Title

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

Authors

Gino Agbota[1,2*], Nadine Fievet[1], Barbara Heude[3,4], Manfred Accrombessi[2,5], Urbain Ahouayito[2], Emmanuel Yovo[2], Djamirou Dossa[2], Latifou Dramane[2], Agnès Gartner[6], Sem Ezinmègnon[7,8], Javier Yugueros Marcos[7], Laurence Vachot[7], Pierre Tissières[8], Achille Massougbodji[2,5], Yves Martin-Prével[6], Michel Cot[1], Valérie Briand[1]

Affiliation

[1] MERIT, IRD, Université Paris 5, Sorbonne Paris Cité, Paris, 75006, France

[2] Centre d'Etude et de Recherche sur le Paludisme Associé à la Grossesse et à l'Enfance (CERPAGE), Cotonou, Benin

[3] INSERM, UMR 1153, Centre for Research in Epidemiology and StatisticS (CRESS), Team "EArly life Research on later Health" (EARoH), Paris, France.

[4] Paris Descartes University, Paris, France.

[5] Clinical Research Institute of Benin (IRCB), Abomey-Calavi, Benin

[6] Nutripass, UMR204, IRD, Université de Montpellier, SupAgro, Montpellier, France

[7] Medical Diagnostic Discovery Department (MD3), bioMérieux, Marcy l'Etoile, France

[8] UMR 9198, Institut de biologie Intégrative de la Cellule, Université Paris Saclay, France

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* **Corresponding author**

Gino Agbota

MERIT / IRD « Mother and child face to tropical infections »

Faculté des sciences pharmaceutiques Paris Descartes

4 avenue de l'Observatoire. 75006 Paris, France

E-mail: ginodric@yahoo.fr

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Abstract

Background

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

Methods

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

Results

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

Conclusion

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

INTRODUCTION

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

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

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

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

MATERIAL AND METHODS

Study site and population

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

Study procedures

Maternal follow-up

The protocol of women's follow-up from the preconception period to pregnancy, then throughout pregnancy has been described elsewhere [19]. Briefly:

Preconception period

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

Gestational follow-up

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

Infant follow-up

The SEPSIS study was set up in a sub-sample of infants born from RECIPAL mothers. All infants born from April 2016 onwards were included in the cohort and followed actively (scheduled visits) each month from birth to 3 months of age, then quarterly to 12 months of age. At each scheduled visit, anthropometric data (same as at birth), breastfeeding and dietary practices, vaccine coverage and clinical symptoms were collected. Any time during follow-up, mothers were encouraged to attend the health facility in case of symptoms of their children. In January 2017, while the SEPSIS project was ongoing, we decided to collect anthropometric data in an additional sub-sample of infants born from RECIPAL mothers before April 2016, who had not been included in SEPSIS study.

Anthropometric data collection

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

Definitions

Before conception, the mother's anthropometric status was based on body mass index (BMI), and during pregnancy it was based on gestational weight gain (GWG). BMI at the first ANC visit, which occurred before 7 weeks' gestation for most women, was used as a proxy for pre-pregnancy BMI, which was not retained because of a high variability in time-to-pregnancy and to a less complete set of data. In accordance with World Health Organization (WHO) classification, underweight was defined as BMI < 18.5 kg/m^2, normal weight as BMI between 18.5 and 24.9 kg/m^2, overweight as BMI between 25 and 29.9 kg/m^2 and obesity as BMI ≥ 30 kg/m^2. The total maternal GWG was calculated as the difference between weight at delivery and weight at the first ANC visit. Then, the GWG was categorized into 3 classes according to the observed distribution: low GWG (< 1st quartile, i.e. <7 kg, ranging from -1.4 to 6.9 kg), mild GWG (1st-3rd quartile, i.e. 7-12 kg) and high GWG (> 3rd quartile, i.e. >12 kg, ranging from 12.1 to 22.7 kg). Anemia was defined as Hb level <12 g/dL before conception and at least one episode of Hb level < 11g/dL during pregnancy.

