05.

For the outcomes BMI z-score and FMI, multivariable hierarchical regression analysis was performed on an *a priori* basis, as follows: Model (1a) crude model for HFDP exposure; Model (1b) (for FMI) M1a + child sex and age; Model (2) Model 1b + maternal and household factors (maternal BMI in pregnancy, maternal HIV status in pregnancy, parity, alcohol, and smoking during pregnancy, and socioeconomic household score).

In order to explore the direct and indirect effects of maternal BMI in pregnancy on childhood FMI and BMI in the context of HFDP, generalised structural equation modelling (GSEM) was performed to explore the relationship between maternal BMI, HFDP (GDM and DIP), other significant maternal/household and mediating variables, and FMI/BMI, fitted with the multinomial family and logit link function. GSEM was performed because it allows for a pictographic representation of hypothesis-driven relationships between variables, including potential mediators, confounders, and composite latent variables (not applicable for this dataset). GSEM estimates path equations simultaneously, and allows for calculations of direct, indirect, and total effects (Lei and Wu 2007). We started with a hypothesised model, based on theoretical meaning and results from regression analyses, as shown in Figure S1. Modifications to pathways and adding/removing variables were made iteratively and the Aikake and Bayesian Information Criteria (IC) of each model was compared. The final model was selected for having a low IC and high theoretical relevance (Figure 2, Table S1). Direct, indirect, and total effects were calculated using non-linear combination estimates.

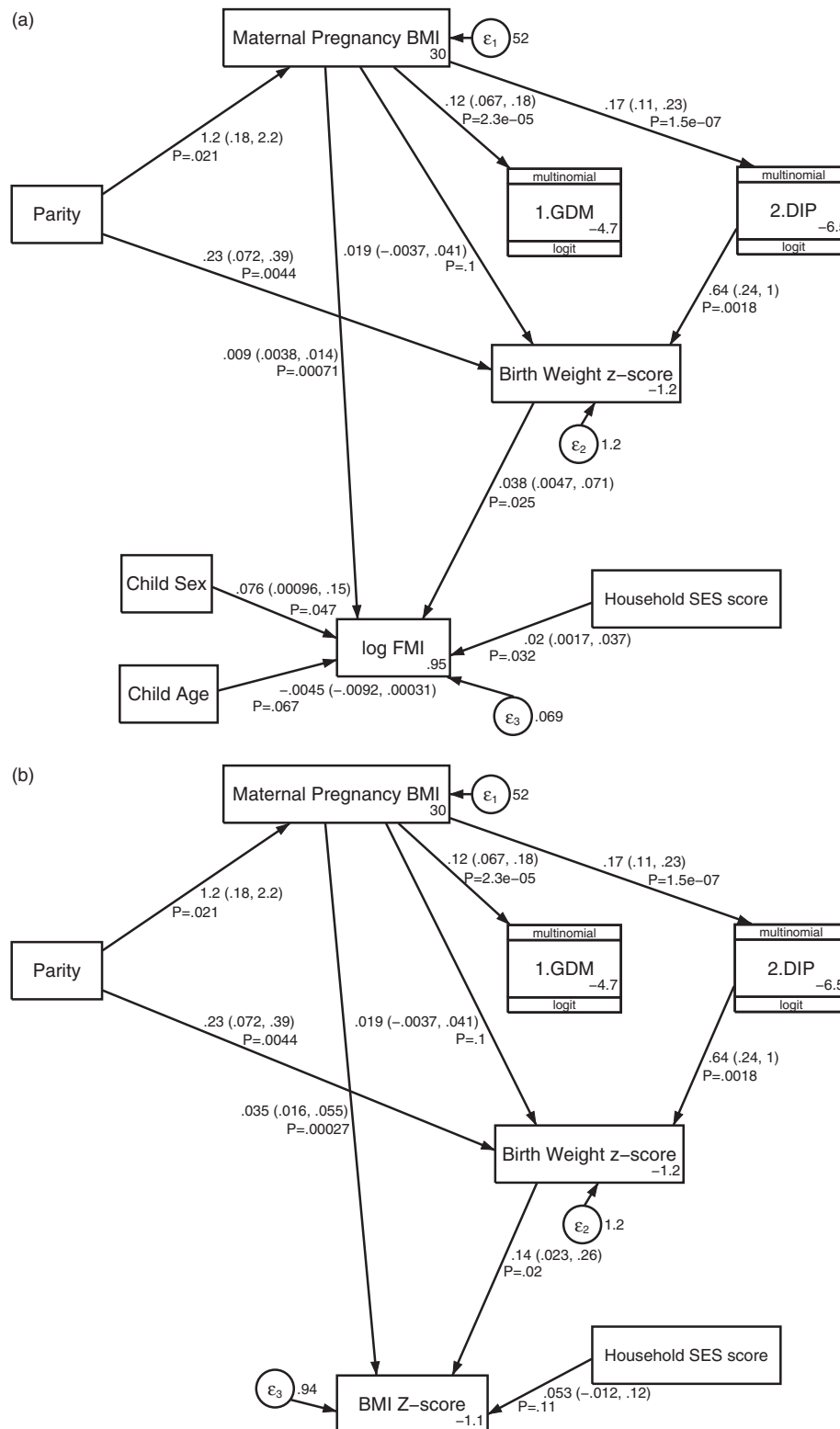


Figure 2. GSEM best-fit model of maternal and household variables, birth weight, and GDM/DIP for (a) log-FMI, adjusting for sex and age, and (b) BMI z-score. Unstandardised coefficient (95% CI) and p values are displayed.

Results

Baseline characteristics

Of 211 participants that attended the data collection appointment, 7 did not meet the inclusion criteria, resulting in 204 included participants.

The median age of participants was similar between the HFDP-unexposed and exposed groups at 3.5 years (IQR 3.1–4.1) and 3.4 years (IQR 3.1–4.1), respectively (Table 2). Of the participants exposed to HFDP, 45 (44.1%) were exposed to DIP, and 57 (55.9%) to GDM. The number of participants born *via* caesarean section was high in both groups at 58.8%

Table 2. Baseline characteristics of participants per group.

