

## Maternal anthropometric measurements in pregnancy and child neurocognitive and behavioral development at 1 and 6 years of age: A cohort study in Benin, Sub-Saharan Africa

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### ABSTRACT

**Background:** Low and high body mass index (BMI) are hypothesized to impact offspring neurodevelopment, but less is known in sub-Saharan Africa where undernutrition is highly prevalent.

**Objective:** The aim of this study was to investigate the association between maternal anthropometric measurements during pregnancy and neurocognitive and behavioral development in children at age 1 and 6 years, in a mother-child cohort from Benin.

**Methods:** This prospective cohort study included surviving singletons born to pregnant women in Allada, Benin. Cognitive and motor functions of 747 and 574 children were assessed at 1 and 6 years of age, respectively, in addition to behavioral difficulties and attention deficit and hyperactivity disorders. Statistical analysis using multiple linear regression models tested main associations, potential mediating factors were additionally adjusted for.

**Results:** Total of 17%, 72.5%, 7.7% and 2.5% of women were estimated to be underweight, normal weight, overweight and obese before pregnancy, respectively. Women who were underweight had a higher median weight gain (240 [170–300]) over the course of pregnancy, compared to normal BMI women (210 [160–260]), and overweight/obese women (150 [110–240]). After exclusion of obese women, estimated pre pregnancy BMI was significantly associated with higher motor scores (0.26, 95% CI 0.002–0.53) and cognitive scores (0.37, 95% CI 0.02–0.72) after adjustment for confounding factors. There was no association between gestational weight gain and offspring neurodevelopment at 1 and 6 years of age. There was no association between maternal BMI and gestational weight gain and behavior and attention deficit and hyperactivity disorders at 6 years of age.

**Conclusions:** Our study suggests that low BMI before pregnancy may impair short- and long-term neurocognition in children in the Beninese context. Undernutrition in childhood has great impact and efforts to adequate prevention for both child and maternal undernutrition should be enforced in low- and middle-income countries.

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**Abbreviations:** ANV, Antenatal Visit; BMI, Body Mass Index; BOT, Bruininks-Oseretsky Test of Motor Proficiency; DOHaD, Development Origins of Health and Disease; ELC, Early Learning Composite score; EXPLORE, Lead and Manganese Exposure and Child Risk; GWG, Gestational Weight Gain; HOME, Home Observation for the Measurement of the Environment; IPTp, Intermittent Preventive Treatment of Malaria in Pregnancy; KABC, Kaufman Assessment Battery for children; MiPPAD, Malaria in Pregnancy Preventive Alternative Drugs; MSEL, Mullen Scales of Early Learning; SDQ, Strengths and Difficulties Questionnaire; SES, Socio-economic

Status; TOVA, Test of Variables of Attention; TOVI, Fon Language; VIF, Variance Inflation Factor; WHO, World Health Organization

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## Introduction

Optimal child development is essential to adult health and wellbeing, and critical to achieving the Sustainable Development Goals. The human brain is particularly susceptible to adverse exposures during 2 sensitive periods: *in utero* and early years of life [1]. As the Development Origins of Health and Disease (DOHaD) states, exposure to adverse environmental influences in intrauterine life can impact short- and long-term disease risk in adulthood [2]. The first 1000 days of life—the time spanning between conception and second postnatal year—is the most crucial period to developing foundational neurocognitive competencies and ultimately, for integrating to the society and becoming economically successful [3]. Yet, more than 250 million children under-5 in low- and middle-income countries (LMICs) (43%) fail to attain their potential in neurocognitive and behavioral development (Lu, Black, & Richter, 2016). As a result, such loss of human potential leads to a 19.8% deficit in adult annual income [4], with a global economic cost of \$177 billion for growth faltering alone (Fink et al., 2016).

Developing countries, particularly in Sub-Saharan Africa, are now facing a double burden of nutrition transition, characterized by undernutrition along with overweight and obesity in women of reproductive age [5]. According to the 2017–2018 demographic questionnaire, the percentage of underweight and overweight/obese women has increased in comparison to year 2006, from 9% to 11% and 19% to 26%, respectively [6].

Most of the recent studies on the effect of the body mass index (BMI) and gestational weight gain (GWG) on child neurodevelopment comes from high-income countries, focusing on maternal overweight and obesity as modifiable factors that have subsequent consequences in the impaired offspring development, along with sub-optimal GWG [7,8]. Research has suggested that there might exist an inverted U-shaped association between maternal pre pregnancy BMI and children's cognitive scores [9]. However, these studies are usually prone to misclassification bias due to the self-reported pre pregnancy weight or collection of such information from medical records. Few longitudinal birth-cohort studies have examined both undernutrition and overweight and child development in the long term by using a life course approach [10]. Even fewer studies have evaluated the effect of pre pregnancy maternal underweight on child neurocognitive development in low- and middle-resource settings. Results are also inconsistent, with a study carried out in rural China reporting a positive association between pre pregnancy underweight and intellectual development of early-school aged children, whereas another one in Brazil, concluding that maternal underweight and excessive GWG were negatively associated with child development [11,12].

