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## **Poor maternal anthropometric status before conception is associated with a deleterious infant growth during the first year of life: a longitudinal preconceptional cohort**

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### ► To cite this version:

G. Agbota, Nadine Fievet, B. Heude, M. Accrombessi, U. Ahouayito, et al.. Poor maternal anthropometric status before conception is associated with a deleterious infant growth during the first year of life: a longitudinal preconceptional cohort. *Pediatric Obesity*, 2019, 15 (1), e12573 [11 p.]. <10.1111/ijpo.12573>. <hal-04894467>

**HAL Id: hal-04894467**

**<https://hal.science/hal-04894467v1>**

Submitted on 1 Jun 2025

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HAL Authorization

1 **Title**

2 Poor maternal anthropometric status before conception is associated with a deleterious infant  
3 growth during the first year of life: A longitudinal preconceptional cohort

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17 **Keywords**

18 Preconception period, maternal anthropometric status, infant growth, pregnancy, study cohort,

19 Benin

20 **Running title**

21 Maternal anthropometry linked to infant growth

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28 **Word count**

29 Abstract: 250; Full text: 4021

30 **Abstract**

31 **Background**

32 According to the Developmental Origins of Health and Diseases concept, exposures in the  
33 preconception period may be critical. For the first time, we evaluated the effect of preconception  
34 poor anthropometric status on infant's growth in sub-Saharan Africa.

35 **Methods**

36 A mother-child cohort was followed prospectively from preconception to 1 year old in Benin.  
37 Maternal anthropometric status was assessed by pre-pregnancy body mass index (BMI),  
38 approximated by BMI at the 1<sup>st</sup> antenatal visit before 7weeks' gestation, and gestational weight  
39 gain (GWG). BMI was categorized as underweight, normal, overweight and obesity according  
40 to World Health Organization standards. GWG was categorized as low (<7kg), mild (7-12kg)  
41 and high (>12kg). In infant, stunting and wasting were defined as length-for-age and weight-  
42 for-length z-scores <-2SD, respectively. We evaluated the association between BMI/GWG and  
43 infant's weight and length at birth and during the first year of life, as well as with stunting and  
44 wasting at 12 months using mixed linear and logistic regression models.

45 **Results**

46 In multivariate, preconceptional underweight was associated with a lower infant's weight at  
47 birth and during the first year (-164g, 95%CI [-307;-22] and -342g, 95%CI [-624;-61],  
48 respectively), and with a higher risk of stunting at 1 year of age (aOR=3.98, 95%CI  
49 [1.01;15.85]). Furthermore, preconceptional obesity and a high GWG were associated with a  
50 higher weight and length at birth and during the first year.

51 **Conclusion**

52 Underweight and obesity before conception as well as GWG were associated with infant's  
53 growth. These results argue for preventive interventions starting as early as the preconception  
54 period to support child long-term health.

## 55 INTRODUCTION

56 According to the Developmental Origins of Health and Diseases (DOHaD) concept, the  
57 environment during the preconception, gestation and early post-natal periods shapes the  
58 development of individuals and, in the case of a deleterious environment, leads to a  
59 predisposition to adult-onset chronic diseases <sup>1</sup>. Maternal malnutrition before and during  
60 pregnancy is a recognized stress factor involved in fetal programming <sup>2-4</sup>. In animals, maternal  
61 nutritional status in the preconception period has been associated with placental growth,  
62 birthweight and, cardiovascular and metabolic responses in offspring <sup>5,6</sup>, underlining the  
63 importance of this period.

64 In high-income countries (HICs), maternal nutritional status during pregnancy has been related  
65 to short-term (fetal growth restriction) and medium/long-term adverse outcomes such as growth  
66 disorders (obesity) <sup>7</sup> and chronic lung diseases (asthma) during childhood <sup>8</sup>, as well as adulthood  
67 diseases (cardiovascular diseases and diabetes) <sup>9-11</sup>. Maternal nutritional status before  
68 conception has also been related to growth disorders in childhood and to adulthood chronic  
69 diseases <sup>12,13</sup>. However, in most of these studies, the mother's pre-pregnancy status was either  
70 self-reported or collected retrospectively from medical records, leading to potential biases.

71 In low and middle-income countries (LMICs), especially in sub-Saharan Africa (SSA), few  
72 studies have evaluated the effect of maternal nutritional status on infant health <sup>14</sup>. There are  
73 even less evidence-based data on the effect of maternal conditions, including nutritional status,  
74 in the preconception period on child health in SSA <sup>14,15</sup>. While the prevalence of undernutrition  
75 remains high in African countries, most of them are now facing growing overweight/obesity <sup>16</sup>.  
76 The concomitant increase in non-communicable diseases in adulthood has been linked to the  
77 nutritional transition operating in these countries <sup>17,18</sup>. However, maternal malnutrition before  
78 or in early pregnancy might also be a contributor.

79 Using data from a recent preconceptional mother-child cohort in Benin, we aimed to assess the  
80 effect of maternal anthropometric status before conception and during pregnancy on fetal and  
81 postnatal growth, up to 12 months of age.

82

## 83 **MATERIAL AND METHODS**

### 84 **Study site and population**

85 Between June 2014 and August 2018, a preconceptional mother-child cohort was followed up  
86 in the districts of Sô-Ava (a rural lakeside area) and Abomey-Calavi (a semi-urban area) in  
87 southern Benin. Women of reproductive age (18-45 years old) were recruited and followed up  
88 monthly from the preconception period to pregnancy, then throughout pregnancy, in the  
89 framework of the “REtard de Croissance Intra-uterin et PALudisme” (RECIPAL) study <sup>19</sup>.  
90 Then, their infants were followed from birth to 12 months in the framework of another study  
91 called SEPSIS “Neonatal immune function and risk of SEPSIS in infants in a malaria endemic  
92 area”. The RECIPAL study aimed to assess the effect of malaria in the first trimester of  
93 pregnancy on maternal health and fetal growth <sup>19</sup>. The SEPSIS study aimed to assess the  
94 immune mechanisms involved in the propensity of premature or malaria-infected newborns to  
95 develop neonatal infections. Our study population consisted in mother-child pairs followed  
96 from the preconception period to 12 months of age in the framework of RECIPAL and SEPSIS  
97 studies.

98

### 99 **Study procedures**

#### 100 *Maternal follow-up*

101 The protocol of women’s follow-up from the preconception period to pregnancy, then  
102 throughout pregnancy has been described elsewhere <sup>19</sup>. Briefly:

103            *Preconception period*

104    At enrolment, demographic, socioeconomic and household characteristics were collected. At  
105    this occasion, hemoglobin (Hb) level was determined and women were screened for  
106    microscopic malaria. Then, women were visited at home monthly for recording the first day of  
107    last menstrual period (LMP) and performing a urinary pregnancy test. Anthropometric  
108    measurements including weight, height and mid-upper-arm circumference were recorded using  
109    standard procedures <sup>20</sup>, at inclusion and then every 3 months until becoming pregnant.