	<i>n</i>	HFDP-unexposed	<i>n</i>	Hyperglycaemia first detected in pregnancy			
				Total group	<i>n</i>	GDM	DIP
Number of participants	–	102	–	102	–	57	45
Age, year (median, IQR ^a)	102	3.5 (3.1–4.1)	102	3.4 (3.1–4.1)	57	3.3 (3.0–4.0)	3.7 (3.2–4.2)
Male (<i>n</i> %)	102	49 (48.0)	102	56 (54.9)	57	30 (52.6)	26 (57.8)
Early life factors							
Received breastfeeding (<i>n</i> %)	102	82 (80.4)	102	73 (71.6)	57	39 (68.4)	34 (75.6)
Exclusive breastfeeding	102	77 (75.5)	102	62 (60.8)	57	34 (59.7)	28 (62.2)
Hospitalised <2 years (<i>n</i> %)	102	20 (19.6)	102	15 (14.7)	57	11 (19.3)	4 (8.9)
Pregnancy factors							
OGTT ^b results (mean, SD ^c)	102		95		56		39
Fasting		4.0 (0.5)		6.7 (1.9)		5.6 (0.7)	8.2 (2.0)
2-hour		5.4 (1.2)		10.5 (3.5)		8.6 (1.7)	13.1 (3.6)
HbA1c (median, IQR)		–	94				
First visit %				6.3 (5.6–7.1)	51	5.7 (5.3–6.1)	43
3rd trimester %				6.1 (5.6–6.6)	50	5.8 (5.5–6.3)	42
Exposure to: (<i>n</i> , %)		–	102		57		45
Metformin				63 (61.8)		39 (68.42)	24 (53.3)
Glibenclamide				30 (29.4)		13 (22.8)	17 (37.8)
Insulin				32 (31.4)		7 (12.3)	25 (55.6)
Gestational age OGTT (median, IQR)	102	26 (25–27)	102	30.4 (25.6–33.6)	57	30.6 (27.3–34.1)	45
Parity (<i>n</i> , %): 0	102	36 (35.3)	102	12 (11.8)	57	8 (14.0)	45
1–2		59 (57.8)		78 (76.5)		43 (75.4)	
>3		7 (6.9)		12 (11.8)		6 (10.5)	
BMI at OGTT (median, IQR)	102	29.4 (24.8–33)	102	35.1 (30.8–40.0)	52	33.9 (30.5–37.5)	42
HIV-infection pregnancy (<i>n</i> , %)	102	20 (19.6)	102	17 (16.7)	57	13 (22.8)	45
Caesarean section (<i>n</i> , %)	102	60 (58.8)	99	69 (69.7)	56	40 (71.4)	43
Obstetric complication (<i>n</i> , %)	102	11 (10.8)	102	15 (14.7)	57	6 (10.5)	45
Macrosomia (<i>n</i> , %)	102	5 (4.9)	99	5 (5.1)	56	3 (5.4)	43
Large for gestational age (<i>n</i> , %)	102	11 (10.8)	99	21 (21.2)	56	6 (10.7)	43
Low birth weight (<i>n</i> , %)	102	17 (16.7)	99	16 (16.2)	56	10 (17.9)	43
Prematurity (<i>n</i> , %)	102	13 (12.8)	102	22 (21.6)	57	11 (19.3)	11
Maternal and household characteristics at visit 3–6 years postpartum							
Highest education level	101		102		57		45
1 None/primary school		0		3 (2.9)		2 (3.6)	1 (2.2)
2 Secondary school		73 (72.3)		66 (64.7)		40 (70.2)	26 (57.8)
3 Prof. training/university		28 (27.7)		33 (32.4)		15 (26.3)	18 (40.0)
Household SES ^d (mean, SD)	102	8.6 (2.1)	102	8.0 (2.2)	57	7.8 (2.1)	45
Maternal BMI (mean, SD)	98	30.1 (7.4)	95	33.8 (7.1)	54	33.2 (7.1)	41
Blood pressure >140/90 (<i>n</i> , %)	102	20 (19.6)	102	37 (36.3)	57	16 (28.1)	45
HIV-infection (<i>n</i> , %)	102	23 (22.6)	102	20 (19.6)	57	15 (26.3)	45
Taking FDC ^e (<i>n</i> , %)	19	17 (89.4)	20	16 (80.0)	15	12 (80.0)	5

^aIQR: interquartile range; ^bOGTT: oral glucose tolerance test; ^cSD: standard deviation; ^dSES: socioeconomic score; ^eFDC: fixed dose combination antiretroviral medication.

(*n*=60) and 69.7% (*n*=69) in the HFDP-unexposed and HFDP-exposed group, respectively. The rate of prematurity was higher in the HFDP-exposed group than the HFDP-unexposed group (12.8% (*n*=13) vs. 21.6% (*n*=21.6), and highest in the DIP group at 24.4% (*n*=11). Macrosomia rates were notably similar between the HFDP-unexposed and HFDP exposed groups, but the birth weight z-score adjusted for gestational age was higher in the DIP group (Table 3). Breastfeeding was received in 80.4% (*n*=82) of the HFDP-unexposed group but only 71.6% (*n*=73) of the HFDP-exposed group.

At the time of the pregnancy OGTT, mothers with DIP had higher BMI, age, and fasting plasma glucose levels. The number of primiparous women was higher in the HFDP-unexposed group than in the HFDP-exposed group (35.3 vs. 11.8%). In total, only six mothers reported smoking during pregnancy (2.9%), and two reported alcohol consumption during pregnancy (0.9%). The majority of mothers diagnosed with DIP or GDM were managed with medical therapy, including metformin or glibenclamide, rather than diet (*n*=88, 86.3%). Upon measurement at the postpartum visit, maternal BMI was high across all three groups (median 31.4,

IQR 26.7–36.1). The total maternal HIV infection rate at the follow-up visit was 43 (21.1%), with 86.0% diagnosed at or before the index pregnancy (*n*=37).

Childhood overweight and adiposity

In the HFDP-unexposed group, four (3.9%) children were overweight/obese by WHO definitions, compared to six (10.5%) and five (11.1%) in the GDM and DIP groups, respectively (Table 3). Additionally, 22.6% (*n*=23) of the HFDP-unexposed group and 17.7% (*n*=18) were “at risk of overweight.” BMI z-score, waist circumference by height, and height z-score were higher in the DIP group. The mean weight z-score was lower in the HFDP-unexposed group (−0.3±0.9) than in the HFDP-exposed groups (−0.1±1.1). Although fat-free mass index was similar between the groups (12.2±0.7 and 12.1±1.1 in the HFDP-unexposed and HFDP-exposed groups, respectively), FMI was highest in the DIP exposed group at 4.0 (IQR 3.2–4.7), compared to 3.5 (IQR 3.1–4.2) in the HFDP-unexposed group. The highest rate of stunting at 9 (15.8%) was found in the GDM group.