Recent epidemiological studies in Sub-Saharan Africa have focused on the association between micronutrient deficiency, stunting, wasting and child development [13–15]. For instance, Mireku et al. found no association between prenatal iron deficiency and cognitive and motor function of children at age 1 year [16]. However, studies on pre pregnancy underweight and associated outcomes are scarce. To the best of our knowledge, there has been only 1 study conducted previously in Benin that has assessed the relationship between maternal pre pregnancy BMI and child's cognitive development, but in children of 1 and 3 months of age [17]. The long-term health consequences of maternal anthropometric measurements in the offspring could have profound public health implications and have rarely been investigated in a resource-poor setting. Anthropometric measurements with BMI could be an indicator of overall poor nutrition and health policies to tackle the issue are more complex compared to micronutrient deficiencies, where usually supplementation is the solution.

Several studies have shown the positive impact of breastfeeding and nutrients in early postnatal life on cognitive function in children, focusing this way on child's growth [18]. However, with the rise of DOHaD hypothesis, there has been a shift of research-focus from child growth and pregnancy to the health of women before pregnancy. This is of particular importance as it can inform policies on more interventions targeted towards women of reproductive age before becoming pregnant. In this context, less is known on the health consequences of peri-conceptional maternal nutrition on child development.

Therefore, the aim of this study was to investigate the association between maternal anthropometric measurements before and during pregnancy and neurocognitive and behavioral development in children at age 1 and 6 years, in a mother-child cohort from Benin.

## Methods

### Study design and population

This prospective cohort study included surviving singletons born to pregnant women enrolled in the *Malaria in Pregnancy Preventive Alternative Drugs (MiPPAD)* randomized controlled trial (NCT00811421), evaluating the efficacy of 2 intermittent preventive treatment of malaria in pregnancy (IPTp). The clinical trial was conducted in the district of Allada, Benin, and women with gestational age of  $\leq 28$  weeks were recruited in these local maternity clinics at their first antenatal visit (ANV). Detailed eligibility criteria for MiPPAD clinical trial are fully explained elsewhere [19]. All live-born singletons of women enrolled in MiPPAD trial were invited to participate in a cross-sectional study called TOVI (Tovi means child in the Fon language of Benin) for neurocognitive assessment at 1 year of age [20]. The aim of this study was to assess the association between anemia of women during pregnancy and child neurodevelopment at 1 year of age. A continuation of TOVI study was *Lead and Manganese Exposure and Child Risk (EXPLORE)* study, which followed-up children at 6 years of age and investigated their neurocognitive and behavioral development.

### Main exposures of interest

The main exposures of our study were maternal estimate pre pregnancy BMI and GWG. Women who were enrolled in MiPPAD trial were examined at 2 ANV visits at least 1 month apart and at delivery. Estimate pre pregnancy BMI was determined using weight (kilograms), height (meters) and gestational age recorded at the first ANV (uterine height). Weight was measured by using an electronic scale (Sesa Corp., Hanover, MD) and height by a bodymeter device (Seca 206 Bodymeter, Seca Corp.). Pregnant women are expected to gain approximately 1 kg per month from the end of the first trimester until delivery (ACC/SCN, 2000). Therefore, using gestational age at inclusion, the expected weight gain since the beginning of pregnancy was estimated. A rough estimate of the weight before pregnancy was then calculated by subtracting the expected weight gain from women's weight at the first ANV ([Supplementary Table 1](#)). According to WHO recommendations, estimate pre pregnancy BMI was categorized as underweight ( $<18.5 \text{ kg/m}^2$ ), normal ( $18.5\text{--}24.9 \text{ kg/m}^2$ ), overweight ( $25\text{--}29.9 \text{ kg/m}^2$ ) and obese ( $\geq 30 \text{ kg/m}^2$ ) (World Health Organization, 2000). Gestational weight gain was calculated by subtracting the estimated pre pregnancy weight from the last weight measured at delivery.

## Main outcomes of interest

### Child development at 1 year

Child development in children of 1 year of age was assessed using the Mullen Scales of Early Learning (MSEL). MSEL is an assessment battery for cognitive and motor functions in children aged up to 68 months [21]. The MSEL is organized in 5 subscales: Gross Motor, Fine Motor, Visual Reception, Receptive Language and Expressive Language. Initially, each item is scored and raw scores are calculated, which in turn are then transformed into standardized T-scores. An Early Learning Composite score (ELC) is derived from combining T-scores of Fine Motor, Visual Reception, Receptive Language and Expressive Language which represents the cognitive performance of the child. The MSEL was translated from English to French. Items were administered in the Fon language. The MSEL showed good construct validity in a previous study [22].