Malaria during pregnancy was defined as at least one malarial infection during pregnancy. Maternal socioeconomic level was approximated using a synthetic score combining occupation (employed or not), ownership of assets (family possessions such as pirogue, bicycle, motorcycle, car, radio, television, fridge, mobile phone, domestic animals, fish farm) and home characteristics, which was then categorized according to the tertiles in low, medium and high.

Infant's growth was assessed from birth to 12 months of age. Weight-for-age, weight-for-length and length-for-age z-scores at 3, 6, 9 and 12 months were calculated based on WHO sex-specific growth standards, using a WHO macro for STATA software [22]. Underweight, wasting and stunting at 12 months of age were defined as weight-for-age, weight-for-length and length-for-age z-scores < -2 SD, respectively [22]. Low birthweight (LBW) and small-for-gestational age (SGA) were defined as birthweight < 2500 g and birthweight < 10th percentile according to sex-specific INTERGROWTH-21st charts [21], respectively.

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

Statistical analysis

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

In all models, the main exposure variables were maternal pre-pregnancy BMI and GWG. Potential confounders were maternal age, gravidity, birth interval, ethnicity, marital status, maternal socioeconomic and education level, household size, gestational conditions (malaria, hypertension), anemia (before and during pregnancy), study center as well as infant's sex, gestational age at birth, breastfeeding, vaccine coverage, anemia and clinical symptoms during the first year follow-up. All variables with a p-value below 0.2 in univariate analysis were included in the multivariate analysis. Then, the variables with a p-value less than 0.05 after a step-by-step backward selection procedure were kept in the multivariate model. Statistical analysis was performed with Stata version 13.1 for Windows (Stata Corp., College Station, TX).

Ethics statement

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

RESULTS

Study profile

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

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

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

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

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

Mean weight and length at birth, 3, 6, 9 and 12 months were compared according to maternal pre-pregnancy BMI and GWG (Table 2 and Figure 2). At birth, the infant's weight increased with increasing maternal pre-pregnancy BMI and GWG (2835 g for underweight to 3134 g for obesity, p=0.056, and 2979 g for low GWG to 3223 g for high GWG, p<0.001), but this variation was only marginally significant for pre-pregnancy BMI. The proportion of infants affected by LBW and SGA decreased with increasing maternal GWG; although same trends were observed with pre-pregnancy BMI, they were not statistically significant. Infants born from mothers with overweight and normal weight seemed to have comparable weight-growth trajectory from birth to 12 months. In contrast, infants born from mothers with underweight and obesity seemed to have lower and higher weight-growth trajectories, respectively (Figure 2). Same trends were observed for infants' length according to pre-pregnancy BMI, but the differences in length-growth trajectory were less pronounced. Finally, infants born from mothers with a high GWG seemed to have higher weight and length growth trajectories compared to infants born from mothers with a low or mild GWG (Figure 2).

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

At birth

In multivariate analysis, we showed a statistically significant effect of both maternal pre-pregnancy BMI and GWG on infant's weight and length at birth (Table 3). Indeed, infants born from mothers who were affected by underweight before conception had a significantly lower birthweight than infants born from mothers with a normal weight (-164 g, p=0.024). Infants born from women with overweight or obesity had a higher birthweight compared to infants born from women with a normal weight, but only the first association was statistically significant (+119 g, p=0.045 and +123 g, p=0.091, for women with overweight and obesity respectively). Obesity before conception was also associated with a higher infant's length at birth (+0.94 cm, p=0.042). A high GWG was significantly associated with both higher weight and length at birth compared to mild GWG (+199 g, p<0.001 and +0.81 cm, p=0.005, respectively). The other factors significantly associated with both a higher weight and a higher length at birth were birth interval (12-24 and > 24 months) and increasing gestational age at birth (Supplementary table S1). Sensitivity analyses using weight and length z-scores at birth did not change our results (data not shown).