For multivariable regression analyses, none of the included variables showed multicollinearity, with variance

Table 3. Infant and childhood anthropometric and fat mass outcomes per group: HFDP-unexposed vs. HFDP, subdivided into GDM and DIP.

	<i>n</i>	HFDP-unexposed	<i>n</i>	HFDP-exposed				
				Total group	<i>n</i>	GDM	<i>n</i>	DIP
Birth weight, g (median, IQR)	102	3040 (2800–3350)	99	3100 (2670–3100)	56	3042.5 (2667–3327)	43	3170 (2765–3685)
Birth weight z-score ^a (mean, SD)	102	−0.1 (1.2)	99	0.3 (1.1)	56	−0.02 (1.1)	43	0.7 (1.1)
Body composition by anthropometry								
Weight, kg (median, IQR)	102	14.8 (13.5–16)	102	15 (13.7–16.8)	57	14.7 (13.5–16.4)	45	15.2 (14.2–16.9)
Weight z-score (mean, SD)	102	−0.3 (0.9)	102	−0.1 (1.1)	57	−0.1 (1.1)	45	−0.1 (1.1)
Conditional weight gain (median, IQR)	102	−0.3 (−0.6–0.4)	99	−0.2 (−0.6–0.5)	56	−0.2 (−0.8–0.4)	43	−0.1 (−0.5–0.7)
BMI, kg/m ² (median, IQR)	102	15.6 (14.9–17.0)	102	16.0 (15.2–16.8)	57	15.9 (15.3–16.8)	45	16.0 (15.1–16.8)
BMI z-score (mean, SD)	102	0.3 (0.9)	102	0.5 (1.2)	57	0.5 (1.1)	45	0.6 (1.2)
At risk for overweight		23 (22.6)		18 (17.7)		10 (17.5)		8 (17.8)
Overweight		3 (2.9)		9 (8.8)		5 (8.8)		4 (8.9)
Obese		1 (1.0)		2 (2.0)		1 (1.8)		1 (2.2)
MUAC ^b , cm (mean, SD)	102	16.5 (1.22)	101	16.7 (1.6)	56	16.5 (1.5)	45	17.0 (1.7)
MUAC z-score	97	0.2 (−0.2–0.8)	98	0.4 (−0.3–1.0)	55	0.3 (−0.4–0.9)	43	0.6 (−0.0–1.2)
WC ^c (mean, SD)	102	49.8 (3.0)	100	50.9 (4.3)	55	50.5 (3.9)	44	51.4 (4.7)
WC by height index, cm/m	102	0.5 (0.04)	100	0.5 (0.04)	55	0.5 (0.04)	44	0.5 (0.05)
Fat mass by deuterium method								
FFM ^d , kg (mean, SD)	102	11.6 (1.6)	100	11.5 (1.8)	56	11.5 (1.9)	44	11.6 (1.5)
% (median, IQR)		76.7 (74.4–79.6)		76.3 (72.4–78.8)		76.1 (73.1–78.8)		76.3 (70.1–78.8)
FFMI (mean, SD)	102	12.2 (0.7)	100	12.1 (1.1)	56	12.2 (1.2)	44	12.0 (1.0)
FM, kg (median, IQR)	102	3.4 (2.9–4.1)	100	3.6 (3.0–4.5)	56	3.5 (2.9–4.4)	44	3.8 (3.1–4.6)
% (Median, IQR)		23.3 (20.4–25.6)		23.7 (21.2–27.6)		23.9 (21.2–26.9)		23.7 (21.2–29.9)
FMI (median, IQR)	102	3.5 (3.1–4.2)	100	3.9 (3.2–4.5)	56	3.8 (3.3–4.4)	44	4.0 (3.2–4.7)
Height								
Height, cm (mean, SD)	102	97.3 (6.5)	102	97.3 (6.8)	57	96.8 (7.2)	45	97.9 (6.2)
Height z-score (mean, SD)	102	−0.8 (0.9)	102	−0.8 (1.1)	57	−0.7 (1.2)	45	−0.8 (1.0)
Stunted (<i>n</i> , %)	102	10 (9.8)	102	14 (13.7)	57	9 (15.8)	45	5 (11.1)

All z-scores and cut-offs according to WHO standards. ^aBirth weight z-score adjusted for sex and gestational age (Intergrowth 21); ^bMUAC: mid-upper arm circumference; ^cWC: waist circumference; ^dFFM: fat-free mass; FFMI: fat-free mass index; FM: fat mass; FMI: fat mass index.

Table 4. Linear regression model for BMI z-score and log-transformed FMI, reporting standardised regression coefficients (β) with 95% confidence interval, and *p* values.

Outcome: BMI z-score	M1a: crude model		M1b: N/A		M2: M1+ maternal factors	
	β (95% CI)	<i>p</i> Value			β (95% CI)	<i>p</i> Value
Hyperglycaemia first detected in pregnancy						
True GDM	0.075 (−0.167–0.518)	.312			0.067 (−0.202–0.511)	.393
DIP	0.099 (−0.121–0.621)	.185			−0.001 (−0.402–0.395)	.987
<i>Maternal and household factors</i>						
Maternal pregnancy BMI					0.292 (0.019–0.063)	<.001*
Parity					−0.049 (−0.207–0.104)	.518
Socioeconomic household score					0.100 (−0.020–0.117)	.163
HIV positive during pregnancy					−0.014 (−0.246–0.421)	.848
	N 204; adj. <i>R</i> ² 0.1%				N 196; adj. <i>R</i> ² 7.0%	
Outcome: log-transformed FMI	M1a: crude model		M1b: crude model + sex + age		M2: M1b + maternal factors	
	β (95% CI)	<i>p</i> Value	β (95% CI)	<i>p</i> Value	β (95% CI)	<i>p</i> Value
Hyperglycaemia first detected in pregnancy						
True GDM	0.103 (−0.028–0.159)	.167	0.101 (−0.028–0.157)	.169	0.099 (−0.034–0.161)	.200
DIP	0.166 (0.014–0.217)	.026*	0.182 (0.026–0.226)	.014*	0.117 (−0.029–0.191)	.148
Child age			−0.088 (−0.008–0.002)	.206	−0.133 (−0.010–0.000)	.059
Child sex (female)			0.172 (0.021–0.177)	.014*	0.133 (−0.002–0.152)	.058
<i>Maternal and household factors</i>						
Maternal pregnancy BMI					0.226 (0.003–0.015)	.004*
Parity					−0.093 (−0.070–0.016)	.221
Socioeconomic household score					0.129 (−0.002–0.036)	.072
HIV positive during pregnancy					−0.034 (−0.130–0.080)	.641
	N 202; adj. <i>R</i> ² 1.7%		N 202; adj. <i>R</i> ² 4.7%		N 194; adj. <i>R</i> ² 10.0%	

*Indicates *p* value <.05.

inflation factors <2 for each model. Due to low rates of maternal alcohol consumption and smoking during pregnancy (*n*=2 and 6, respectively), these variables were not included in presented analyses. FMI was log-transformed to increase normality of residuals.