### Child development at 6 years

Participants in EXPLORE study were mothers and their children that were recruited in the health centres of Attogon and Sékou in Benin. Mothers gave written consent and filled in a questionnaire administered by trained assessors. Meanwhile, blood and stool samples were collected from children and they were then assessed for neurodevelopment outcomes. Children that presented with fever on the day of the visit, underwent a blood test for the investigation of infections and were asked to come back at a later date. National treatment guidelines were followed to treat those diagnosed with malaria, anaemia or helminth infection.

Neurocognitive development in children of 6 years of age was assessed using 3 tests: 1) the Kaufman Assessment Battery for Children, second edition (KABC-II) [23]; 2) the Bruininks-Oseretsky Test of Motor Proficiency Edition 2 (BOT-2); 3) the Test of Variables of Attention (TOVA) [24]. KABC-II is an individually administered instrument measuring cognitive, processing ability, planning and learning capabilities. A quality control for KABC-II was done in a health center in Uganda where videos were sent. Mental Processing Index (MPI), a global cognitive ability index of KABC-II was included in the analysis. BOT-2 provides a comprehensive measurement of gross and fine motor skills, and standardized scores for both these skills were used in analysis. At last, TOVA evaluates attention deficit and hyperactivity disorders, and for the purpose of this study the Attention Deficit and Hyperactivity Disorder (ADHD) score was analyzed.

The parent-reported Strengths and Difficulties Questionnaire (SDQ) administered to mothers in the Fon language, was used to assess emotional and behavioral development [25]. The screening questionnaire comprises 25 items on psychological attributes divided between 5 scales: emotional symptoms, conduct problems, hyperactivity, peer relationship problems and prosocial behavior. Beside the total SDQ score, externalizing scores were calculated to assess behavioral problems. Given the high proportion of illiteracy, questionnaires were administered by assessors to all caregivers.

### Other variables

Socio-economic status (SES) was assessed by family wealth index and maternal education. Family wealth score was generated through a questionnaire administered to mothers asking about objects that the families might possess such as television, radio, bicycle etc. Maternal age and education information were collected from women during assessment in TOVI. The Home Observation for the Measurement of the Environment (HOME) score was used to assess parent-child interactions and the learning opportunities offered to the child in the home environment. Data about gravidity

was collected during the first ANV. Birthweight and child's gender were assessed at delivery, and gestational age was estimated using fundal height.

### Statistical analysis

Baseline and exposure characteristics of our study population followed up to 6 years after delivery were described and compared to lost-to-follow-up and deceased children using Chi-square test, Fisher exact test for small numbers and Wilcoxon rank sum test. Estimate prepregnancy BMI was described and GWG was assessed across the BMI groups and compared by using Kruskal-Wallis test. Univariate analysis was carried out to test for associations between maternal-child characteristics and exposures, as well as outcomes of interest to this study.

Multiple linear regression was used to test the association between exposures and outcomes at 1 and 6 years. Several potential confounders for the association between maternal anthropometric measurements during pregnancy and child neurodevelopment at the age of 1 and 6 years were identified a priori in previous literature and directed acyclic graphs (DAG) were used in selecting confounders in multiple regression analysis. Postestimation diagnostics were run to check for the normality of residuals through plotting, homoscedasticity of residuals through graphing the residuals against the fitted values, multicollinearity by using the variation inflation factor (VIF), linearity and specification of the models. Given the low number of obese women and potentially different impact, obese women were excluded from the analyses on estimate prepregnancy BMI and offspring cognitive outcomes.

Infant characteristics at birth such as birthweight, preterm births and maternal characteristics including gestational weight gain were hypothesized to be within the causal pathway in the association between estimate prepregnancy BMI and child neurocognition. Since preterm births and birthweight were hypothesized as mediators, we additionally adjusted for these variables in sensitivity analyses. Maternal BMI might act as a confounder for the relationship between gestational weight gain and neurocognition outcomes, and women who are overweight or obese before pregnancy gain less weight during pregnancy. To address this confounder, we adjusted for it when running multiple linear models for the association between GWG and neurocognition and behavioral development outcomes

Due to the difference between primigravida and multigravida in terms of malaria prevalence, micro-nutrients deficiencies and BMI shown elsewhere [16], we further stratified for it to explore a potential modification effect for the association between BMI and child neurocognition and behavioral development.

Statistical analyses were completed using STATA 16 (StataCorp. 2019. *Stata Statistical Software: Release 16*. College Station, TX: StataCorp LLC.) for Mac OSX. A *P*-value < 0.05 was considered significant.