110            *Gestational follow-up*

111    In women who became pregnant, clinical (temperature, blood pressure, use of insecticide  
112    treated nets “ITN”, intake of intermittent preventive treatment for malaria and of micronutrient  
113    supplements) and obstetrical data were collected at each monthly antenatal care (ANC) visit.  
114    Anthropometric data (same as before conception) was recorded at the first ANC visit and then  
115    each month until delivery. Women were screened monthly for malaria as well as for proteinuria,  
116    glycosuria and urinary infection. Hb level was determined in the first and third trimester of  
117    pregnancy. The first ultrasound scan for dating the pregnancy was performed between 9 and 13  
118    weeks of gestation, and 5 other ultrasound scans were performed over the pregnancy for fetal  
119    growth monitoring. Estimation of gestational age (GA) was based on either LMP - when the  
120    difference between GA estimated by LMP and ultrasound scan was less than 7 days, or  
121    ultrasound scan when this difference was  $>7$  days <sup>21</sup>. At birth, weight, length, head  
122    circumference and mid-upper-arm circumference of the newborn were recorded.

123            *Infant follow-up*

124    The SEPSIS study was set up in a sub-sample of infants born from RECIPAL mothers. All  
125    infants born from April 2016 onwards were included in the cohort and followed actively  
126    (scheduled visits) each month from birth to 3 months of age, then quarterly to 12 months of  
127    age. At each scheduled visit, anthropometric data (same as at birth), breastfeeding and dietary

128 practices, vaccine coverage and clinical symptoms were collected. Any time during follow-up,  
129 mothers were encouraged to attend the health facility in case of symptoms of their children. In  
130 January 2017, while the SEPSIS project was ongoing, we decided to collect anthropometric  
131 data in an additional sub-sample of infants born from RECIPAL mothers before April 2016,  
132 who had not been included in SEPSIS study.

### 133 *Anthropometric data collection*

134 During the preconception period and throughout pregnancy, women were weighed with a  
135 Tanita MC-780 body composition device (Tanita, Tokyo, Japan). Height was measured to the  
136 nearest millimeter with a SECA 206 (Hamburg, Germany) gauge. At birth, newborns were  
137 weighted within 1 hour to the nearest 2 g using a SECA 757 electronic digital scale (Germany)  
138 and length was measured to the nearest millimeter with a SECA infantometer 416 (Germany).  
139 From birth to 3 months of age, same procedures were used. At 6, 9 and 12 months of age, weight  
140 was recorded to the nearest 5 g with a babyline CH 213 1020 (Germany) and length was  
141 measured to the nearest millimeter with a fold-up SECA 417 (Germany). All anthropometric  
142 measurements were performed twice by the same investigator. A third measurement was  
143 performed in case of discrepancy between the first two measurements. The two nearest  
144 measurements were then averaged. A quality control of anthropometric data was performed  
145 periodically by AG, a senior research scientist in nutrition.

146

### 147 **Definitions**

148 Before conception, the mother's anthropometric status was based on body mass index (BMI),  
149 and during pregnancy it was based on gestational weight gain (GWG). BMI at the first ANC  
150 visit, which occurred before 7 weeks' gestation for most women, was used as a proxy for pre-  
151 pregnancy BMI, which was not retained because of a high variability in time-to-pregnancy and  
152 to a less complete set of data. In accordance with World Health Organization (WHO)

153 classification, underweight was defined as BMI < 18.5 kg/m<sup>2</sup>, normal weight as BMI between  
154 18.5 and 24.9 kg/m<sup>2</sup>, overweight as BMI between 25 and 29.9 kg/m<sup>2</sup> and obesity as BMI ≥ 30  
155 kg/m<sup>2</sup>. The total maternal GWG was calculated as the difference between weight at delivery  
156 and weight at the first ANC visit. Then, the GWG was categorized into 3 classes according to  
157 the observed distribution: low GWG (< 1<sup>st</sup> quartile, i.e. <7 kg, ranging from -1.4 to 6.9 kg),  
158 mild GWG (1<sup>st</sup>-3<sup>rd</sup> quartile, i.e. 7-12 kg) and high GWG (> 3<sup>rd</sup> quartile, i.e. >12 kg, ranging  
159 from 12.1 to 22.7 kg). Anemia was defined as Hb level <12 g/dL before conception and at least  
160 one episode of Hb level < 11g/dL during pregnancy.

161 Malaria during pregnancy was defined as at least one malarial infection during pregnancy.  
162 Maternal socioeconomic level was approximated using a synthetic score combining occupation  
163 (employed or not), ownership of assets (family possessions such as pirogue, bicycle,  
164 motorcycle, car, radio, television, fridge, mobile phone, domestic animals, fish farm) and home  
165 characteristics, which was then categorized according to the tertiles in low, medium and high.  
166 Infant's growth was assessed from birth to 12 months of age. Weight-for-age, weight-for-length  
167 and length-for-age z-scores at 3, 6, 9 and 12 months were calculated based on WHO sex-specific  
168 growth standards, using a WHO macro for STATA software <sup>22</sup>. Underweight, wasting and  
169 stunting at 12 months of age were defined as weight-for-age, weight-for-length and length-for-  
170 age z-scores < -2 SD, respectively <sup>22</sup>. Low birthweight (LBW) and small-for-gestational age  
171 (SGA) were defined as birthweight < 2500 g and birthweight < 10<sup>th</sup> percentile according to sex-  
172 specific INTERGROWTH-21<sup>st</sup> charts <sup>21</sup>, respectively.

173 Infant's breastfeeding was categorized as maternal breastfeeding (including both exclusive and  
174 predominant maternal breastfeeding, the latter corresponding to infants who received water or  
175 water-based drinks in addition to breast milk), mixed breastfeeding or exclusive formula  
176 feeding <sup>23</sup> between birth and 6 months of age.

177

## 178 **Statistical analysis**

179 Firstly, we described the general characteristics of the mother-child pairs as well as infant's  
180 growth during the first year of life according to mother's anthropometric status before and  
181 during pregnancy. Differences in proportions and means were tested using Fisher exact and  
182 Anova tests, respectively. Secondly, we used a linear regression model to assess the association  
183 between mother's anthropometric status before conception and during pregnancy and birth  
184 weight and birth length. Thirdly, we used a linear mixed regression model with a random  
185 intercept at the individual level (considering that successive anthropometric measurements  
186 during follow-up in the same child were correlated) to assess the association between mother's  
187 anthropometric status before conception and during pregnancy and infant's raw weights and  
188 lengths from birth to 12 months of age. To take into account the non-linearity of infant's growth,  
189 age and age-square were introduced in these models. At 12 months of age, we assessed the  
190 association between mother's anthropometric status before conception and during pregnancy  
191 and infant's underweight, stunting and wasting. Sensitivity analyses were performed using the  
192 last pre-pregnancy BMI measured prior to pregnancy instead of BMI at the 1<sup>st</sup> ANC visit. In  
193 addition, sensitivity analyses were conducted using weight and length z-scores at birth (z-scores  
194 were defined according to WHO sex-specific growth standards <sup>22</sup>).