Log-FMI was higher in the children exposed to HFDP, even after correcting for age and sex, significantly so in the

DIP group (β = 0.18, 95% CI 0.03–0.23, *p* = .014) (Table 4). In this model, being female was associated with having a higher FMI (β = 0.17, 95% CI 0.02–0.18, *p* = .014). In model 2, correcting for maternal/household factors, DIP-exposure was no longer significantly associated with log-FMI, and maternal BMI during pregnancy had the strongest association with log-FMI (β = maternal BMI = 0.23, 95% CI 0.003–0.015,

$p=.004$). Household socioeconomic score was positively associated with log-FMI ($\beta=0.13$, 95% CI $-0.002-0.036$, $p=.072$).

The (non-statistically significant) positive association between DIP/GDM and BMI z-score was attenuated in Model 2, with DIP exposure showing a slight inverse association with BMI ($\beta=-0.001$, 95% CI $-0.402-0.395$, $p=.987$). Maternal BMI was the main significant predictor of BMI z-score ($\beta=0.29$, 95% CI $0.02-0.06$, $p<.001$). Maternal HIV infection was not significantly associated with either BMI or log-FMI. No significant interaction effect was found between maternal BMI and HFDP, for either BMI or log-FMI.

In an additional analysis of early life variables, birth weight z-score was significantly associated with both log-FMI and BMI z-score when additionally introduced to Model 2 ($\beta=0.16$, 95% CI $0.004-0.074$, $p=.028$, $\beta=0.18$, 95% CI $0.035-0.291$, $p=.013$, respectively), but breastfeeding was not.

GSEM showed a significant direct effect of maternal pregnancy BMI on log-FMI and BMI, and the total effect through DIP and birth weight was also significant (Figure 2). Birth weight z-score was significantly associated with both FMI and BMI (Unstandardized coefficient $B=0.04$ 95% CI $0.005-0.07$, $p=.025$; $B=0.14$, 95% CI $0.02-0.26$, $p=.020$). The total effect of GDM-exposure was not significant for FMI or BMI, and there was no significant association between GDM and birth weight z-score. DIP-exposure had a significant positive effect on birth weight z-score, but the total DIP-effect on FMI/BMI was not significant (Figure 2 and Table S1). Household socioeconomic score had a positive total effect on log-FMI ($B=0.02$, 95% CI $0.002-0.04$, $p=.032$). In GSEM, parity had an indirect and total effect on BMI/log-FMI through the maternal BMI, DIP-exposure, and birth weight z-score pathway. No significant association was found between parity and childhood BMI/log-FMI in regression analysis (Table 4), which adjusts for the pathway variables rather than calculating indirect effects through them, as in GSEM.

Discussion

In our study, the association between exposure to HFDP and subsequent adiposity (FMI) in 3–6-year-old children was not independent of maternal BMI. The association between HFDP exposure and childhood BMI was not statistically significant. Maternal BMI, which was found to have a direct effect on childhood adiposity and BMI, may therefore be of greater concern than HFDP at pre-school age in our setting in SSA.

Previous literature from high- and middle-income countries presents a heterogeneous picture of the impact of HFDP on childhood BMI. While some studies have found an independent effect of HFDP on BMI and overweight/obesity (Nehring et al. 2013; Hillier et al. 2016; Zhu et al. 2016; Grunnet et al. 2017; Tam et al. 2017; Wang et al. 2018; Gu et al. 2019), others showed no significant association (Pettitt et al. 2010; Pham et al. 2013; Bider-Canfield et al. 2017; Kaseva et al. 2018; Kearney et al. 2018; Lowe et al. 2018; Pitchika et al. 2018). Interestingly, some studies found a significant association in school-aged children and adolescents

that was not evident in earlier childhood (Pettitt et al. 2010; Crume et al. 2011; Zhu et al. 2016), possibly due to the accumulation of environmental and behavioural risks for obesity throughout childhood (Silverman et al. 1991; Crume et al. 2011). The overweight/obesity prevalence in our cohort did not exceed national estimates of 11–13%, but 26% of the HFDP-unexposed and 28–29% of the exposed group were at least “at-risk of overweight,” raising concerns for progression to overweight/obesity in later childhood (South African National Department of Health et al. 2019). Since exposure to additional obesogenic factors might not occur in the same pattern in high vs. low-middle income countries, a longitudinal prospective analysis in our setting would provide valuable additional insight.

A number of recent studies exploring adiposity, as opposed to BMI or overweight status alone, found a positive association with HFDP (Chandler-Laney et al. 2012; Zhao et al. 2016; Kaseva et al. 2018; Kearney et al. 2018; Lowe et al. 2018). This was mirrored in our results by the significant unadjusted association between DIP-exposure and childhood FMI. Exposure may thus impact fat rather than lean mass, increasing adiposity ahead of a detectable difference in weight or BMI (Chandler-Laney et al. 2012; Lowe et al. 2018). This has particular clinical relevance because adiposity is associated with increased metabolic risk (Shah et al. 2014), potentially contributing to the rise in early onset of metabolic conditions, including Type 2 diabetes (Jensen and Dabelea 2018; Twig et al. 2020).

However, we did not find the association with FMI to be significant in the less severely hyperglycaemic GDM group. This finding should be interpreted in the context of changing diagnostic criteria, since existing evidence is largely based on definitions of “GDM” that align more closely with our DIP group. A significant impact of GDM by the lower IADPSG criteria used in our study has only been previously shown in an untreated context by the HAPO follow-up studies, in 10–14-year-old children. In pre-school-aged children of mothers with treated GDM, we could not corroborate their findings that an effect of maternal glucose levels on childhood adiposity is evident even at levels lower than those diagnostic of GDM (Lowe et al. 2019).