### Ethical consideration

Ethical approval for all studies used for the purpose of this article were obtained by the following institutions: MiPPAD clinical trial and TOVI studies were approved by the Comité Consultatif de Déontologie et d'Éthique of the Institut de Recherche pour le Développement (France), and Ethics Committee of the the Faculté des Sciences de la Santé, Benin. EXPLORE study was approved by the Ethics Committee of the Institut des Sciences Biomédicales Appliquées and the Research Institute for Development's Consultative Ethics Committee in France.

## Results

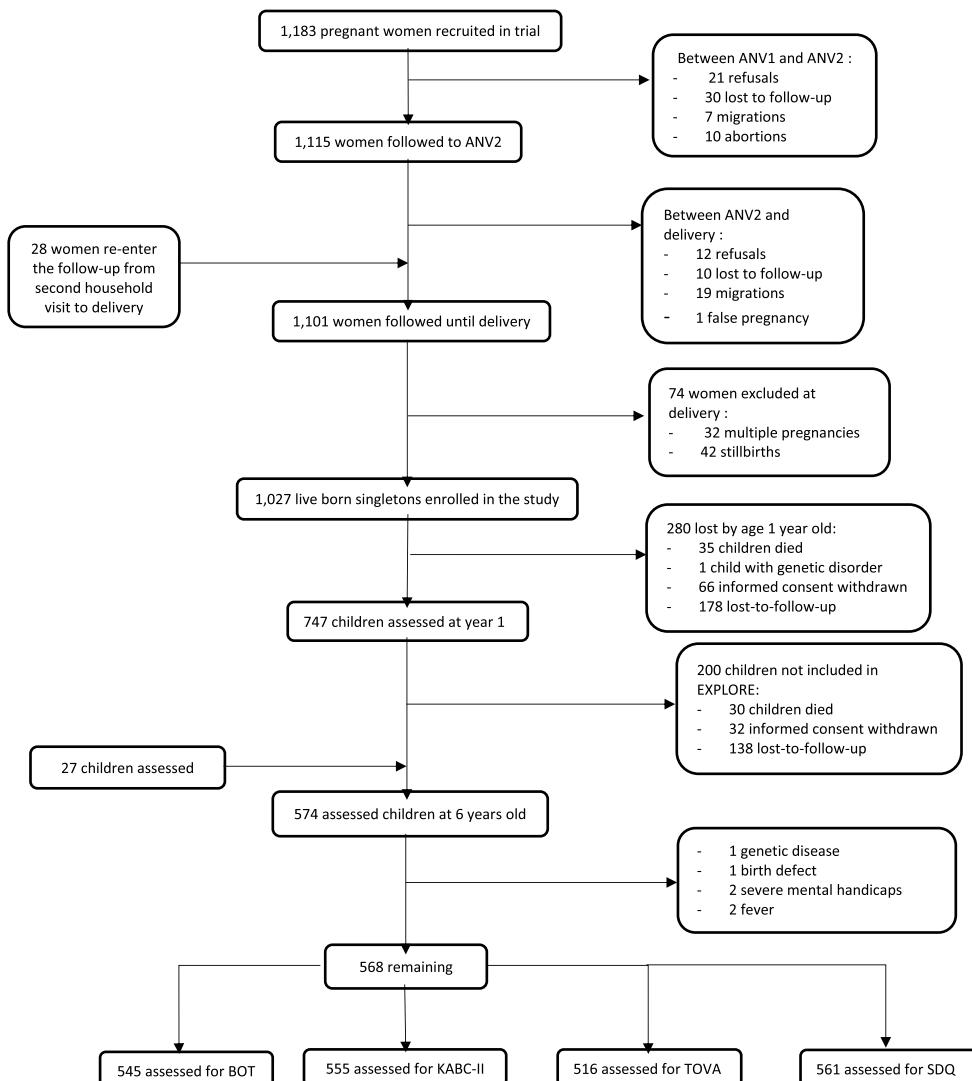
Of the 1183 pregnant women enrolled in the MiPPAD clinical trial, 1101 were followed until delivery (Fig. 1). Sixty-eight (6%) were lost from recruitment to second ANV, meanwhile from second ANV until delivery, 42 (4%) were lost and 28 re-entered the follow-up. At delivery, 32 multiple pregnancies and 42 stillbirths were excluded. In all, 1027 live born singletons were eligible for follow-up from birth to 1 year of age. Among them, 280 (27%) were lost by age 1. Of the 747 children assessed at year 1 in TOVI study, 200 were not assessed at 6 years of age. Another 27 eligible singletons were assessed in EXPLORE but not in TOVI study. As a result, 568 eligible children were assessed at 6 years of age in EXPLORE study. Out of the 574 eligible children, 2 children with severe mental disorders, 1 with birth defect and another with genetic disease were excluded from analysis, along with 2 children that presented with fever ( $\geq 37.5^{\circ}\text{C}$ ) at the time of assessment or whose scores were not valid.