195 In all models, the main exposure variables were maternal pre-pregnancy BMI and GWG.  
196 Potential confounders were maternal age, gravidity, birth interval, ethnicity, marital status,  
197 maternal socioeconomic and education level, household size, gestational conditions (malaria,  
198 hypertension), anemia (before and during pregnancy), study center as well as infant's sex,  
199 gestational age at birth, breastfeeding, vaccine coverage, anemia and clinical symptoms during  
200 the first year follow-up. All variables with a p-value below 0.2 in univariate analysis were  
201 included in the multivariate analysis. Then, the variables with a p-value less than 0.05 after a  
202 step-by-step backward selection procedure were kept in the multivariate model. Statistical

203 analysis was performed with Stata version 13.1 for Windows (Stata Corp., College Station,  
204 TX).

## 205 **Ethics statement**

206 The Ethics Committee of the Institut des Sciences Biomédicales Appliquées in Benin approved  
207 RECIPAL (decision N° 39 of 05/16/2014) and SEPSIS (decision N°85 of 04/05/2016) projects.  
208 Women and their infants were included after providing a signed written informed consent for  
209 each project.

210

## 211 **RESULTS**

### 212 **Study profile**

213 Figure 1 presents the flowchart of the study. Out of a total of 1214 women of reproductive age  
214 enrolled in the RECIPAL study, 411 became pregnant. Among them, 273 were followed until  
215 delivery and 260 gave birth to a live singleton. At birth, 3, 6, 9 and 12 months of age, 260, 154,  
216 139, 136 and 155 infants had anthropometric measurements, respectively. The main reasons for  
217 missing anthropometric data were migration of the family outside the study area and infant  
218 death before 1 year of age mainly due to severe anemia (n=13). Baseline characteristics of  
219 mother-infant pairs who completed the 12 month-follow-up and those who did not were  
220 compared. We did not evidence any difference in pre-pregnancy BMI (22.9 vs 23.0 kg/m<sup>2</sup>,  
221 p=0.80) or GWG (9.0 vs 9.8 kg, p=0.20) between groups. Also, they did not differ in terms of  
222 maternal age, gravidity, education, socioeconomic status. The only statistically difference  
223 related to ethnicity (67% vs. 85% of Toffin in, respectively, children who completed, or not,  
224 the follow-up, p=0.001).

225 **General characteristics of the study population and according to maternal**  
226 **anthropometric status**

227 Before conception, 8.9% and 23.8% of women were affected by underweight and  
228 overweight/obesity, respectively, and 58.1% had anemia. During pregnancy, the mean (SD)  
229 GWG was 9.2 (4.1) kg. A total of 8.5% of infants were born prematurely (< 37 weeks of  
230 gestation). Mean (SD) weight and length at birth were 3029 (413) g and 48.6 (2.0) cm. At 12  
231 months of age, 17.7%, 21.8% and 10.2% of infants were affected by underweight, stunting and  
232 wasting, respectively. Between birth and 6 months of age, the majority of infants (96.5%) were  
233 breastfed (including exclusive and predominant maternal breastfeeding) and none received  
234 exclusive formula feeding. From birth to 12 months of age, 63.1% of infants presented clinical  
235 symptoms and 95 % received all the recommended vaccinations for their age (data not shown).

236 In Table 1, the baseline characteristics of the mother-infant pairs included in this analysis were  
237 compared according to maternal anthropometric status before and during pregnancy. In  
238 particular, women were more likely to be primigravid and of a young age in the lowest pre-  
239 pregnancy BMI categories. In addition, GWG decreased significantly with increasing pre-  
240 pregnancy BMI.

241 **Differences in infant's anthropometric measurements according to maternal**  
242 **anthropometric status before conception and during pregnancy: descriptive data**

243 Mean weight and length at birth, 3, 6, 9 and 12 months were compared according to maternal  
244 pre-pregnancy BMI and GWG (Table 2 and Figure 2). At birth, the infant's weight increased  
245 with increasing maternal pre-pregnancy BMI and GWG (2835 g for underweight to 3134 g for  
246 obesity,  $p=0.056$ , and 2979 g for low GWG to 3223 g for high GWG,  $p<0.001$ ), but this  
247 variation was only marginally significant for pre-pregnancy BMI. The proportion of infants  
248 affected by LBW and SGA decreased with increasing maternal GWG; although same trends

249 were observed with pre-pregnancy BMI, they were not statistically significant. Infants born  
250 from mothers with overweight and normal weight seemed to have comparable weight-growth  
251 trajectory from birth to 12 months. In contrast, infants born from mothers with underweight and  
252 obesity seemed to have lower and higher weight-growth trajectories, respectively (Figure 2).  
253 Same trends were observed for infants' length according to pre-pregnancy BMI, but the  
254 differences in length-growth trajectory were less pronounced. Finally, infants born from  
255 mothers with a high GWG seemed to have higher weight and length growth trajectories  
256 compared to infants born from mothers with a low or mild GWG (Figure 2).

257 **Relationship between infant's anthropometric measurements, at birth and from birth to**  
258 **12 months, and maternal anthropometric status before conception and during pregnancy:**  
259 **regression models**

260 *At birth*

261 In multivariate analysis, we showed a statistically significant effect of both maternal pre-  
262 pregnancy BMI and GWG on infant's weight and length at birth (Table 3). Indeed, infants born  
263 from mothers who were affected by underweight before conception had a significantly lower  
264 birthweight than infants born from mothers with a normal weight (-164 g,  $p=0.024$ ). Infants  
265 born from women with overweight or obesity had a higher birthweight compared to infants  
266 born from women with a normal weight, but only the first association was statistically  
267 significant (+119 g,  $p=0.045$  and +123 g,  $p=0.091$ , for women with overweight and obesity  
268 respectively). Obesity before conception was also associated with a higher infant's length at  
269 birth (+0.94 cm,  $p=0.042$ ). A high GWG was significantly associated with both higher weight  
270 and length at birth compared to mild GWG (+199 g,  $p<0.001$  and +0.81 cm,  $p=0.005$ ,  
271 respectively). The other factors significantly associated with both a higher weight and a higher  
272 length at birth were birth interval (12-24 and > 24 months) and increasing gestational age at

273 birth (Supplementary table S1). Sensitivity analyses using weight and length z-scores at birth  
274 did not change our results (data not shown).

#### 275 *From birth to 12 months of age*

276 Infants born from mothers who were affected by underweight before conception or with a low  
277 GWG had a significantly lower weight from birth to 1 year of age compared to infants born  
278 from mothers with a normal weight or a mild GWG (-342 g,  $p=0.017$  and -237 g,  $p=0.021$ ,  
279 respectively) (Table 4). In contrast, obesity before conception and a high GWG (compared to a  
280 normal weight and a mild GWG) were both associated with a significantly higher weight during  
281 the first year of life (+384 g,  $p=0.027$  and +287 g,  $p=0.007$ , respectively). Same trends were  
282 observed for infant's length, which was higher in case of mothers with obesity before  
283 conception and with a high GWG (Table 4). The other factors significantly associated with a  
284 lower weight and length during the first year of life were maternal age (>30 years old) and  
285 female sex, while a higher gestational age at birth was associated with a higher weight and  
286 length in infancy (Supplementary table S2). Sensitivity analyses using the last BMI measured  
287 prior to pregnancy yielded similar results (data not shown).