The majority of existing studies show an attenuating effect of maternal BMI on the association between HFDP and childhood adiposity and overweight (Patel et al. 2012; Zhao et al. 2016; Grunnet et al. 2017; Gingras et al. 2018; Kearney et al. 2018; Lowe et al. 2018), and a number of these, including two systematic reviews (Kim et al. 2002; Kawasaki et al. 2018), also found no remaining significant independent effect of maternal hyperglycaemia. It has been suggested that the effect of HFDP might be more pronounced in normal weight maternal populations, based on a stratified analysis of the impact of HFDP in normal weight, overweight, and obese mothers within the Danish Birth Cohort (Zhu et al. 2016; Grunnet et al. 2017). The consequences of high maternal BMI in cohorts such as ours might thus override consequences of HFDP, although more evidence is needed to corroborate this. The significant impact of maternal pregnancy BMI on childhood overweight and adiposity

(Gebremedhin 2015; Heslehurst et al. 2019) is likely due, in part, to shared genetics and lifestyle. However, foetal programming in response to intrauterine exposures, such as the maternal metabolome (Kadakia et al. 2019), has also been shown to play a role (Lakshman et al. 2012). In particular, based on both animal (Ren et al. 2018) and human studies (Boyle et al. 2017; Hjort et al. 2018), programming may occur through DNA methylation, while changes to hypothalamic development and functioning have additionally been suggested as a possible mechanism (Page et al. 2019). As a modifiable risk factor with alarming prevalence in our participants and South African women of reproductive age in general (Kruger 2018), our findings highlight the importance of maternal obesity as a major target for (preconception) prevention to improve both maternal and child health (Ware et al. 2019).

In GSEM analysis, birth weight was shown to significantly impact BMI and FMI. Changes to an array of nutrients during a hyperglycaemic pregnancy, as opposed to glucose dysregulation and subsequent foetal hyperinsulinaemia alone, are thought to be responsible for excess foetal growth through intrauterine programming (Freinkel 1980; Barbour and Hernandez 2018). While exposure to DIP significantly increased birth weight, exposure to GDM did not. Treatment of hyperglycaemia in pregnancy, including early induction of labour to reduce the risk of macrosomia (Soepnel et al. 2019), could have restricted birth weight and thereby minimised differences in FMI/BMI, particularly in the group exposed to GDM (Macaulay, Munthali, et al. 2018; Macaulay, Ngoben, et al. 2018). However, this does not rule out the possibility of a programming effect manifesting in later childhood in our population, especially since foetal changes have been measured prior to treatment initiation, at 16–18 weeks' gestation, in a population similar to our GDM group (Macaulay, Munthali, et al. 2018; Macaulay, Ngoben, et al. 2018). Further research into the timing and biological mechanisms of such programming is needed in our setting.

A higher household socioeconomic score was positively associated with children's FMI in GSEM and linear regression, a relationship typically described in LMICs as opposed to the inverse association found in high-income countries (Wang 2001). The early life exposures involved in this require further exploration, especially in light of recent findings suggesting an association between GDM, parent-reported nutritional risk score at 2 years, and metabolic risk at 5 years (Patel et al. 2020). Of early childhood nutritional exposures, breastfeeding has been shown to decrease childhood adiposity, including in rural South Africa (Houle et al. 2014), but the role in hyperglycaemic pregnancies is less clear (Kaul et al. 2019), and we found no association with breastfeeding and FMI/BMI in our study.

We did not find an association between HIV infection and childhood BMI/FMI. Although body composition trends of HIV-exposed, uninfected children (HEU) remain unclear, previous evidence has indicated that HEU children who are obese may have inferior cardiovascular outcomes compared to unexposed obese children, and maternal ART may play a role (Jao et al. 2019), possibly mirroring the metabolic effect

of certain ART regimens on mothers (Soepnel et al. 2017). In our study, the majority of HIV-infected women were likely on ART during pregnancy. However, the impact of maternal HIV-exposure and -treatment on such childhood outcomes requires exploration in a larger sample of HEU children with more detailed data on maternal ART use.

A strength of this study was the use of a reference method for determining fat mass, which allowed us to explore both obesity and adiposity. Another strength is the findings' relevance to African settings, where data on the topic are scarce but increasingly important. This includes exploring the rate of stunting, which was similar to regional averages of 11.9% in HFDP-unexposed and DIP groups, and slightly higher in the GDM group at 15.8% (Shisana et al. 2013). Stunting remains a large public health problem in South Africa (Said-Mohamed et al. 2015), and, as an example of the double burden of malnutrition, children exposed to maternal hyperglycaemia do not seem to be less vulnerable to stunting at 3–6 years old.

Difficulties tracing participants 3–6 years after delivery, mostly due to relocation or change of contact details, resulted in a lower sample size and hence less power for between-group comparisons, particularly for the GDM and DIP subgroups. As a result, the study was not powered to assess between-sex differences or the role of HFDP treatments on the outcomes. Another limitation is that, since the study design was not a prospective pregnancy cohort, the pregnancy and early childhood data was retrospective, and we were consequently unable to explore the role of childhood nutrition, physical activity/sedentary behaviour, or paternal factors. Furthermore, the higher gestational age at OGTT in the exposed group opens up the possibility that a small number of participants might have been sorted into a different group if the timing of OGTT's was the same between the two groups (whether later in the HFDP-unexposed, or earlier in the exposed group). This may have minimised differences between the groups and resulting outcomes. Lastly, we did not have data for maternal pre-pregnancy BMI or gestational weight gain. By using BMI measured during pregnancy, weight gain during pregnancy may have resulted in an overestimation of maternal BMI, but there was no significant interaction between pregnancy BMI and the gestational age at measurement.

This study is, to our knowledge, the first in an SSA population to compare BMI and adiposity at pre-school age in children exposed and unexposed to HFDP. The relevance of our findings extends to LMICs similarly experiencing an increase in maternal hyperglycaemia and obesity. We did not find a significant difference in FMI or BMI at 3–6 years old when correcting for maternal BMI. Birth weight, which was limited in the HFDP group by clinical management, likely impacts adiposity and BMI at this age, and additional longitudinal data is required to further explore these associations into later childhood in our setting. Our results also indicate that changes in children's adiposity may reflect before a difference in BMI is detectable at pre-school age. The association of maternal BMI with childhood adiposity raises concerns for an intergenerational cycle of obesity in this

urban African population and calls for increased efforts to curb maternal obesity for promotion of both maternal and child health.