Table 1 presents the comparison of maternal and child characteristics, as well as maternal exposure between children included and excluded in our analysis. Mother-child pairs included in our analysis were of higher maternal age, lower maternal education,

higher maternal occupation levels and multigravidity women. Children who died during the 6-year follow-up period were more likely to have been born preterm (<37 weeks), with a low birth-weight (<2500 grams) and to primigravida women, compared to children who were included for assessment at 6 years of age.

Table 2 in provides a description of the anthropometric assessment of women before and during pregnancy. Due to the small number of observations for the obese 19 (2.5%) and overweight 57 (7.6%) category, obese women were excluded from the analysis. Total 72.5% of women had a normal estimate pre pregnancy BMI, while 17.3% were underweight and 2.5% had obesity. Women who were estimated to be underweight before pregnancy had a higher median weight gain (0.24 [0.17–0.30]) over the course of pregnancy, compared to those who had a normal BMI (0.21 [0.16–0.26]) or were overweight/obese (0.15 [0.11–0.24]). This difference was statistically significant ( $P < 0.0001$ , Kruskal–Wallis).

In crude analyses, maternal overweight before conception was significantly associated with a higher ELC score (5.31, 95% CI 1.06; 9.6), Gross Motor score (5.48 95% CI 1.02–9.93), and KABC-II MPI score (4.31, 95% CI 0.02–8.60) compared to underweight women (Table 3). However, these associations were no longer significant



**Fig. 1.** Population flowchart of pregnant women and children follow-up.

**Table 1**

Maternal and child characteristics at 1 and 6 years of age

Parameter <sup>†</sup>	Included (N = 568) n (%) or median (range)	Lost (N = 394) n (%) or median (range)	P-value*	Deceased (N = 65) n (%) or median (range)	P-value*
<i>Demographic characteristics<sup>1</sup></i>					
<b>Maternal age</b>	26 (23–31)	26 (21–30)	<b>0.007</b>	26 (21–31)	0.288
<b>Mother education</b>			<b>0.029</b>		0.174
No education	355/567 (62.6)	94/176 (53.4)		19/25 (76)	
Primary education/+	212/567 (37.4)	82/176 (46.6)		6/25 (24)	
<b>Mother occupation</b>			<b>0.016</b>		0.793
Not employed	36/541 (6.7)	22/179 (12.3)		2/25 (8)	
Employed	505/541 (93.4)	157/179 (87.7)		23/25 (92)	
<b>Father occupation</b>			<b>0.049</b>		
Not employed	1/535 (0.2)	3/176 (1.7)		-	
Employed	534/535 (99.8)	173/176 (98.3)		25/25 (100)	
<b>Gravidity</b>			<b>0.001</b>		<b>0.014</b>
Primigravida	82/568 (14.4)	89/393 (22.7)		17/65 (26)	
Multigravida	486/568 (85.6)	304/393 (77.3)		48/65 (74)	
<b>Family possession score</b>	5 (3–8)	6 (3–9)	0.244	4 (3–5)	0.061
<b>Marital status</b>			<b>0.011</b>		0.858
Monogamous	324/539 (60.1)	127/76 (72.2)		16/25 (64)	
Polygamous	211/539 (39.2)	49/176 (27.8)		9/25 (36)	
Widow	4/539 (0.7)	-		-	
<b>Child sex</b>			0.173		0.786
Female	281/568 (49.5)	212/393 (53.9)		31/65 (47.7)	
Male	287/568 (50.5)	181/393 (46.1)		34/65 (52.3)	
<b>Birthweight</b>			0.127		<b>0.000</b>
Low (<2500g)	47/564 (8.3)	44/390 (11.3)		17/65 (26.2)	
Normal (≥ 2500g)	517/564 (91.7)	346/390 (88.7)		48/65 (73.8)	
<b>Gestational age</b>			0.943		<b>0.002</b>
Preterm (<37 weeks)	36/563 (6.4)	25/384 (6.5)		11/64 (17.2)	
Term (≥ 37 weeks)	527/563 (93.6)	359/384 (93.5)		53/64 (82.8)	
<i>Exposure characteristics</i>					
<b>Estimate prepregnancy BMI</b>			0.395		0.152
Underweight (<18.5)	100/568 (17.6)	59/394 (15)		11/65 (16.9)	
Normal (18.5–24.9)	409/568 (72.0)	286/394 (72.6)		52/65 (80)	
Overweight/Obese (≥25)	59/568 (10.4)	49/394 (12.4)		2/65 (3.1)	
<b>Gestational weight gain</b>	8 (6–10.5)	8 (6–10.5)	0.693	7.5 (6–9.5)	0.229

Boldface indicates statistical significance ( $P < 0.05$ ).\*P-values from  $\chi^2$  test (for categorical variables) or Fisher's exact (if small numbers) or Wilcoxon rank-sum test (for continuous variables).<sup>†</sup>All parental demographic variables were assessed when the child was 1 year old.

after adjustment although a positive trend was observed. When estimate prepregnancy BMI was considered as a continuous variable in the model, the associations held significant for both KABC-II MPI and BOT-2 Standard Score in crude and adjusted models. After further adjustment for birthweight and preterm births in sensitivity analysis, these associations were no longer significant suggesting a potential mediating effect of preterm birth and low birth weight (Supplementary Table 1). Table 4 illustrates that gestational weight gain during pregnancy was not associated with neurodevelopment or behavioral outcomes at 1 and 6-year-old children.

