Associations of fat and fat-free mass at birth and accretion from 0-5 years with cognitive function at later childhood: The Ethiopian iABC birth cohort

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A running title

Early childhood body composition and cognitive function

Abbreviation

FM = Fat mass

FFM = Fat-free mass

PPVT = Peabody Picture Vocabulary Test

LSMEM = Linear spline mixed effect modelling

Keywords

Fat mass, Fat-free mass, Peabody Picture Vocabulary Test, cognitive function, Ethiopia

Abstract

Early childhood growth is associated with cognitive function. However, the independent associations of fat mass (FM) and fat-free mass (FFM) with cognitive function are not well understood. We investigated associations of FM and FFM at birth and 0-5 years accretion with cognitive function at 10 years. Healthy term newborns were enrolled in this cohort. FM and FFM were measured at birth, 1.5, 2.5, 3.5, 4.5, 6 months, 4 and 5 years. Cognitive function was assessed using Peabody Picture Vocabulary Test (PPVT) at 10 years. FM and FFM accretion were computed using statistically independent conditional accretion from 0-3 months, 3-6 months, 6 months-4 years, and 4-5 years. Multiple linear regression was used to assess associations. At the 10-year follow-up, we assessed 318 children with mean (SD) age of 9.8 (1.0) years. A 1 SD higher birth FFM was associated with a 0.14 SD (95% CI: 0.01, 0.28) higher PPVT at 10 years. FFM accretion from 0-3 and 3-6 months was associated with PPVT at 10 year, $\beta = 0.5$ SD (95% CI: 0.08, 0.93) and $\beta = -0.48$ SD (95% CI: -0.90, -0.07, respectively. FFM accretion after 6 months showed no association with PPVT. Neither FM at birth nor 0-5 years accretion showed association with PPVT. Overall, birth FFM, but not FM was associated with cognitive function at 10 years, while the association of FFM accretion and cognitive function varied across distinct developmental stages in infancy. The mechanisms underlying this varying association between body composition and cognitive function need further investigation.

Introduction

A third of all preschool-aged children living in low and middle-income countries (LMICs) do not reach their cognitive developmental potential due to factors such as undernutrition and poverty [1]. Genetic and environmental factors influence cognitive development through the nature-nurture interaction [2,3]. While genetic factors have a strong influence on brain development, environmental factors, particularly nutrition, also play a fundamental role [3,4]. Early childhood is an important period when physiological and epigenetic changes can impact brain development [4–6]. The effect and intensity of both adverse and favorable influences during these developmental periods are dependent on the timing of their occurrence [5].

The Developmental Origins of Health and Disease hypothesis suggests that fetal growth has an impact on growth, neurodevelopment, health and disease vulnerability [7]. The evidence is particularly strong for low birth weight and preterm children [8]. However, the association of birth weight with cognitive development extends beyond low birth weight since there is variability within the normal range of birth weight [9]. In studies among children born at term and with a normal birth weight, birth weight was associated with different domains of cognitive development or intellectual quotient (IQ) scores during childhood [10–13] and early adolescence [12,14]. However, postnatal body mass index (BMI) shows inconsistent associations with children's cognitive development, with some studies reporting inverse associations with perceptual reasoning, working memory, and IQ scores [15], while others demonstrate no significant association across different cognitive domains or with IQ [16,17]. One possible explanation for this inconsistency is that BMI is not a good marker of body fat or fat-free mass [18,19].

Despite the distinct association of FM and FFM with children's growth and health [20–25], studies examining the relationship of FM and FFM with childhood cognitive function are scarce, particularly in LMICs and among full term children. Among very low birth weight preterm children, it has been shown that higher FFM, but not FM, accretion in early infancy was associated with better neurodevelopment at 1 year [26]. Another study among a similar population also revealed that FFM accretion in early infancy was associated with higher full-scale IQ, whereas FM accretion was associated with poorer working memory at 4 years [27].