From birth to 12 months of age

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

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

DISCUSSION

In this analysis of fetal outcomes and subsequent growth within a mother-child cohort, our results showed an independent association between maternal anthropometric status before and during pregnancy and infant's weight and length at birth and during the first year of life. In particular, maternal underweight before conception was associated with a lower infant's weight at birth and during the first year of life as well as with a higher risk of stunting at 1 year old. In addition, obesity before conception and a high GWG were associated with a higher infant's length at birth and during the first year of life as well as with a higher infant's weight from birth to 12 months of age.

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

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

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

Our results are consistent with the literature. Indeed, most of the previous studies conducted in HICs, and the few carried in Asia and Latin America, reported an association between high values of maternal BMI, particularly during pregnancy, and a high birthweight or a higher risk of obesity in child- and adulthood [12,13,25–27]. In a study conducted in USA, in which pre-pregnancy BMI was self-reported, a pre-pregnancy BMI > 25 kg/m² or an excessive GWG was associated with higher z-scores for birth weight and weight-for-age at 3 months [13]. Also, one of the largest cohort including 38,539 mother-child pairs in China, showed that pre-pregnancy overweight/obesity and excessive GWG were associated with higher weight and length at birth and in the first year of life [28]. Concerning mother's underweight, recently in France, "the EDEN mother-child cohort" reported an association between mothers affected by underweight before conception and a low birthweight, a low weight and a low instantaneous weight-growth velocity in infants at 3 months of age [29]. Besides, infant's nutritional status early in life has been shown to be predictive of growth and chronic diseases later in life. In particular, overweight/obesity or a higher weight gain in infancy have been associated with an increased risk of obesity in adulthood [30,31]. Studies in HICs have also suggested a link between maternal obesity during pregnancy and a higher risk of stunting early in life [32], which we did not find. In our study, infants born from women with obesity before pregnancy had higher weight and length during the first year of life. Our analysis focused on preconceptional maternal obesity, with possibly a different effect of the mother's anthropometric status depending on the period considered (preconception or early pregnancy vs. last trimester of pregnancy) [33].

In SSA, most studies have assessed the effect of maternal anthropometric status during pregnancy on infant growth at birth, yielding comparable results as in our study [15]. In particular, in studies conducted in Sudan [34], Ghana [35] and South Africa [36], obesity during pregnancy was associated with macrosomia at birth. Gondwe *et al.* in Malawi reported a higher risk of stunting at birth in infants born from underweight mothers during pregnancy as well as an association between inadequate GWG and a higher risk of LBW and SGA [37].

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

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

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

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

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

Conflict of interest

None declared

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

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Figure legends

Figure 1: Flow chart of the study

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

BMI: body mass index; Underweight: <18.5 kg/m²; Normal: 18.5-24.9 kg/m²; Overweight: 25-29.9 kg/m²; Obesity: ≥ 30 kg/m²; GWG: gestational weight gain; Low GWG: <7 kg; Mild GWG: 7-12 kg; High GWG: >12 kg.

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

Characteristics	Categories	n	Pre-pregnancy BMI					Gestational weight gain (GWG)			
			Underweight (n=23, 8.9%)	Normal (n=175, 67.3%)	Overweight (n=43, 16.5%)	Obesity (n=19, 7.3%)	p	Low (n=65, 25.7%)	Mild (n=132, 52.2%)	High (n=56, 22.1%)	p
			17.6 (0.7)[a]	21.4 (1.6)[a]	27.3 (1.4)[a]	34.3 (3.9)[a]	¥	25.2 (4.7)[a]	22.2 (3.9)[a]	21.7 (4.2)[a]	¥
			10.7 (2.2)[b]	9.9 (3.8)[b]	7.0 (4.1)[b]	5.4 (4.9)[b]	¥	4.0 (2.5)[b]	9.5 (1.4)[b]	14.5 (2.3)[b]	¥
Maternal characteristics											
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, %	*Toffin*	194	69.6	73.7	76.7	84.2	0.740	76.9	70.5	78.6	0.464
	Other	66	30.4	26.3	23.3	15.8		23.1	29.5	21.4	
Education, %	*Illiterate*	185	73.9	69.1	69.8	89.5	0.316	78.5	69.7	66.1	0.290
Socioeconomic status, %	*Low*	90	47.8	36.6	27.9	15.8	0.062	32.3	39.4	28.6	0.121
	Medium	97	34.8	39.4	37.9	52.6		33.9	33.3	51.8	