Multiple removal of outliers for the relationship of both estimate prepregnancy BMI and gestational weight gain to neurodevelopment and behavioral outcomes, did not alter the association. Analysis between estimate prepregnancy BMI and child neurological and behavioral outcomes stratified by gravidity and by child's gender (Table S2), did not suggest any interaction. However, because of the low number of observations in the models, 95% CI were very large.

## Discussion

Based on this mother-child cohort, we found some evidence for the association of prepregnancy BMI and gestational weight gain with child neurocognitive and behavioral development in crude analysis. However, of a wide range of outcome measured—impaired cognitive performance and gross motor function at 1 year of age; cognitive ability, gross and fine motor skills, hyperactivity disorder, emotional and behavioral development at 6 years of age—these associations did not persist after controlling for confounders. Overall, children born to mothers who belonged to the overweight category, presented better scores than those born to underweight women. Overall, we found no evidence of inverted U-shape relationship between maternal estimate prepregnancy BMI and children's cognitive scores, in this population where we excluded obese women from the analyses.

A previous study involving 150 infants found that children of mothers who were underweight before conception had poor

**Table 2**

Anthropometric measurements of pregnant women before and during pregnancy

Maternal characteristics	Total (N = 746) N (%)	Total weight gain (kg) (N = 585) Median (IQR)	Total weight gain* (kg/week) (N = 584) Median (IQR)
<b>Estimate prepregnancy BMI</b>			
Underweight (<18.5)	129 (17.3)	9 (6.5–12)	0.24 (0.17–0.30)
Normal (18.5–24.9)	541 (72.5)	8 (6–10)	0.21 (0.16–0.26)
Overweight/Obese (>=25)	76 (10.2)	6 (4.5–10)	0.15 (0.11–0.24)

\*Significant difference of total weight gain across the 3 categories of estimate prepregnancy BMI ( $P < 0.0001$ , Kruskal–Wallis).

**Table 3**

Multiple linear regression models between estimate prepregnancy BMI and child neurodevelopment and behavioral outcomes at 1 and 6 years of age

ELC score	Underweight (<18.5)	Model I $\beta$ (95% CI)	Model II <sup>†</sup> $\beta$ (95% CI)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	3.25 (−0.48 to 6.97)	1.46 (−2.11 to 5.03)
	<b>Estimate prepregnancy BMI<sup>a</sup></b>	0.49 (0.12; 0.85)*	0.34 (−0.09; 0.78)
<b>Gross motor score</b>	<b>Underweight (&lt;18.5)</b>	−1.53 (−4.27 to 1.22)	−1.09 (−3.85 to 1.66)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	3.95 (0.05–7.85)*	2.56 (−1.39 to 6.50)
	<b>Estimate prepregnancy BMI<sup>b</sup></b>	0.58 (0.19; 0.96)*	0.24 (−0.22; 0.69)
<b>KABC-II MPI score</b>	<b>Underweight (&lt;18.5)</b>	−1.91 (−4.57 to 0.76)	−0.79 (−3.29 to 1.71)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	2.41 (−1.36 to 6.17)	1.27 (−2.29 to 4.82)
	<b>Estimate prepregnancy BMI<sup>c</sup></b>	0.68 (0.32; 1.05)*	0.37 (0.02; 0.72)*
<b>BOT-2 standard score</b>	<b>Underweight (&lt;18.5)</b>	−1.72 (−3.78 to 0.33)	−0.94 (−2.79 to 0.92)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	1.26 (−1.61 to 4.14)	1.13 (−1.49 to 3.74)
	<b>Estimate prepregnancy BMI<sup>d</sup></b>	0.44 (0.16; 0.72)*	0.26 (0.002; 0.53)*
<b>ADHD total score</b>	<b>Underweight (&lt;18.5)</b>	−0.44 (−1.07 to 0.18)	−0.06 (−0.68 to 0.55)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	0.06 (−0.86 to 0.98)	0.07 (−0.84 to 0.97)
	<b>Estimate prepregnancy BMI<sup>e</sup></b>	0.08 (−0.01; 0.17)	0.02 (−0.07; 0.11)
<b>SDQ total score</b>	<b>Underweight (&lt;18.5)</b>	0.21 (−1.06 to 1.47)	−0.34 (−1.57 to 0.86)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	−0.51 (−2.29 to 1.28)	−0.38 (−2.11 to 1.35)
	<b>Estimate prepregnancy BMI<sup>f</sup></b>	−0.01 (−0.18; 0.18)	0.11 (−0.07; 0.28)
<b>SDQ externalizing score</b>	<b>Underweight (&lt;18.5)</b>	0.32 (−0.39 to 1.03)	−0.05 (−0.74 to 0.64)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	−1.15 (−1.16 to 0.86)	−0.25 (−1.22 to 0.73)
	<b>Estimate prepregnancy BMI<sup>g</sup></b>	−0.02 (−0.11; 0.08)	0.04 (−0.06; 0.14)
<b>KABC-II NVI score</b>	<b>Underweight (&lt;18.5)</b>	−0.51 (−2.23 to 1.22)	−0.17 (−1.83 to 1.49)
	<b>Normal (18.5–24.9)</b>	Ref.	Ref.
	<b>Overweight (<math>\geq 25</math> &amp; <math>&lt; 30</math>)</b>	0.27 (−2.17 to 2.71)	0.04 (−2.32 to 2.39)
	<b>Estimate prepregnancy BMI<sup>h</sup></b>	0.15 (−0.08; 0.39)	0.06 (−0.18; 0.29)