The Ethiopian infant Anthropometry and Body Composition (iABC) cohort data showed wide variability of FM and FFM across the spectrum of birth weight [9]. From this cohort, we previously reported positive associations of FFM at birth with cognitive development at 2 years of age [25] and developmental progression from 1 to 5 years assessed using the Denver-II Developmental Screening Test (DDST-II) [24]. Given the prolonged nature of brain development throughout childhood [28], it is crucial to investigate the association of FM and FFM with cognitive function in later childhood. Therefore, we aimed to investigate the association of FM and FFM at birth and 0-5 years accretion with cognitive function at 10 years.

Methods

Study setting and participants

The study participants were recruited from Jimma Medical center, Jimma, Ethiopia. Jimma town is located 350 km southwest of Addis Ababa, the capital city of Ethiopia. It is the largest town in the southwestern Ethiopia and has a population of approximately 240,000 [29]. Jimma Medical Center, located in this town, serves as a referral hospital for a catchment area with about 15 million people [31].

This is a 10-year follow-up of the iABC birth cohort, initially established from December 2008 to October 2012. At enrollment, newborns and their mothers were recruited from Jimma Medical Center within 48 hours after delivery. As described elsewhere [9,32], the cohort included term newborns who resided in Jimma Town (to ensure participation in follow-up visits), had a birth weight above 1500 g and no congenital malformation. Mothers with their children were invited for visits, at birth, 1.5, 2.5, 3.5, 4.5, 6 months, 4 and 5 years of child's age. In the current follow-up visit the children's age ranged from 7-12 years, henceforward referred as the 10-year follow-up. Mothers/caregivers with their children were traced using their last registered phone number and address.

At enrollment 644 mother-newborn pairs were examined. Of these, 571 children met the inclusion criteria and were followed up. At the 10-year follow-up, 355 children attended, and 318 of them had PPVT data

Exposure variables

Body composition measurement

FM and FFM of newborns and infants at 1.5, 2.5, 3.5, 4.5 and 6 months were measured using air-displacement plethysmography (ADP; PEA POD, COSMED, Rome, Italy). PEA POD is an infant-sized ADP that measures infant body composition using a two-component densitometry model [9,20,32].

A child/adult version of ADP (BOD POD, COSMED) was used to measure body composition starting from 4 years of child's age [20]. A two-point calibration process, with the empty chamber and using a calibration cylinder, was done every time the BOD POD was used. Before the measurement, children were asked to remove all clothes and put on a swim cap and tight-fitting underwear. Children were also informed about the measurement, to ensure relaxation. Finally, children were sat on a pediatric chair insert in the chamber and FM and FFM were then measured in kg by trained research nurses.

Covariables

Head circumference at birth was measured in duplicate to the nearest 0.1 cm using a non-stretchable tape. Gestational age as per the Ballard score [33], sex of the newborn and birth order were recorded at birth. In addition, maternal age and socioeconomic characteristics were collected at birth. At 10 years follow-up, height was measured in duplicate using SECA 213 (Seca, Hamburg, Germany). Data on the child's current school grade was collected from school records using questioner. Breastfeeding status was assessed at 4.5 and 6 months of child's age with the following categories: exclusive (no other foods given), almost exclusive (no other foods given except water), predominant (breast milk as primary food), and partial/no (breast milk not the primary food/not breastfeeding).

Outcome variable

Cognitive function at age 10 years follow-up was assessed using the Peabody Picture Vocabulary Test Fourth Edition (PPVT IV). PPVT assesses receptive vocabulary, an important component of general intelligence that is predictive of academic success [34,35]. PPVT was translated into local Ethiopian languages (Amharic and Affan Oromo) and has been used in earlier cohort studies to assess cognitive function of Ethiopian children [36,37]. The test was developed for individuals aged from 2.5 to 90+ years. PPVT IV is composed of 228 items, divided into 19 sets of 12 items each. Each PPVT IV item consists of 2 parts. The first part consists of stimulus words (for the examiner) and a corresponding page composed of four colored pictures (for the examinee). The test requires the child to choose one of the four items (pictures) displayed on a test card illustrating the word spoken by the examiner. The test items are arranged from left to right in an increasing order of difficulty. The test procedure starts at age-appropriate test items/sets. Then the child is tested for items/sets arranged to the left of the start set until the child makes one or zero error (basal set) and the test continued to the right of the start set until the child makes 8 or more errors (ceiling set).