288 At 12 months of age, underweight before conception was significantly associated with a higher  
289 risk of stunting in infants (adjusted Odds Ratio (aOR)= 3.98,  $p=0.049$ ), while high GWG was  
290 associated with a lower risk of underweight in infants (aOR= 0.09,  $p=0.030$ ) (Table 5).

291

## 292 **DISCUSSION**

293 In this analysis of fetal outcomes and subsequent growth within a mother-child cohort, our  
294 results showed an independent association between maternal anthropometric status before and  
295 during pregnancy and infant's weight and length at birth and during the first year of life. In  
296 particular, maternal underweight before conception was associated with a lower infant's weight

297 at birth and during the first year of life as well as with a higher risk of stunting at 1 year old. In  
298 addition, obesity before conception and a high GWG were associated with a higher infant's  
299 length at birth and during the first year of life as well as with a higher infant's weight from birth  
300 to 12 months of age.

301 The main strengths of our work were that maternal anthropometric status was assessed  
302 prospectively from the preconception period to delivery, and that a large number of other  
303 potential determinants of infant's growth during pregnancy and in infancy were taken into  
304 account in the analysis. Furthermore, we were able to assess the association between maternal  
305 anthropometric status and infant growth not only at birth, but also in the postnatal period from  
306 birth to 12 months using data collected longitudinally.

307 We chose to use BMI at the 1<sup>st</sup> ANC visit instead of BMI at enrolment in the preconceptional  
308 cohort for three main reasons: first, there was a high variability in time-to-pregnancy (mean  
309 (interquartile range) = 3.9 (0.6-21.2) months in women who became pregnant), with variations  
310 in women's weight between inclusion in the preconception period and the beginning of  
311 pregnancy. Second, the 1<sup>st</sup> ANC visit was performed very early in pregnancy at a mean (SD) of  
312 6.7 ( $\pm$  2.1) weeks, allowing us to use BMI at the 1<sup>st</sup> ANC visit as a proxy for BMI before  
313 conception <sup>24</sup>. Finally, this allowed us to have a more complete data set. Sensitivity analyses  
314 using last BMI measured in the preconceptional period yielded similar results.

315 Underweight and overweight/obesity before conception was highly prevalent in our cohort,  
316 affecting 1 in 3 women (32.7%). The variation in infant's weight and length related to mother's  
317 poor anthropometric status seemed to be higher for pre-pregnancy BMI (+/- 300-400 g and  
318 +1.20 cm) than for GWG (+/- 200-300 g and +1 cm), highlighting the importance of the  
319 preconception period.

320 Our results are consistent with the literature. Indeed, most of the previous studies conducted in  
321 HICs, and the few carried in Asia and Latin America, reported an association between high  
322 values of maternal BMI, particularly during pregnancy, and a high birthweight or a higher risk  
323 of obesity in child- and adulthood<sup>12,13,25-27</sup>. In a study conducted in USA, in which pre-  
324 pregnancy BMI was self-reported, a pre-pregnancy BMI > 25 kg/m<sup>2</sup> or an excessive GWG was  
325 associated with higher z-scores for birth weight and weight-for-age at 3 months<sup>13</sup>. Also, one of  
326 the largest cohort including 38,539 mother-child pairs in China, showed that pre-pregnancy  
327 overweight/obesity and excessive GWG were associated with higher weight and length at birth  
328 and in the first year of life<sup>28</sup>. Concerning mother's underweight, recently in France, "the EDEN  
329 mother-child cohort" reported an association between mothers affected by underweight before  
330 conception and a low birthweight, a low weight and a low instantaneous weight-growth velocity  
331 in infants at 3 months of age<sup>29</sup>. Besides, infant's nutritional status early in life has been shown  
332 to be predictive of growth and chronic diseases later in life. In particular, overweight/obesity or  
333 a higher weight gain in infancy have been associated with an increased risk of obesity in  
334 adulthood<sup>30,31</sup>. Studies in HICs have also suggested a link between maternal obesity during  
335 pregnancy and a higher risk of stunting early in life<sup>32</sup>, which we did not find. In our study,  
336 infants born from women with obesity before pregnancy had higher weight and length during  
337 the first year of life. Our analysis focused on preconceptional maternal obesity, with possibly a  
338 different effect of the mother's anthropometric status depending on the period considered  
339 (preconception or early pregnancy vs. last trimester of pregnancy)<sup>33</sup>.

340 In SSA, most studies have assessed the effect of maternal anthropometric status during  
341 pregnancy on infant growth at birth, yielding comparable results as in our study<sup>15</sup>. In particular,  
342 in studies conducted in Sudan<sup>34</sup>, Ghana<sup>35</sup> and South Africa<sup>36</sup>, obesity during pregnancy was  
343 associated with macrosomia at birth. Gondwe *et al.* in Malawi reported a higher risk of stunting

344 at birth in infants born from underweight mothers during pregnancy as well as an association  
345 between inadequate GWG and a higher risk of LBW and SGA <sup>37</sup>.

346 In our study, the infant's growth trajectory differed strongly as early as birth between infants  
347 born from mothers affected by obesity vs. underweight, suggesting the effect of early maternal  
348 determinants. This observation is in line with the DOHaD concept. Different underlying  
349 pathophysiological mechanisms, including epigenetic changes, have been proposed to explain  
350 the impact of maternal determinants on child and adult health <sup>7,38,39</sup>. Epigenetics has mainly  
351 been documented in animals, with the demonstration of changes in body's structure and  
352 functions related to epigenetic modifications after fetal undernutrition (either by maternal  
353 undernutrition or by fetal growth restriction) <sup>40,41</sup>. In humans, epigenetic changes related to  
354 maternal nutrition have also been shown in newborns conceived during the hungry vs. the  
355 harvest season and in offspring of women exposed to the Dutch famine <sup>42</sup>.

356 Although maternal supplementation during pregnancy has been associated with a reduction of  
357 both maternal nutritional deficiencies and LBW, it did not appear to have any beneficial effects  
358 on childhood survival, growth, blood pressure, respiratory and neurocognitive outcomes <sup>43</sup>.  
359 Studies in Taiwan <sup>44</sup> and USA <sup>45</sup> have found an increased birthweight in subsequent babies from  
360 mothers that were supplemented in micro/macronutrients for several months after the birth of  
361 their first baby. Our results support preventive interventions started prior to conception or even  
362 early in pregnancy to improve nutritional status of women such as supplementation or  
363 preventive strategies against malaria and helminthic diseases, which could influence nutritional  
364 status <sup>46</sup>.