\* $P < 0.05$ .<sup>†</sup>Model I, crude analysis; Model II, Model I + linear model adjusted for investigator, family possession score, maternal age, maternal education, gravidity, HOME score, child gender and age at assessment. Model I Model II.<sup>a</sup>N = 727 <sup>a</sup>N = 517.<sup>b</sup>N = 726 <sup>b</sup>N = 505.<sup>c</sup>N = 516 <sup>c</sup>N = 472.<sup>d</sup>N = 506 <sup>d</sup>N = 495.<sup>e</sup>N = 483 <sup>e</sup>N = 472.<sup>f</sup>N = 523 <sup>f</sup>N = 512.<sup>g</sup>N = 523 <sup>g</sup>N = 512.<sup>h</sup>N = 515 <sup>h</sup>N = 504.

neurocognitive functions during early infancy [17]. Although our study provided a long prospective follow-up to test whether maternal underweight would be associated with poorer neurodevelopment outcomes at children of 1 and 6 years of age, our analysis revealed that maternal anthropometric measurements

influenced short- and long-term child neurocognitive development.

Additionally, our study investigated how maternal anthropometric measurements during pregnancy could impact behavioral development measured by the parent-rated SDQ. The externalizing

**Table 4**

Multiple linear regression models between gestational weight gain and child neurodevelopment and behavioral outcomes at 1 and 6 years of age

		Crude $\beta$ (95% CI)	Adjusted $\beta$ (95% CI) <sup>j</sup>
<b>ELC score</b>	<b>Gestational weight gain<sup>a</sup></b>	0.13 (−0.09; 0.36)	0.09 (−0.12; 0.31)
<b>Gross motor score</b>	<b>Gestational weight gain<sup>b</sup></b>	0.06 (−0.18; 0.29)	0.07 (−0.16; 0.30)
<b>KABC-II MPI score</b>	<b>Gestational weight gain<sup>c</sup></b>	0.04 (−0.19; 0.26)	0.07 (−0.14; 0.28)
<b>BOT-2 standard score</b>	<b>Gestational weight gain<sup>d</sup></b>	−0.11 (−0.27; 0.05)	−0.04 (−0.19; 0.11)
<b>ADHD total score</b>	<b>Gestational weight gain<sup>e</sup></b>	−0.004 (−0.06; 0.05)	0.002 (−0.05; 0.05)
<b>SDQ total score</b>	<b>Gestational weight gain<sup>f</sup></b>	0.06 (−0.04; 0.17)	0.08 (−0.02; 0.17)
<b>SDQ externalizing score</b>	<b>Gestational weight gain<sup>g</sup></b>	0.03 (−0.03; 0.09)	0.04 (−0.02; 0.09)

<sup>j</sup>Adjusted for estimate prepregnancy BMI, investigator, family possession score, maternal age, maternal education, gravidity, HOME score, child gender and age at assessment. Crude adjusted.<sup>a</sup>N = 585 <sup>a</sup>N = 580.<sup>b</sup>N = 584 <sup>b</sup>N = 579.<sup>c</sup>N = 427 <sup>c</sup>N = 422.<sup>d</sup>N = 417 <sup>d</sup>N = 412.<sup>e</sup>N = 395 <sup>e</sup>N = 390.<sup>f</sup>N = 431 <sup>f</sup>N = 426.<sup>g</sup>N = 431 <sup>g</sup>N = 426.

score, indicating behavioral issues, was computed by combining the hyperactivity and conduct problems score. We found that neither estimate prepregnancy BMI nor gestational weight gain was associated with any of the behavioral or emotional scores. The findings of 2 previous studies are consistent with our results [26,27]. Chen et al. emphasized the importance of familial confounding, however our study adjusted for HOME environment and the lack of an association still persisted.