Prior to data collection, research nurses were trained on how to administer PPVT which was conducted in a private room. Ninety-seven participants were identified as having examination errors, where their testing was terminated before ceiling set was established. Subsequently, we re-examined these children at their homes. Place of test administered was categorized as home or facility administered and controlled in all regression models.

Statistical analysis

Data were double entered in EpiData version 4.4.2.0 and exported to Stata version 17 (StataCorp LLC College Station, Texas, USA) for further cleaning and analysis. Descriptive results were presented as mean and standard deviation (SD) for normally distributed continuous data and count (percent) for categorical variables. Wealth index was computed from self-reported ownership of 12 material assets: car, motorcycle, bicycle, electric stove, refrigerator, mobile phone, land, telephone, television, radio, access to electricity, source of drinking water and type of latrine. Principal component analysis was used to compute wealth index, and the first component grouped into wealth quintiles [38] and used in subsequent analyses. Grade-for-age was computed based on the United Nations Educational Scientific and Cultural Organization criteria [39]. Height-for-age Z-score (HAZ) at 10 years was computed using the WHO Reference 2007 STATA macro package [40]. To ensure comparability in the model estimates, FM and FFM measurements, as well as the PPVT score, were standardized.

Association between body composition and cognitive function

Individual growth measurements at consecutive time-intervals might be correlated. Thus, conditional growth modeling was used to assess the association of postnatal FM and FFM accretion over selected time periods from 0-5 years of age with cognitive function at 10 years of age. However, conditional growth modelling requires participants to have complete data at all time points, which reduces the sample size due to the exclusion of individuals with missing observations at different time points [41]. Thus, three analytical steps were carried out in this study. In the first step, we predicted FM and FFM data using linear spline mixed effect modelling (LSMEM) using R statistical software version 4.2.2 (R Foundation for Statistical Computing, Vienna, Austria). LSMEM assumes the child to have linear pattern of growth within a set of pre-defined knot points and different rates of growth across sets of knot points [42]. We determined knot points based on a previous study from this cohort [20], and Akaike- and Bayesian information criterion. Finally knot points at 3, 6, 48 and 60 months were selected. Children having at least 3 measurements were included in LSMEM (one at birth, one measurement from 0-6 months, and one measurement from 4-5 years of age) -.

In the second steps, using the estimated FM and FFM data, we computed conditional FM and FFM accretion from 0-3 months, 3-6 months, 6 months-4 years and 4-5 years. Conditional growth modeling produces statistically independent conditional estimates, that represent the difference between the actual growth and expected growth over a specific period, based on the prior FM and FFM z-scores [41]. These estimates will be referred to as accretions. Positive values indicate that the child grew faster than expected while negative values indicate that the child grew slower than expected based on standardized previous measurements.

In the third step, multiple linear regression analyses were used to assess the association of FM and FFM accretion 0-5 years with cognitive function at 10 years in separate models. Model 1 included age at the 10-year follow-up, sex, and place of test. Model 2 was additionally adjusted for child characteristics at birth (head circumference, gestational age, birth order), HAZ and academic grade at 10 years follow-up. Model 3 was further adjusted for maternal characteristics: wealth index, maternal age and maternal education. Covariables were selected based on related literature [24,25,43]. Separate models were fitted for FM and FFM accretions. Since accretions computed from conditional growth modelling are uncorrelated [41], they were included simultaneously in a regression model. As an example, FM accretion model was specified as, $f_{(\text{cognitive function})} = FM_{0\text{-}3\text{months}} + FM_{3\text{-}6\text{months}} + FM_{6\text{-}48\text{months}} + FM_{48\text{-}60\text{months}} + \text{sex} + \ldots\ldots + \text{covariable}_{N}$.

Similar models were built to assess the association of birth FM and FFM with cognitive function. For example, model for FFM at birth was specified as, $f\,(_{\text{cognitive function}}) = FFM_{\text{at birth}} + \text{sex} + \ldots\ldots + \text{covariable}_{N}$. Model assumptions were checked: normal distribution of residuals was visually examined using pnorm and qnorm plots; homoscedasticity was visually checked by plotting residuals against fitted values. Multicollinearity between exposure variables was assessed using variance inflation factor.