365 Our study has some limitations that should be considered. First, we were not able to take into  
366 account paternal BMI, which has been associated with offspring's anthropometrics from birth  
367 to 12 months of age, independently of maternal BMI <sup>29,47</sup>. Second, GWG was not assessed  
368 regarding adequate/recommended gain vs. inadequate gain, as proposed by the Institute of

369 Medicine (IOM) 2009 guidelines <sup>48</sup>. Women were classified according to their relative GWG.  
370 Using IOM guidelines would have required stratifying on pre-pregnancy BMI because of the  
371 strong correlation between pre-pregnancy BMI and GWG. This analysis could not be performed  
372 because of our small sample size. Finally, apart breastfeeding practices, infant's dietary  
373 intakes—which also influence infant's growth—were not taken into account in the analysis.

374 In conclusion, we showed that pre-pregnancy BMI as well as GWG were independently  
375 associated with infant's weight and length at birth and in the first year of life. According to  
376 WHO standards, 22% of infants were affected by stunting at 12 months of age with a higher  
377 risk in infants born from mothers with underweight before conception. These results reinforce  
378 the need for improving maternal nutritional conditions as early as in the preconception period  
379 <sup>46</sup>.

380 **Conflict of interest**

381 None declared

382 **Financial support**

383 This work was supported by the French Agence Nationale de la Recherche [ANR-13-JSV1-  
384 0004, grant 2013], the Fondation Simone Beer under the auspices of the Fondation de France  
385 [00074147, grant 2017] and bioMérieux.

386 **Acknowledgments**

387 GA, MC and VB conceived and designed the study with substantial inputs from BH and YM-  
388 P. GA and VB analyzed the data. GA, NF, MA, UA, EY, DD, LD, AG, SE, AP, LG, PT, AM,  
389 YM-P, MC and VB contributed reagents/materials/analysis tools. GA, MC and VB drafted and  
390 finalized the manuscript. The final manuscript was read and approved by all authors.

391 We thank Cyrille Delpierre and Anne Forhan for their contribution to this work. We are  
392 extremely grateful to all families who took part in this study, the midwives, nurses and  
393 community-health workers for recruiting and following them, and the whole RECIPAL and  
394 SEPSIS team, including research scientists, engineers, technicians, managers. GA was funded  
395 by the Fondation pour la Recherche Médicale (FRM grant number ECO20160736054 to GA)  
396 for PhD scholarship.

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540 **Figure legends**

541 **Figure 1:** Flow chart of the study

542 **Figure 2:** Crude plots of mean weight and length according to pre-pregnancy BMI or  
543 gestational weight gain from birth to 12 months of age. Southern Benin, 2014-2018.

544 BMI: body mass index; Underweight:  $<18.5 \text{ kg/m}^2$ ; Normal:  $18.5\text{-}24.9 \text{ kg/m}^2$ ; Overweight:  $25\text{-}$   
545  $29.9 \text{ kg/m}^2$ ; Obesity:  $\geq 30 \text{ kg/m}^2$ ; GWG: gestational weight gain; Low GWG:  $<7 \text{ kg}$ ; Mild  
546 GWG:  $7\text{-}12 \text{ kg}$ ; High GWG:  $>12 \text{ kg}$ .

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Table 1: Characteristics of mother-child pairs included in the analysis, Southern Benin, 2014-2018

Characteristics	Categories	n	Pre-pregnancy BMI				p	Gestational weight gain (GWG)			
			Underweight	Normal	Overweight	Obesity		Low	Mild	High	p
			(n=23, 8.9%)	(n=175, 67.3%)	(n=43, 16.5%)	(n=19, 7.3%)		(n=65, 25.7%)	(n=132, 52.2%)	(n=56, 22.1%)	
			17.6 (0.7) <sup>a</sup>	21.4 (1.6) <sup>a</sup>	27.3 (1.4) <sup>a</sup>	34.3 (3.9) <sup>a</sup>	¥	25.2 (4.7) <sup>a</sup>	22.2 (3.9) <sup>a</sup>	21.7 (4.2) <sup>a</sup>	¥
			10.7 (2.2) <sup>b</sup>	9.9 (3.8) <sup>b</sup>	7.0 (4.1) <sup>b</sup>	5.4 (4.9) <sup>b</sup>	¥	4.0 (2.5) <sup>b</sup>	9.5 (1.4) <sup>b</sup>	14.5 (2.3) <sup>b</sup>	¥
<b><i>Maternal characteristics</i></b>											
Age at recruitment (y), mean (SD)		260	24.0 (4.5)	26.0 (4.6)	29.2 (4.7)	30.9 (5.1)	<0.001	27.4 (5.0)	26.5 (4.9)	26.3 (4.9)	0.409
	≤ 20 y	35	30.4	15.4	2.3	0	<0.001	10.8	14.4	16.1	0.805
	21 – 30 y	175	56.5	69.7	69.8	52.6		67.7	65.9	69.6	
	> 30 y	50	13.0	14.9	27.9	47.4		21.5	19.7	14.3	
Ethnic group, %	<i>Toffin</i>	194	69.6	73.7	76.7	84.2	0.740	76.9	70.5	78.6	0.464
	<i>Other</i>	66	30.4	26.3	23.3	15.8		23.1	29.5	21.4	
Education, %	<i>Illiterate</i>	185	73.9	69.1	69.8	89.5	0.316	78.5	69.7	66.1	0.290
Socioeconomic status, %	<i>Low</i>	90	47.8	36.6	27.9	15.8	0.062	32.3	39.4	28.6	0.121
	<i>Medium</i>	97	34.8	39.4	37.9	52.6		33.9	33.3	51.8	

	<i>High</i>	73	17.4	24.0	44.2	31.6		33.8	27.3	19.6	
Gravidity, %	<i>1-2</i>	54	30.4	24.6	9.3	0	0.005	23.1	20.5	19.6	0.897
	$\geq 3$	206	69.6	75.4	90.7	100		76.9	79.5	80.4	
Household size, %	$\leq 5$	135	60.9	50.9	48.8	57.9	0.741	44.6	53.8	57.1	0.346
Birth interval (months), %	<i>&lt; 12</i>	14	4.4	6.3	4.7	0	0.598	6.1	6.1	3.6	0.911
	<i>12 – 24</i>	98	43.5	39.4	34.9	21.1		33.9	39.4	37.5	
	<i>&gt; 24 *</i>	148	52.1	54.3	60.5	78.9		60.0	54.5	58.9	
Anemia before conception ( <i>&lt; 12 g/dL</i> ), %	<i>Yes</i>	151	60.9	59.4	51.2	57.9	0.791	56.9	56.8	66.1	0.488
Microscopic malaria in pregnancy, %	$\geq 1$ <i>episode(s)</i>	111	52.2	38.9	46.5	57.9	0.262	46.2	42.4	37.5	0.649
<b><i>Infant's characteristics</i></b>											
Sex, %	<i>Female</i>	120	56.5	45.7	41.5	52.6	0.636	44.6	50.0	41.1	0.504
Gestational age at birth (weeks), mean (SD)		260	39.0 (2.4)	39.5 (1.5)	38.8 (2.3)	39.3 (2.4)	0.111	39.4 (1.9)	39.4 (1.6)	39.4 (2.1)	0.966
Preterm birth ( <i>&lt; 37 weeks</i> ), %	<i>Yes</i>	22	17.4	6.3	9.3	15.8	0.120	6.2	8.3	7.1	0.950