Acknowledgements

The authors thank CHBAH for access to hospital records, and the study participants and their mothers for attending the data collection appointment.

Ethical standards

The authors assert that all procedures contributing to this work comply with the Helsinki Declaration of 1975, as revised in 2008, and have been approved by the Human Research Ethics Committee of the University of the Witwatersrand (ref: M180317). The parent and/or legal guardian of each participant gave written informed consent for participation in the study prior to the start of any study procedures. Participant data was fully anonymised to protect participants' privacy.

Author contributions

SAN, KKG, NL, VN, and LMS contributed to the research conceptualisation. VN and LMS contributed to the study project coordination and data collection. CS advised on the deuterium dilution method and assisted with calculations of body composition. GC contributed to statistical methodology. LMS contributed to data analysis and wrote the initial manuscript version, and all the authors contributed to interpretation of data, editing, and revising the manuscript. All authors had final approval of this submitted version.

Disclosure statement

The authors have no conflict of interest to declare.

Funding

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

ORCID

Larske M. Soepnel  <http://orcid.org/0000-0002-0076-7477>
 Glory Chidumwa  <http://orcid.org/0000-0002-8743-9045>
 Naomi S. Levitt  <http://orcid.org/0000-0001-6480-8066>
 Kerstin Klipstein-Grobusch  <http://orcid.org/0000-0002-5462-9889>
 Shane A. Norris  <http://orcid.org/0000-0001-7124-3788>

Data availability statement

The data that support the findings of this study are available from the corresponding author, LMS, upon reasonable request.

References

Barbour LA, Hernandez TL. 2018. Maternal non-glycemic contributors to fetal growth in obesity and gestational diabetes: spotlight on lipids. *Curr Diab Rep.* 18(6):1–10.
 Bider-Canfield Z, Martinez MP, Wang X, Yu W, Bautista MP, Brookey J, Page KA, et al. 2017. Maternal obesity, gestational diabetes,

breastfeeding and childhood overweight at age 2 years. *Pediatr Obes.* 12(2):171–178.
 Black RE, Victora CG, Walker SP, Bhutta ZA, Christian P, De Onis M, Ezzati M, et al. 2013. Maternal and child undernutrition and overweight in low-income and middle-income countries. *Lancet.* 382(9890):427–451.
 Boyle KE, Patinkin ZW, Shapiro ALB, Bader C, Vanderlinden L, Kechris K, Janssen RC, et al. 2017. Maternal obesity alters fatty acid oxidation, AMPK activity, and associated DNA methylation in mesenchymal stem cells from human infants. *Mol Metab.* 6(11):1503–1516.
 Catalano PM. 2010. The impact of gestational diabetes and maternal obesity on the mother and her offspring. *J Dev Orig Health Dis.* 1(4): 208–215.
 Chandler-Laney PC, Bush NC, Granger WM, Rouse DJ, Mancuso MS, Gower BA. 2012. Overweight status and intrauterine exposure to gestational diabetes are associated with children's metabolic health. *Pediatr Obes.* 7(1):44–52.
 Chatfield A, Caglia J, Dhillon S, Hirst J, Cheikh Ismail L, Abawi K, Kac G, et al. 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(2):139–142.
 Crume TL, Ogden L, Daniels S, Hamman RF, Norris JM, Dabelea D. 2011. The impact of in utero exposure to diabetes on childhood body mass index growth trajectories: the EPOCH study. *J Pediatr.* 158(6):941–946.
 de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. 2007. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ.* 85(9):660–667.
 Draper CE, Tomaz SA, Stone M, Hinkley T, Jones RA, Louw J, Twine R, et al. 2017. Developing intervention strategies to optimise body composition in early childhood in South Africa. *Biomed Res Int.* 2017: 1–13.
 Freinkel N. 1980. Banting Lecture 1980. Of pregnancy and progeny. *Diabetes.* 29(12):1023–1035.
 Gebremedhin S. 2015. Prevalence and differentials of overweight and obesity in preschool children in Sub-Saharan Africa. *BMJ Open.* 5(12): e009005.
 Gillman MW, Ludwig DS. 2013. How early should obesity prevention start? *N Engl J Med.* 369(23):2173–2175.
 Gingras V, Rifas-Shiman SL, Derks IPM, Aris IM, Oken E, Hivert MF. 2018. Associations of gestational glucose tolerance with offspring body composition and estimated insulin resistance in early adolescence. *Diabetes Care.* 41(12):e164–e166.
 Goldfield GS, Harvey A, Grattan K, Adamo KB. 2012. Physical activity promotion in the preschool years: a critical period to intervene. *Int J Environ Res Public Health.* 9(4):1326–1342.
 Grunnet LG, Hansen S, Hjort L, Madsen CM, Kampmann FB, Thuesen ACB, Granström C, et al. 2017. Adiposity, dysmetabolic traits, and earlier onset of female puberty in adolescent offspring of women with gestational diabetes mellitus: a clinical study within the Danish national birth cohort. *Diabetes Care.* 40(12):1746–1755.
 Gu Y, Lu J, Li W, Liu H, Wang L, Leng J, Li Wei Zhang S, et al. 2019. Joint associations of maternal gestational diabetes and hypertensive disorders of pregnancy with overweight in offspring. *Front Endocrinol (Lausanne).* 10:645.
 Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. 2009. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inf.* 42(2):377–381.
 Heslehurst N, Vieira R, Akhter Z, Bailey H, Slack E, Ngongalah L, Pemu A, Rankin J. 2019. The association between maternal body mass index and child obesity: a systematic review and meta-analysis. *PLoS Med.* 16(6):e1002817.
 Hillier TA, Pedula KL, Vesco KK, Oshiro CES, Ogasawara KK. 2016. Impact of maternal glucose and gestational weight gain on child obesity over the first decade of life in normal birth weight infants. *Matern Child Health J.* 20(8):1559–1568.
 Hjort L, Martino D, Grunnet LG, Naeem H, Maksimovic J, Olsson AH, Zhang C, et al. 2018. Gestational diabetes and maternal obesity are associated with epigenome-wide methylation changes in children. *JCI Insight.* 3(17):e122572