	High	73	17.4	24.0	44.2	31.6		33.8	27.3	19.6	
Gravidity, %	*1-2*	54	30.4	24.6	9.3	0	0.005	23.1	20.5	19.6	0.897
	≥ 3	206	69.6	75.4	90.7	100		76.9	79.5	80.4	
Household size, %	*≤ 5*	135	60.9	50.9	48.8	57.9	0.741	44.6	53.8	57.1	0.346
Birth interval (months), %	*< 12*	14	4.4	6.3	4.7	0	0.598	6.1	6.1	3.6	0.911
	12 – 24	98	43.5	39.4	34.9	21.1		33.9	39.4	37.5	
	> 24 *	148	52.1	54.3	60.5	78.9		60.0	54.5	58.9	
Anemia before conception (< 12 g/dL), %	*Yes*	151	60.9	59.4	51.2	57.9	0.791	56.9	56.8	66.1	0.488
Microscopic malaria in pregnancy, %	*≥ 1 episode(s)*	111	52.2	38.9	46.5	57.9	0.262	46.2	42.4	37.5	0.649
Infant's characteristics											
Sex, %	*Female*	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 (< 37 weeks), %	*Yes*	22	17.4	6.3	9.3	15.8	0.120	6.2	8.3	7.1	0.950

Maternal breastfeeding (0-6 months)**, %	*Yes*	251	100	96.6	93.0	100	0.556	95.4	96.2	98.2	0.747

[a]: mean (SD) pre-pregnancy BMI (Kg/m^2); [b]: mean (SD) gestational weight gain (kg); [¥]: 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

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 ± SD) grams									
At birth	2835 ± 454	3030 ± 403	3071 ± 391	3164 ± 438	0.056	2979 ± 365	2982 ± 409	3223 ± 359	<0.001
At 3 months	5450 ± 826	5707 ± 759	5589 ± 614	5931 ± 925	0.403	5528 ± 761	5611 ± 740	6040 ± 692	0.008
At 6 months	6583 ± 800	7060 ± 866	6815 ± 648	7587 ± 1133	0.083	6906 ± 905	6954 ± 967	7200 ± 739	0.442
At 9 months	7224 ± 1010	7717 ± 1044	7693 ± 660	7994 ± 1249	0.276	7495 ± 1139	7652 ± 994	8033 ± 1101	0.145
At 12 months	8136 ± 1377	8378 ± 1119	8398 ± 812	8949 ± 1331	0.351	8150 ± 1023	8348 ± 1091	8871 ± 1199	0.020
Length (Mean ± SD) cm									
At birth	48.3 ± 2.0	48.5 ± 1.9	48.5 ± 2.0	48.8 ± 2.6	0.876	48.3 ± 1.9	48.4 ± 1.9	49.3 ± 1.8	0.007
At 3 months	59.2 ± 2.8	59.2 ± 2.7	59.2 ± 2.4	59.8 ± 2.9	0.922	58.8 ± 2.5	59.0 ± 2.8	60.3 ± 2.4	0.036
At 6 months	64.8 ± 3.0	66.0 ± 2.4	65.2 ± 3.2	66.4 ± 3.1	0.405	65.6 ± 3.3	65.5 ± 2.5	66.6 ± 2.7	0.259
At 9 months	68.5 ± 3.3	69.2 ± 2.7	69.4 ± 2.1	69.6 ± 3.8	0.692	68.5 ± 3.0	69.2 ± 2.7	70.1 ± 2.5	0.070