Maternal breastfeeding (0-6 months)**, %	<i>Yes</i>	251	100	96.6	93.0	100	0.556	95.4	96.2	98.2	0.747
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<sup>a</sup>: mean (SD) pre-pregnancy BMI (Kg/m<sup>2</sup>); <sup>b</sup>: mean (SD) gestational weight gain (kg); <sup>¥</sup>: p-value < 0.001; n: effective; y: years; %: proportion; SD: standard deviation; \*: including primigravidae; \*\*: including exclusive (31.1%) and predominant breastfeeding (65.4%); p: p-value for Fisher exact or Anova test

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Table 2: Infant's anthropometric measurements at birth and during the first year of life according to pre-pregnancy BMI and gestational weight gain. Southern Benin, 2014-2018

Fetal and infant's growth	Pre-pregnancy BMI					Gestational weight gain (GWG)			
	Underweight	Normal	Overweight	Obesity	p	Low	Mild	High	p
Low birthweight (%)	21.7	9.1	5.0	0	0.084	10.8	10.6	0	0.017
SGA (%)	34.8	20.8	15.0	10.5	0.215	21.5	25.2	7.4	0.016
Weight (Mean $\pm$ SD) grams									
<i>At birth</i>	2835 $\pm$ 454	3030 $\pm$ 403	3071 $\pm$ 391	3164 $\pm$ 438	0.056	2979 $\pm$ 365	2982 $\pm$ 409	3223 $\pm$ 359	<0.001
<i>At 3 months</i>	5450 $\pm$ 826	5707 $\pm$ 759	5589 $\pm$ 614	5931 $\pm$ 925	0.403	5528 $\pm$ 761	5611 $\pm$ 740	6040 $\pm$ 692	0.008
<i>At 6 months</i>	6583 $\pm$ 800	7060 $\pm$ 866	6815 $\pm$ 648	7587 $\pm$ 1133	0.083	6906 $\pm$ 905	6954 $\pm$ 967	7200 $\pm$ 739	0.442
<i>At 9 months</i>	7224 $\pm$ 1010	7717 $\pm$ 1044	7693 $\pm$ 660	7994 $\pm$ 1249	0.276	7495 $\pm$ 1139	7652 $\pm$ 994	8033 $\pm$ 1101	0.145
<i>At 12 months</i>	8136 $\pm$ 1377	8378 $\pm$ 1119	8398 $\pm$ 812	8949 $\pm$ 1331	0.351	8150 $\pm$ 1023	8348 $\pm$ 1091	8871 $\pm$ 1199	0.020
Length (Mean $\pm$ SD) cm									
<i>At birth</i>	48.3 $\pm$ 2.0	48.5 $\pm$ 1.9	48.5 $\pm$ 2.0	48.8 $\pm$ 2.6	0.876	48.3 $\pm$ 1.9	48.4 $\pm$ 1.9	49.3 $\pm$ 1.8	0.007
<i>At 3 months</i>	59.2 $\pm$ 2.8	59.2 $\pm$ 2.7	59.2 $\pm$ 2.4	59.8 $\pm$ 2.9	0.922	58.8 $\pm$ 2.5	59.0 $\pm$ 2.8	60.3 $\pm$ 2.4	0.036
<i>At 6 months</i>	64.8 $\pm$ 3.0	66.0 $\pm$ 2.4	65.2 $\pm$ 3.2	66.4 $\pm$ 3.1	0.405	65.6 $\pm$ 3.3	65.5 $\pm$ 2.5	66.6 $\pm$ 2.7	0.259
<i>At 9 months</i>	68.5 $\pm$ 3.3	69.2 $\pm$ 2.7	69.4 $\pm$ 2.1	69.6 $\pm$ 3.8	0.692	68.5 $\pm$ 3.0	69.2 $\pm$ 2.7	70.1 $\pm$ 2.5	0.070

<i>At 12 months</i>	71.4 ± 3.8	72.2 ± 2.7	72.9 ± 2.2	73.0 ± 3.9	0.338	71.7 ± 2.8	72.1 ± 2.7	73.5 ± 2.8	0.021
Underweight at 12 months (%)	73.3	46.9	50.0	20.0	0.074	54.6	49.3	36.7	0.315
Stunting at 12 months (%)	70.0	46.0	38.5	40.0	0.091	59.1	48.0	30.0	0.049
Wasting at 12 months (%)	13.3	11.5	7.7	0	0.783	13.6	11.0	3.3	0.375

Numbers at birth, 3, 6, 9 and 12 months: 260, 154, 139, 135 and 155 infants respectively. BMI: body mass index; Underweight: <18.5 kg/m<sup>2</sup>; Normal: 18.5-24.9 kg/m<sup>2</sup>; Overweight: 25-29.9 kg/m<sup>2</sup>; Obesity: ≥ 30 kg/m<sup>2</sup>; Low GWG: <7 kg; Mild GWG: 7-12 kg; High GWG: >12 kg; Low birthweight defined as birthweight < 2500 grams, SGA (small-for-gestational age) defined as birthweight < 10<sup>th</sup> percentile according to sex-specific INTERGROWTH-21<sup>st</sup> charts <sup>21</sup>; Infants with underweight, stunting and wasting at 12 months were defined as a weight-for-age z-score <-2 SD, a length-for-age z-score <-2 SD and a weight-for-length z-score <-2 SD, respectively; Z-scores were calculated based on WHO sex-specific growth standards <sup>22</sup>; SD: standard deviation; p: p-value for Fisher exact or Anova test

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Table 3: Effect of maternal anthropometric status before conception and during pregnancy on infant's growth at birth. Linear regression models. Southern Benin, 2014-2018 (N=250)

Categories	Infant's weight at birth (grams)				Infant's length at birth (cm)			
	Univariate		Multivariate		Univariate		Multivariate	
	Crude $\beta$ [95%CI]	p	Adj. $\beta$ [95%CI]	p	Crude $\beta$ [95%CI]	p	Adj. $\beta$ [95%CI]	p
Pre-pregnancy BMI		0.057		0.009		0.739		0.223
<i>Underweight vs normal</i>	-193 [-370; -16]	0.032	<b>-164 [-307; -22]</b>	<b>0.024</b>	-0.22 [-1.08; 0.64]	0.612	-0.12 [-0.90; 0.66]	0.765
<i>Overweight vs normal</i>	+33 [-108; 175]	0.642	<b>+119 [1; 236]</b>	<b>0.045</b>	-0.17 [-0.86; 0.51]	0.619	+0.19 [-0.46; 0.83]	0.571
<i>Obesity vs normal</i>	+135 [-57; 328]	0.167	+123 [-2; 287]	0.091	+0.37 [-0.56; 1.31]	0.432	<b>+0.94 [0.03; 1.85]</b>	<b>0.042</b>
GWG		<0.001		<0.001		0.002		0.002
<i>Low vs mild</i>	-30 [-146; 85]	0.607	-73 [-174; 27]	0.152	-0.25 [-0.81; 0.30]	0.372	-0.41 [-0.95; 0.14]	0.146
<i>High vs mild</i>	+236 [116; 357]	<0.001	<b>+199 [96; 301]</b>	<b>&lt;0.001</b>	+0.89 [0.31; 1.47]	0.003	<b>+0.81 [0.24; 1.38]</b>	<b>0.005</b>