- Houle B, Clark SJ, Gómez-Olivé FX, Kahn K, Tollman SM. 2014. The unfolding counter-transition in rural South Africa: mortality and cause of death, 1994–2009. *PLoS One*. 9(6):e100420.
- IAEA. 2010. Introduction to body composition assessment using the deuterium dilution technique with analysis of saliva samples by Fourier Transform Infrared Spectrometry. IAEA human health series No. 12. Vienna: IAEA. [accessed 2019 Mar 25]. <http://www.iaea.org/Publications/index.html>.
- Jao J, Jacobson DL, Yu W, Borkowsky W, Geffner ME, McFarland EJ, Patel K, Williams PL, Miller T. 2019. A comparison of metabolic outcomes between obese HIV-exposed uninfected youth from the PHACS SMARTT study and HIV-unexposed youth from the NHANES study in the United States. *J Acquir Immune Defic Syndr*. 81(3):319–327.
- Jensen ET, Dabelea D. 2018. Type 2 diabetes in youth: new lessons from the SEARCH study. *Curr Diab Rep*. 18(6):36.
- Kadokia R, Nodzenski M, Talbot O, Kuang A, Bain JR, Muehlbauer MJ, Stevens RD, et al. 2019. Maternal metabolites during pregnancy are associated with newborn outcomes and hyperinsulinaemia across ancestries. *Diabetologia*. 62(3):473–484.
- Kaseva N, Väärämäki M, Matinlinna HM, Sipilä-Leppänen M, Tikanmäki M, Heinonen K, Lano A, et al. 2018. Pre-pregnancy overweight or obesity and gestational diabetes as predictors of body composition in offspring twenty years later: evidence from two birth cohort studies. *Int J Obes*. 42(4):872–879.
- Kaul P, Bowker SL, Savu A, Yeung RO, Donovan LE, Ryan EA. 2019. Association between maternal diabetes, being large for gestational age and breast-feeding on being overweight or obese in childhood. *Diabetologia*. 62(2):249–258.
- Kawasaki M, Arata N, Miyazaki C, Mori R, Kikuchi T, Ogawa Y, Ota E. 2018. Obesity and abnormal glucose tolerance in offspring of diabetic mothers: a systematic review and meta-analysis. *PLoS One*. 13(1):e0190676.
- Kearney M, Perron J, Marc I, Weisnagel SJ, Tchernof A, Robitaille J. 2018. Association of prenatal exposure to gestational diabetes with offspring body composition and regional body fat distribution. *Clin Obes*. 8(2):81–87.
- Kim C, Newton KM, Knopp RH. 2002. Gestational diabetes and the incidence of type 2 diabetes: a systematic review. *Diabetes Care*. 25(10):1862–1868.
- Kruger HS. 2018. Obesity among women: a complex setting. *South African J Clin Nutr*. 31(4):4–5.
- Lakshman R, Elks CE, Ong KK. 2012. Childhood obesity. *Circulation*. 126(14):1770–1779.
- Lei PW, Wu Q. 2007. Introduction to structural equation modeling: issues and practical considerations. *Educ Meas Issues Pract*. 26(3):33–43.
- Logan KM, Gale C, Hyde MJ, Santhakumaran S, Modi N. 2017. Diabetes in pregnancy and infant adiposity: Systematic review and meta-analysis. *Arch Dis Child Fetal Neonatal Ed*. 102(1):F65–F72.
- Lowe WL, Lowe LP, Kuang A, Catalano PM, Nodzenski M, Talbot O, Tam WH, et al. 2019. Maternal glucose levels during pregnancy and childhood adiposity in the hyperglycemia and adverse pregnancy outcome follow-up study. *Diabetologia*. 62(4):598–610.
- Lowe WL, Scholtens DM, Lowe LP, Kuang A, Nodzenski M, Talbot O, Catalano PM, et al. 2018. Association of gestational diabetes with maternal disorders of glucose metabolism and childhood adiposity. *JAMA*. 320(10):1005–1016.
- Macaulay S, Munthali RJ, Dunger DB, Norris SA. 2018. The effects of gestational diabetes mellitus on fetal growth and neonatal birth measures in an African cohort. *Diabet Med*. 35(10):1425–1433.
- Macaulay S, Ngobeni M, Dunger DB, Norris SA. 2018. The prevalence of gestational diabetes mellitus amongst black South African women is a public health concern. *Diabetes Res Clin Pract*. 139:278–287.
- Nehring I, Chmitorz A, Reulen H, von Kries R, Ensenaer R. 2013. Gestational diabetes predicts the risk of childhood overweight and abdominal circumference independent of maternal obesity. *Diabet Med*. 30(12):1449–1456.
- Onubi OJ, Marais D, Aucott L, Okonofua F, Poobalan AS. 2016. Maternal obesity in Africa: a systematic review and meta-analysis. *J Public Health*. 38(3):e218–e231.
- Oppong SA, Ntuny MY, Amoakoh-Coleman M, Ogum-Alangea D, Modey-Amoah E. 2015. Gestational diabetes mellitus among women attending prenatal care at Korle-Bu Teaching Hospital, Accra, Ghana. *Int J Gynecol Obstet*. 131(3):246–250.
- Page KA, Luo S, Wang X, Chow T, Alves J, Buchanan TA, Xiang AH. 2019. Children exposed to maternal obesity or gestational diabetes mellitus during early fetal development have hypothalamic alterations that predict future weight gain. *Dia Care*. 42(8):1473–1480.
- Patel BP, McLellan SS, Hanley AJ, Retnakaran R, Hamilton JK. 2020. Greater nutritional risk scores in 2-year old children exposed to gestational diabetes mellitus in utero and their relationship to HOMA-IR at age 5-years. *Can J Diabetes*. 1–5. doi: [10.1016/j.jcjd.2020.07.007](https://doi.org/10.1016/j.jcjd.2020.07.007).
- Patel S, Fraser A, Smith GD, Lindsay RS, Sattar N, Nelson SM, Lawlor DA. 2012. Associations of gestational diabetes, existing diabetes, and glycosuria with offspring obesity and cardiometabolic outcomes. *Diabetes Care*. 35(1):63–71.
- Pettitt DJ, McKenna S, McLaughlin C, Patterson CC, Hadden DR, McCance DR. 2010. Maternal glucose at 28 weeks of gestation is not associated with obesity in 2-year-old offspring: the Belfast Hyperglycemia and Adverse Pregnancy Outcome (HAPO) family study. *Diabetes Care*. 33(6):1219–1223.
- Pham MT, Brubaker K, Pruett K, Caughey AB. 2013. Risk of childhood obesity in the toddler offspring of mothers with gestational diabetes. *Obstet Gynecol*. 121(5):976–982.
- Pitchika A, Vehik K, Hummel S, Norris JM, Uusitalo UM, Yang J, Virtanen SM, Koletzko S, Andrén Aronsson C, Ziegler AG et al. 2018. Associations of maternal diabetes during pregnancy with overweight in offspring: results from the prospective TEDDY study. *Obesity*. 26(9):1457–1466.
- Ren J, Cheng Y, Ming ZH, Dong XY, Zhou YZ, Ding GL, Pang HY, et al. 2018. Intrauterine hyperglycemia exposure results in intergenerational inheritance via DNA methylation reprogramming on F1 PGCs. *Epigenet Chromat*. 11(1):20.
- Richter L, Norris S, Pettifor J, Yach D, Cameron N. 2007. Cohort profile: Mandela's children: the 1990 birth to twenty study in South Africa. *Int J Epidemiol*. 36(3):504–511.
- Said-Mohamed R, Micklesfield LK, Pettifor JM, Norris SA. 2015. Has the prevalence of stunting in South African children changed in 40 years? A systematic review. *BMC Public Health*. 15(1):534.
- Samadi M, Sadrzade-Yeganeh H, Azadbakht L, Jafarian K, Rahimi A, Sotoudeh G. 2013. Sensitivity and specificity of body mass index in determining obesity in children. *J Res Med Sci*. 18(7):537–542.
- Shah RV, Murthy VL, Abbasi SA, Blankstein R, Kwong RY, Goldfine AB, Jerosch-Herold M, et al. 2014. Visceral adiposity and the risk of metabolic syndrome across body mass index: the MESA study. *JACC Cardiovasc Imaging*. 7(12):1221–1235.
- Shisana O, Labadaria D, Rehle T, Leickness S, Zuma K, Parker W, Maluleke T, et al. 2013. The South African National Health and nutrition examination survey SANHANES-1. Cape Town, South Africa.
- Silverman BL, Rizzo T, Green OC, Cho NH, Winter RJ, Ogata ES, Richards GE, Metzger BE. 1991. Long-term prospective evaluation of offspring of diabetic mothers. *Diabetes*. 40(2):121–125.
- Soepnel LM, Nicolaou V, Huddle KRL, Klipstein-Grobusch K, Levitt NS, Norris SA. 2019. Maternal and neonatal outcomes following a diabetic pregnancy within the context of HIV. *Int J Gynecol Obstet*. 147(3):404–412.
- Soepnel LM, Norris SA, Schrier VJMM, Browne JL, Rijken MJ, Gray G, Klipstein-Grobusch K. 2017. The association between HIV, antiretroviral therapy, and gestational diabetes mellitus. *AIDS*. 31(1):113–125.
- South African National Department of Health, South African Medical Research Council, ICF. 2019. South Africa demographic and health survey 2016. Pretoria, South Africa: South African National Department of Health, South African Medical Research Council, ICF.
- Statistics South Africa. 2016. Statistics South Africa [Internet]. [accessed 2019 Oct 4]. http://www.statssa.gov.za/?page_id=4286&id=11317.
- Steyn NP, Mchiza ZJ. 2014. Obesity and the nutrition transition in Sub-Saharan Africa. *Ann NY Acad Sci*. 1311(1):88–101.
- Tam WH, Ma RCW, Ozaki R, Li AM, Chan MMH, Yuen LY, Lao TTH, et al. 2017. In utero exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. *Dia Care*. 40(5):679–686.