At 12 months	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/m²; Normal: 18.5-24.9 kg/m²; Overweight: 25-29.9 kg/m²; Obesity: ≥ 30 kg/m²; 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^{th} percentile according to sex-specific INTERGROWTH-21^{st} charts [21]; 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 [22]; SD: standard deviation; p: p-value for Fisher exact or Anova test

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 β [95%CI]	p	Adj. β [95%CI]	p	Crude β [95%CI]	p	Adj. β [95%CI]	p
Pre-pregnancy BMI		0.057		0.009		0.739		0.223
Underweight vs normal	–193 [-370; -16]	0.032	**–164 [-307; -22]**	**0.024**	–0.22 [-1.08; 0.64]	0.612	–0.12 [-0.90; 0.66]	0.765
Overweight vs normal	+33 [-108; 175]	0.642	**+119 [1; 236]**	**0.045**	–0.17 [-0.86; 0.51]	0.619	+0.19 [-0.46; 0.83]	0.571
Obesity vs normal	+135 [-57; 328]	0.167	+123 [-2; 287]	0.091	+0.37 [-0.56; 1.31]	0.432	**+0.94 [0.03; 1.85]**	**0.042**
GWG		<0.001		<0.001		0.002		0.002
Low vs mild	–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
High vs mild	+236 [116; 357]	<0.001	**+199 [96; 301]**	**<0.001**	+0.89 [0.31; 1.47]	0.003	**+0.81 [0.24; 1.38]**	**0.005**

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/m²; Normal: 18.5-24.9 kg/m²; Overweight: 25-29.9 kg/m²; Obesity: ≥ 30 kg/m²; 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

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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 β [95%CI]	p	Adj β [95%CI]	p	Crude β [95%CI]	p	Adj β [95%CI]	p
Pre-pregnancy BMI		0.058		0.006		0.729		0.073
Underweight vs normal	–309 [-609; -9]	0.044	**–342 [-624; -61]**	**0.017**	–0.37 [-1.29; 0.56]	0.438	–0.26 [-1.09; 0.57]	0.535
Overweight vs normal	+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
Obesity vs normal	+279 [-60; 618]	0.107	**+384 [44; 724]**	**0.027**	+0.40 [-0.65; 1.45]	0.456	**+1.19 [0.20; 2.18]**	**0.019**
Gestational weight gain (GWG)		0.003		<0.001		0.001		<0.001
Low vs Mild	–108 [-316; 99]	0.305	**–237 [-438; -36]**	**0.021**	–0.25 [-0.87; 0.37]	0.432	–0.44 [-1.04; 0.16]	0.148
High vs Mild	+313 [93; 534]	0.005	**+287 [80; 495]**	**0.007**	+1.08 [0.41; 1.74]	0.001	**+0.97 [0.35; 1.59]**	**0.002**

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

<u>Coefficients of time variables for infant's weight model:</u>

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

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^2; Normal: 18.5-24.9 kg/m^2; Overweight: 25-29.9 kg/m^2; Obesity: ≥ 30 kg/m^2; Low GWG: <7 kg; Mild GWG: 7-12 kg; High GWG: >12 kg; p: p-value; p < 0.05 in bold

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
Underweight vs normal	2.41 [0.49; 11.87]	0.281	**3.98 [1.01; 15.85]**	**0.049**	3.53 [0.52; 23.85]	0.196
Overweight vs normal	0.34 [0.08; 1.45]	0.146	0.19 [0.04; 1.03]	0.054	0.57 [0.10; 3.24]	0.527
Obesity vs normal	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
Low vs mild	1.77 [0.62; 5.05]	0.282	1.62 [0.58; 4.51]	0.360	1.49 [0.38; 5.91]	0.571
High vs mild	**0.09 [0.01; 0.79]**	**0.030**	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 [22]; OR: odds ratio; Adj: adjusted; CI: confidence interval; BMI: body mass index; Underweight: <18.5 kg/m²; Normal: 18.5-24.9 kg/m²; Overweight: 25-29.9 kg/m²; Obesity: ≥ 30 kg/m²; 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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Figure 1