Sensitivity analysis by further adjusting for birthweight and gestational age suggested a potential mediating effect of these factors as the relationship weakened after adjustment. Preterm births and low birth weight babies were at higher risk of mortality in this cohort. Thirty percent of children with low birth weight died compared with 9% of children born with birthweight higher than 2500 grams. Selection bias due to deceased children excluded from analysis is likely to have influenced the results. Children born to mothers who have low BMI are more likely to have a low birthweight and as a result may have died earlier and not being evaluated at the age of 6 [28].

In this study, we also evaluated the relationship between gestational weight gain and BMI of women before pregnancy. Underweight women had a median total weight gain of 9kg (6.5–12), which was higher compared to normal and overweight/obese women. These results align with the conclusions of a previous study conducted in the same population of interest [17]. However, they had a lower proportion of underweight women (9.5%) and higher proportion of overweight/obese (22.1%) compared to our study (17.3% and 10.2% respectively). This finding is of particular importance in developing countries where women usually start their pregnancy in a state of undernutrition, which then worsens due to increased needs on nutrients.

To our knowledge, this is the first study to assess the association between maternal anthropometric measurements during pregnancy and short- and long-term child development outcomes in Sub-Saharan Africa. A strength of this study is that it followed prospectively mother-child pairs from pregnancy until 6 years of age. We addressed several limitations of previous studies such as examining a wide domain of neurocognitive and behavioral development outcomes. Using a large range of potential confounding factors contributes to the strength of this study. Additionally, we used tests such as MSEL and KABC-II, whose construct validity has been verified in our study population [24,29]. Another addition of this study is that the questionnaires were translated in the local language and administered by trained investigators [22]. The same team of assessors, including psychologists and nurses, were trained several times for cognitive outcomes at 1 and 6 years of age, by Michael J. Boivin and Florence Bodeau-Livinec. Quality control with videos was assessed by an independent team with regular feedback to the team. Good construct validity was shown for the different outcomes [29–31].

One limitation of this study is that maternal prepregnancy BMI was not directly calculated. We used BMI at first ANV as a proxy for BMI before conception. However, the consequence of these probable measurement errors may not be linked to the associations of interest, therefore only leading to a bias towards the null of our results. In addition, the visit was performed during the first trimester at a median 22 (with a relatively narrow interquartile range of gestational weeks: 19–25) weeks. Another limitation for this study is the self-reporting bias due to the parent-rated SDQ for the evaluation of their child's behavior. Also, the SDQ questionnaire was not validated in the population of our study but several other existing studies have used it in Africa [32]. Finally, we present results from a long-term follow-up. Children may experience other events between 1 and 6 years of age that were not taken into

account. However, assessing children at 6 years enables the study of more subtle effects on neurodevelopment. In addition, results presented at 1 and 6 years are coherent and in the same direction, therefore, reinforcing the conclusion.

Maternal malnutrition and poor child development remain public health challenges, especially in low-income settings. Future research with larger sample sizes including more obese women in sub-Saharan Africa should be done to further investigate a potential U-shape association. Obesity in pregnancy may be associated with a detrimental inflammation process, whereas overweight in a context of high prevalence of undernutrition may be beneficial for the fetus. Additionally, undernutrition in childhood has great impact in child development. Efforts to adequate prevention for both child and maternal undernutrition should be enforced in low- and middle-income countries.

## Key messages

Our study confirms the hypothesis that underweight women before conception impacts short- or long-term child development. These findings are important in the light of the double burden of maternal malnutrition in LMICs, and the long-term implications of child neurocognition and behavioral development. This study adds to the limited literature from low-income settings testing the hypothesis that BMI before conception may have an effect on the neurocognitive and behavioral development of children.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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## CRedit authorship contribution statement

AK performed and interpreted data analyses, drafted the initial manuscript, and revised the manuscript; BH supervised and critically reviewed the statistical analysis and revised the manuscript; RZ supervised initial data collection of the TOVI study and critically reviewed and revised the manuscript; AM and MC acquired funding for the Malaria in Pregnancy Preventive Alternative Drugs study, conceptualized, designed and supervised the Malaria in Pregnancy Preventive Alternative Drugs trial, and reviewed and revised the initial manuscript; MJB trained research nurses to use the Mullen Scale of Early Learning cognitive assessment and critically reviewed and revised the manuscript; FBL conceptualized and designed the TOVI study, acquired funding for the TOVI study, trained research nurses to use the Mullen Scale of Early Learning cognitive assessment, supervised initial data collection, and

supervised, reviewed and revised the initial manuscript; and all authors approved the final manuscript as submitted.

### Declaration of generative AI and AI-assisted technologies in the writing process

The was no use of AI in the process of this article.

### Supplementary materials

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