Final multivariate linear regression models were adjusted for gravidity, birth interval, malaria during pregnancy, gestational age at delivery, infant's sex and study center. Adj: adjusted; CI: confidence interval; BMI: body mass index; Underweight: <18.5 kg/m<sup>2</sup>; Normal: 18.5-24.9 kg/m<sup>2</sup>; Overweight: 25-29.9 kg/m<sup>2</sup>; Obesity:  $\geq$  30 kg/m<sup>2</sup>; GWG: gestational weight gain; Low GWG: <7 kg; Mild GWG: 7-12 kg; High GWG: >12 kg; p: p-value; p < 0.05 in bold

Table 4: Association between maternal anthropometric status before conception and during pregnancy and infant's growth from birth to 12 months. Mixed linear regression models. Southern Benin, 2014-2018 (N=175)

Categories	Mean variation in infant's weight from 0-12 months (grams)				Mean variation in infant's length from 0-12 months (cm)			
	Univariate		Multivariate		Univariate		Multivariate	
	Crude $\beta$ [95%CI]	p	Adj $\beta$ [95%CI]	p	Crude $\beta$ [95%CI]	p	Adj $\beta$ [95%CI]	p
Pre-pregnancy BMI		0.058		0.006		0.729		0.073
<i>Underweight vs normal</i>	-309 [-609; -9]	0.044	<b>-342 [-624; -61]</b>	<b>0.017</b>	-0.37 [-1.29; 0.56]	0.438	-0.26 [-1.09; 0.57]	0.535
<i>Overweight vs normal</i>	+8 [-237; 252]	0.952	+147 [-90; 384]	0.223	-0.00 [-0.75; 0.76]	0.997	+0.47 [-0.24; 1.18]	0.191
<i>Obesity vs normal</i>	+279 [-60; 618]	0.107	<b>+384 [44; 724]</b>	<b>0.027</b>	+0.40 [-0.65; 1.45]	0.456	<b>+1.19 [0.20; 2.18]</b>	<b>0.019</b>
Gestational weight gain (GWG)		0.003		<0.001		0.001		<0.001
<i>Low vs Mild</i>	-108 [-316; 99]	0.305	<b>-237 [-438; -36]</b>	<b>0.021</b>	-0.25 [-0.87; 0.37]	0.432	-0.44 [-1.04; 0.16]	0.148
<i>High vs Mild</i>	+313 [93; 534]	0.005	<b>+287 [80; 495]</b>	<b>0.007</b>	+1.08 [0.41; 1.74]	0.001	<b>+0.97 [0.35; 1.59]</b>	<b>0.002</b>

For each variable of interest, the analysis was conducted using a mixed linear mixed model with random intercept.

Coefficients of time variables for infant's weight model:

Age-square: -0.039, 95%CI: [-0.042; -0.036], p<0.001

Age: +28.17, 95%CI: [26.99; 29.36], p<0.001

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Coefficients of time variables for infant's length model:

Age-square: -0.00016, 95%CI: [-0.00017; -0.00014], p<0.001

Age: +0.12, 95%CI: [0.11; 0.13], p<0.001

The final models were adjusted for gravidity, maternal age, gestational age at delivery, infant's sex and age, breastfeeding and study center.

Adj: adjusted; CI: confidence interval; BMI: body mass index; Underweight: <18.5 kg/m<sup>2</sup>; Normal: 18.5-24.9 kg/m<sup>2</sup>; Overweight: 25-29.9 kg/m<sup>2</sup>; Obesity: ≥ 30 kg/m<sup>2</sup>; Low GWG: <7 kg; Mild GWG: 7-12 kg; High GWG: >12 kg; p: p-value; p < 0.05 in bold

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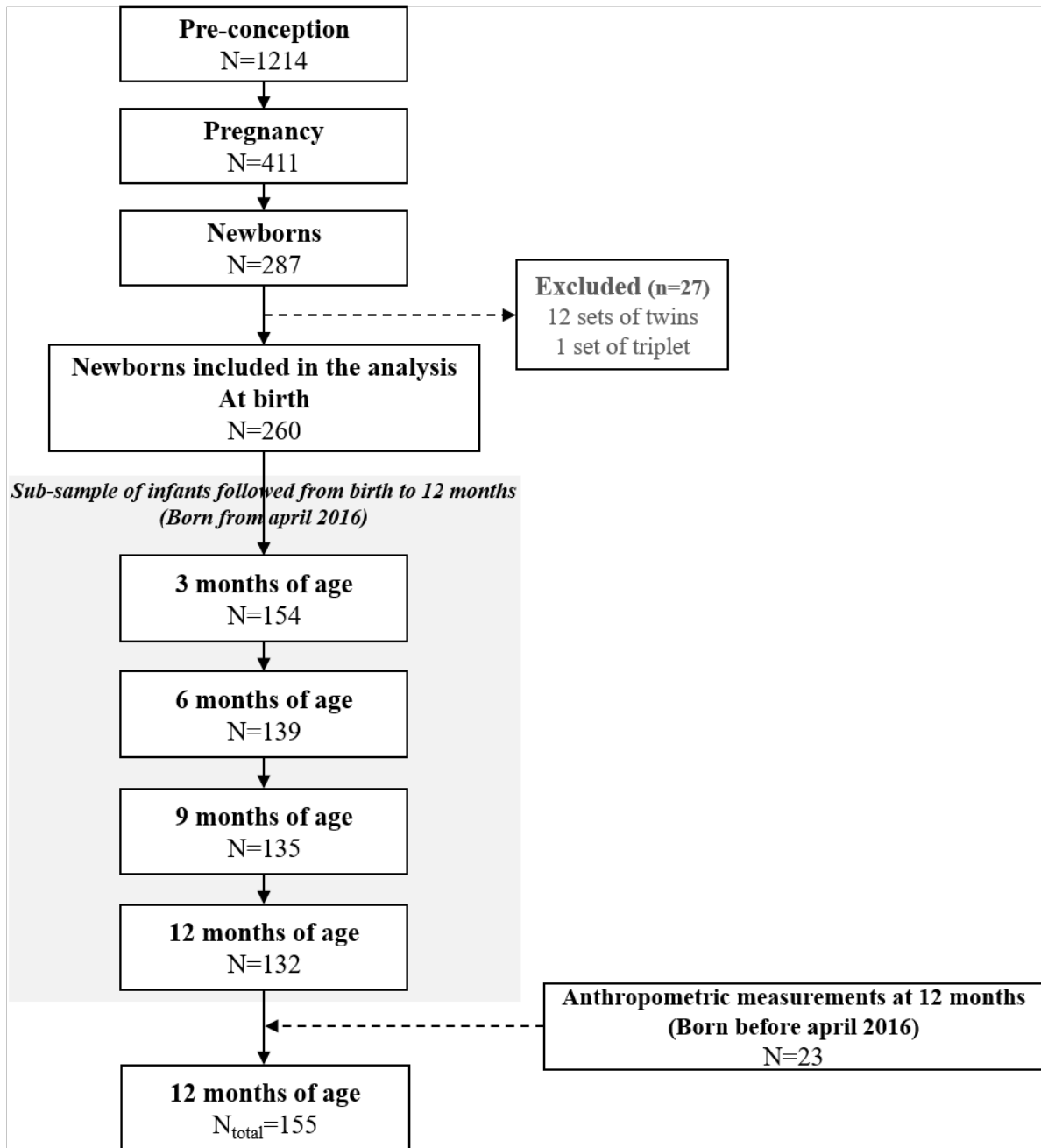
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Table 5: Effect of maternal anthropometric status before conception and during pregnancy on infant's growth at 12 months of age. Logistic regression models. Southern Benin, 2014-2018 (N=155)