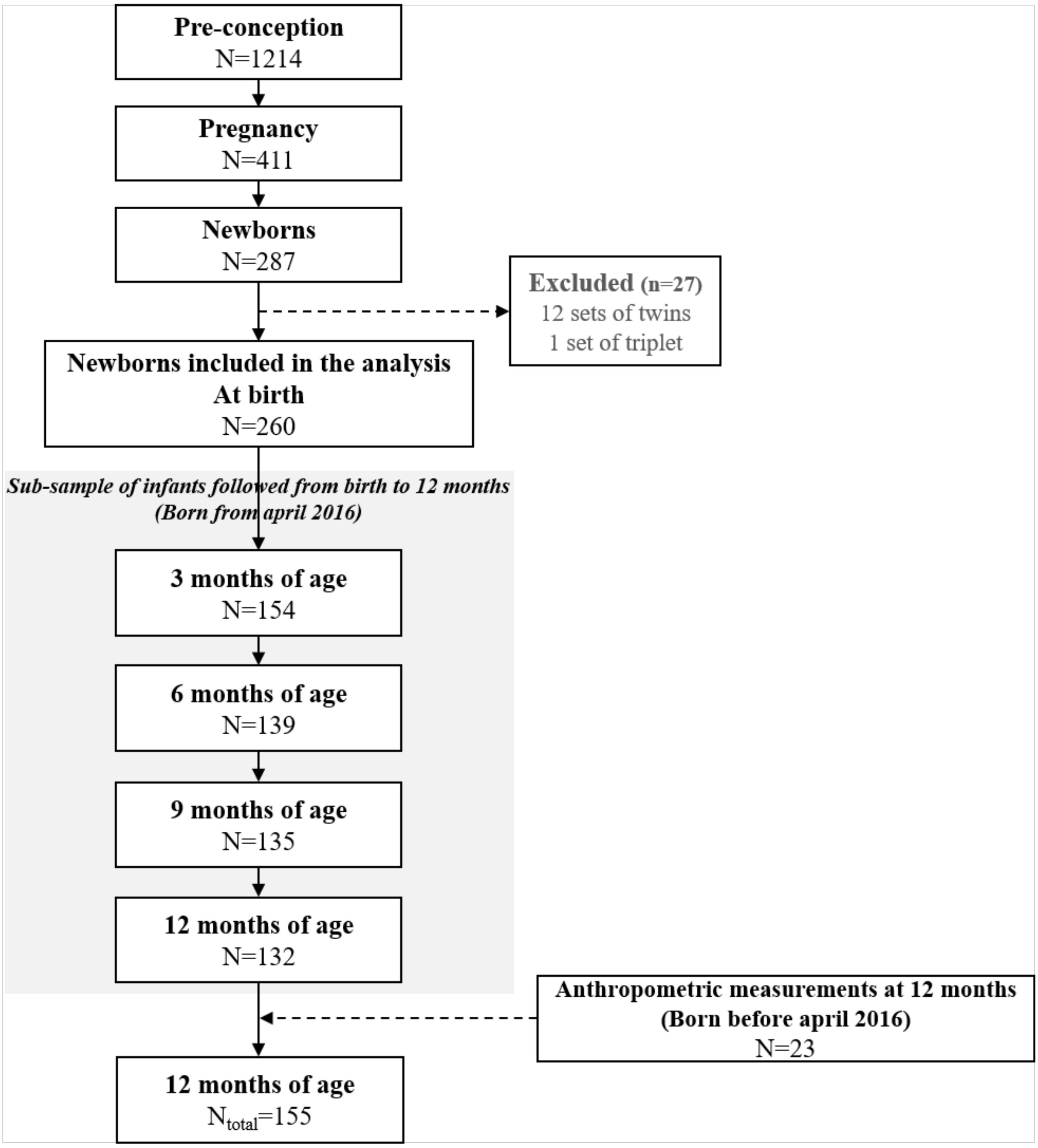
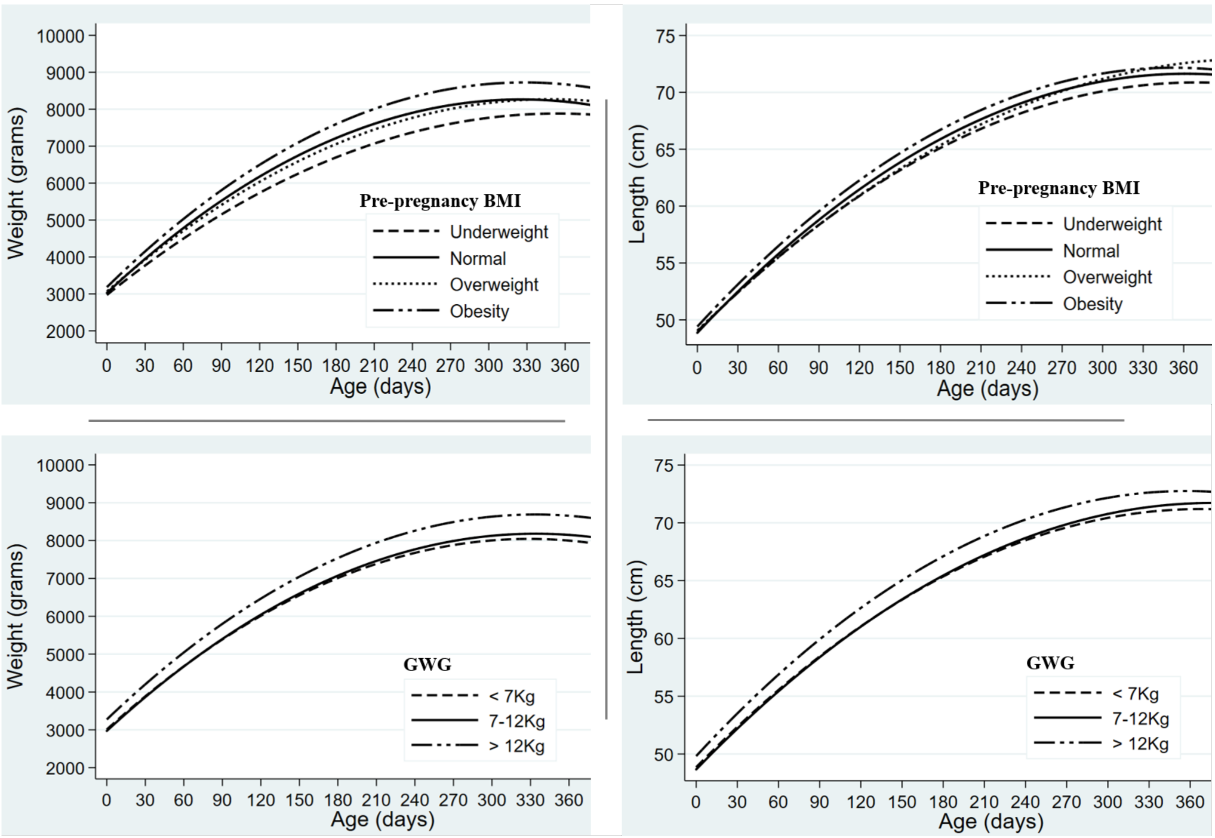

Pre-conception
N=1214
Pregnancy
N=411
Newborns
N=287
Excluded (n=27)
12 sets of twins
1 set of triplet
Newborns included in the analysis
At birth
N=260
Sub-sample of infants followed from birth to 12 months
(Born from april 2016)
3 months of age
N=154
6 months of age
N=139
9 months of age
N=135
12 months of age
N=132
Anthropometric measurements at 12 months
(Born before april 2016)
N=23
12 months of age
N_total=155

Figure 2


Weight (grams)
Age (days)
Pre-pregnancy BMI
Underweight
Normal
Overweight
Obesity
Length (cm)
GWG
< 7Kg
7-12Kg
> 12Kg