- Twig G, Zucker I, Afek A, Cukierman-Yaffe T, Bendor CD, Derazne E, Lutski M, et al. 2020. Adolescent obesity and early-onset type 2 diabetes. *Dia Care*. 43(7):1487–1495.
- UNICEF, WHO, World Bank Group. 2018. Joint child malnutrition estimates - levels and trends in child malnutrition. Geneva, Switzerland; UNICEF, WHO, World Bank Group. [accessed 2019 Aug 19]. <https://www.who.int/nutgrowthdb/2018-jme-brochure.pdf?ua=1>.
- Wang J, Wang L, Liu H, Zhang S, Leng J, Li W, Zhang T, et al. 2018. Maternal gestational diabetes and different indicators of childhood obesity: a large study. *Endocr Connect*. 7(12):1464–1471.
- Wang Y. 2001. Cross-national comparison of childhood obesity: the epidemic and the relationship between obesity and socioeconomic status. *Int J Epidemiol*. 30(5):1129–1136.
- Ware LJ, Prioreschi A, Bosire E, Cohen E, Draper CE, Lye SJ, Norris SA. 2019. Environmental, social, and structural constraints for health behavior: perceptions of young Urban Black Women during the pre-conception period—A healthy life trajectories initiative. *J Nutr Educ Behav*. 51(8):946–957.
- Wells JC, Sawaya AL, Wibaek R, Mwangome M, Poullas MS, Yajnik CS, Demaio A. 2020. Double burden of malnutrition 2: the double burden of malnutrition: aetiological pathways and consequences for health. *Lancet*. 395(10217):75–88.
- World Health Organization [WHO]. 2013. Diagnostic criteria and classification of hyperglycaemia first detected in pregnancy [Internet]. Geneva, Switzerland: World Health Organization https://www.who.int/diabetes/publications/Hyperglycaemia_In_Pregnancy/en/.
- World Health Organization [WHO]. 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. Geneva, Switzerland: World Health Organization. [accessed 2018 Feb 6]. <http://www.who.int/childgrowth/en/>.
- Zhao P, Liu E, Qiao Y, Katzmarzyk PT, Chaput JP, Fogelholm M, Johnson WD, et al. 2016. Maternal gestational diabetes and childhood obesity at age 9–11: results of a multinational study. *Diabetologia*. 59(11):2339–2348.
- Zhu Y, Olsen SF, Mendola P, Yeung EH, Vaag A, Bowers K, Liu A, et al. 2016. Growth and obesity through the first 7 y of life in association with levels of maternal glycemia during pregnancy: a prospective cohort study. *Am J Clin Nutr*. 103(3):794–800.