	Underweight		Stunting		Wasting	
	Adj. OR [95%CI]	p	Adj. OR [95%CI]	p	Adj. OR [95%CI]	p
Pre-pregnancy BMI		0.145		0.040		0.314
<i>Underweight vs normal</i>	2.41 [0.49; 11.87]	0.281	<b>3.98 [1.01; 15.85]</b>	<b>0.049</b>	3.53 [0.52; 23.85]	0.196
<i>Overweight vs normal</i>	0.34 [0.08; 1.45]	0.146	0.19 [0.04; 1.03]	0.054	0.57 [0.10; 3.24]	0.527
<i>Obesity vs normal</i>	0.18 [0.02; 1.82]	0.147	0.71 [0.13; 3.79]	0.689	0.39 [0.08; 2.54]	0.311
Gestational weight gain (GWG)		0.035		0.070		0.383
<i>Low vs mild</i>	1.77 [0.62; 5.05]	0.282	1.62 [0.58; 4.51]	0.360	1.49 [0.38; 5.91]	0.571
<i>High vs mild</i>	<b>0.09 [0.01; 0.79]</b>	<b>0.030</b>	0.25 [0.06; 1.06]	0.061	0.28 [0.03; 2.64]	0.269

Final models adjusted for gravidity, gestational age at delivery, infant's sex, breastfeeding and study center. Infants with underweight, stunting and wasting at 12 months were defined as a weight-for-age z-score <-2 SD, a length-for-age z-score <-2 SD and a weight-for-length z-score <-2 SD, respectively; Z-scores were calculated based on WHO sex-specific growth standards<sup>22</sup>; OR: odds ratio; Adj: adjusted; CI: confidence interval; BMI: body mass index; Underweight: <18.5 kg/m<sup>2</sup>; Normal: 18.5-24.9 kg/m<sup>2</sup>; Overweight: 25-29.9 kg/m<sup>2</sup>; Obesity: ≥ 30 kg/m<sup>2</sup>; Low GWG: <7 kg; Mild GWG: 7-12 kg; High GWG: >12 kg; p: p-value; p < 0.05 in bold

588 Figure 1



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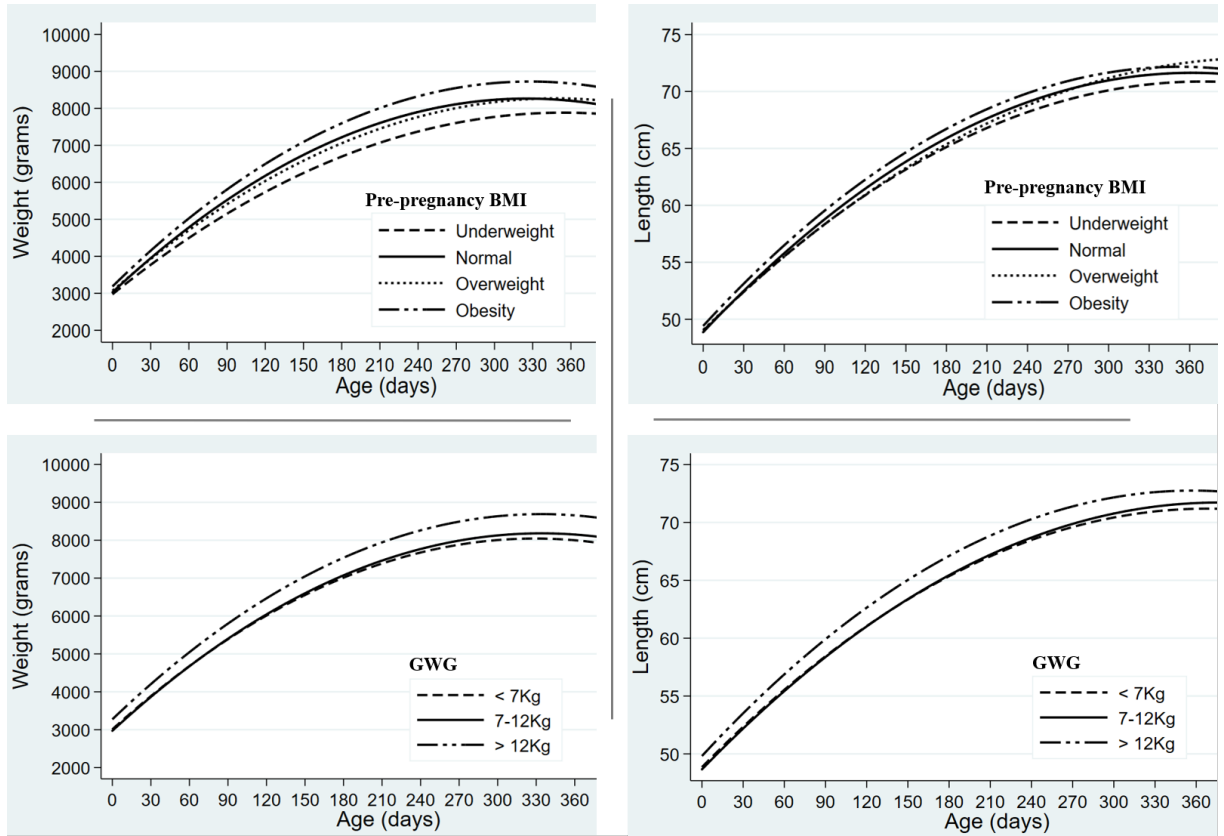
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594 Figure 2



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