As a sensitivity analysis, we also assessed the association between conditional FM and FFM accretion with PPVT score using observed FM and FFM measurements**.** In addition**,** since data of school type had a large number of missing, we ran sensitivity analyses and adjusted school type (private vs government) in models 2 and 3. Since we had only limited breastfeeding data, it was excluded from the main analysis. Instead, we conducted sensitivity analyses to account for breastfeeding status at 4.5-6 months of the child's age.

Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and ethical clearance were obtained from Jimma University Ethical Review Board of the College of Public Health and Medical Sciences (reference IHRPHD/333/18) and the London School of Hygiene and Tropical Medicine (reference 15076)**.** Written informed consent was obtained from all mothers or care givers.

Results

Participant characteristics

A total of 644 children were enrolled at birth, of whom 73 were excluded: 10 because they were preterm and 63 because they lived outside Jimma Town. Among 571 children recruited to the iABC cohort, 318 had PPVT score data at 10 years **(Figure 1)**. These children were not different (all P> 0.05) from those who did not have PPVT data with respect to sex, birth characteristics (gestational age, length, weight, FM, FFM), wealth status, maternal height, and maternal education. However, those who had PPVT data at 10 years were more likely to be firstborns and have younger mothers **(Supplementary table 1)**. The mean (SD) age of children at the 10-year follow-up was 9.8 (1.0) years and ranged from 7-12 years. Mean (SD) HAZ score at 10 year was -0.7 (0.9). Mean (SD) maternal age at the time of birth was 24.8 (4.7) years. At the child's birth, 214 (61.1%) of mothers reported having attained primary education, and 66 (18.9%) had attained secondary education **(Table 1).** The mean (SD) PPVT score was 184 points (40).

Among children who attended the 10-year follow-up, males had higher mean FFM at birth than females (2.9 vs 2.8, P<0.001). Similarly, FFM was different between males and females up to 6 months (P<0.001). However, FM was not different between males and female from birth to 5 years (P>0.05) **(Table 2)**.

Association of FM and FFM at birth with cognitive function at 10 years

FFM at birth was associated with higher PPVT score at 10 years (**Figure 2 and Supplementary Table 2**). A 1 SD (1SD=0.3 kg) higher FFM at birth was associated with a 0.14 SD (95% CI: 0.01, 0.28) or 5.6 points higher PPVT at 10 years. Across all models, FM at birth was not associated with PPVT score at 10 years, and the coefficients were close to zero (**Figure 2 and Supplementary Table 2**).

Association of FM and FFM accretion from 0 to 5 years with cognitive function at 10 years

Higher FFM accretion from 0-3 months was positively associated with PPVT scores (β = 0.5, 95% CI: 0.08, 0.93), whereas FFM accretion from 3-6 months was negatively associated with PPVT scores (β = -0.48, 95% CI: -0.90, -0.07). For instance, a 1 SD higher (1 SD = 0.43 kg) FFM 0-3 months was associated with a 0.50 SD (20 points) higher PPVT score, whereas 1 SD higher (1 SD =0.53 kg) FFM 3-6 months was associated with -0.48 SD (19.2 points) lower PPVT score. After 6 months all effect sizes were close to zero and the association was non-significant **(Figure 3a and Supplementary Table 3)**. FM accretion from 0-5 years was not associated with cognitive function at 10 years of age **(Figure 3b and Supplementary Table 3**).

In the sensitivity analysis, the estimates did not change markedly with the models using the observed data and in school type adjusted models **(Supplementary Table 4 and 5**). The sensitivity analysis adjusting for breastfeeding status at 4.5-6 months of child's age yielded comparable effect sizes, though the level of significance changed (**Supplementary Table 6).** We also ran another sensitivity analysis excluding the measurements taken at 10 years (age and height at 10 years) and the p-value pattern remained similar, with only some changes in effect size.

Discussion

We examined the relationship of birth and early childhood FM and FFM accretion with cognitive function at 10 years of age using a prospective birth cohort with accurate FM and FFM measurements. Birth FFM, but not FM, showed a significant positive association with cognitive function at 10 years. Higher FFM accretion from 0-3 months had a positive association with cognitive function whereas FFM accretion from 3-6 months showed a negative association. For growth periods after 6 months, the effect sizes became negligible and the association was not significant. FM accretion from 0-5 years showed no significant association with cognitive function at 10 years.

This finding of an association between birth FFM and cognitive function is consistent with our previous study from this cohort [24,25]. Notably, FFM at birth was associated with higher global and language development at 2 years of age [25], as well as with favorable global developmental progression from 1 to 5 years of age [24]. Similarly, FFM at birth showed a positive association with cognitive outcomes among term-born Indian children [43]. The enduring positive association between FFM at birth and cognitive function observed at 10 years highlights the long-term and continued impact of fetal FFM on cognitive development and function throughout childhood. However, we cannot rule out that the small effect size seen in this association could be due to residual confounding. Fetal brain development encompasses processes of neural cell production, migration, and differentiation, which are predominantly protein-dependent processes and protein is the building block of FFM [28]. This might explain the close to zero effect size and non-significant association between fat mass at birth and cognitive function in this study. The lack of association of FM at birth is similar to our previous findings at 2 years [25] and developmental progression from 1-5 years of this cohort [24].

As evidenced from other studies, having a larger brain at birth is also associated with late childhood cognitive function [14,44]. In the present study, the association between birth FFM and cognitive function persisted after head circumference was adjusted. This suggests that there might be different pathways to the association between FFM and cognitive function beyond the association of higher FFM with higher fetal brain size.

FFM accretion from 0-3 months was positively associated with cognitive function at 10 years, whereas FFM accretion from 3-6 months was negatively associated. The effect sizes were relatively large in these periods, suggesting a potentially important role of FFM accretion in cognitive function during this timeframe. Infant growth within the first three months of life can include rapid growth after birth [45]. During this period much of FFM accretion may contribute to brain growth. In a previous study of this cohort, it was found that nearly 55% of infants were born with higher FFM, followed by a distinct FFM growth trajectory with a quadratic shape during the first 6 months [46], which might indicate a catch down pattern. This might explain the varying pattern of association seen in this study during early infancy. Currently, we have no explanation for the negative association of higher FFM from 3-6 months and cognitive function and further research is needed to fully elucidate the underlying mechanisms.

We found no association between FFM accretion and cognitive function beyond infancy. Nutrition and environmental stimulation are essential and complementary, each playing a distinct yet interconnected role in shaping the developing brain [47]. Postnatally, the brain undergoes a period of plasticity, where experiences also play an essential role in shaping its neural organization, brain development and function. Greenough [48] termed this process experience-dependent brain development. This might be the reason for the absence of an association and close to zero effect sizes, especially after 6 months.

The present study has the strength of being a birth cohort that followed children from birth to 10 years of age. ADP was used to measure FM and FFM, which is an accurate method of measuring body composition [49]. We used conditional growth modeling, which allowed us to include all the accretion periods together in one model separately for FM and FFM and enabled us to control the effect of tissue accretion at different time points. There are, however, some limitations to this study which should also be taken into account when interpreting this result. Ninety-seven children were re-tested in their homes due to examination errors. Differences in places of testing might result in systematic differences in test scores between those who were examined at home and those who were examined at a facility; however, we adjusted for place of test in all analyses. There was loss to follow-up at the 10-year visit. However, those lost to follow-ups and those included in the analysis were similar in terms of sex, length at birth, gestational age, birth weight, birth FM, birth FFM, wealth status, maternal height, and maternal educational, although children included in this analysis were more likely to be firstborns and had younger mothers. Due to ADP validation and children's inability to sit still inside BODPOD, we did not measure FM and FFM from 6 month-4 years. These missed periods might have given additional insights regarding associations between early childhood growth and cognitive function. We also did not have comprehensive data on infant feeding, which might be an important variable to be considered in this analysis. Furthermore, the evidence from this cohort is representative of children born at health facilities but might not reflect the general population characteristics, as the participants were only newborns delivered at institution.

In conclusion, FFM rather than FM at birth showed significant association with cognitive function at 10 years. The observed association highlights that optimal maternal and fetal nutrition during pregnancy contribute to establishing a strong foundation for cognitive function, paving the way for continued cognitive function throughout late childhood, which will also impact children's academic achievement and future success. FFM accretion during infancy had distinct and potentially more pronounced effect size compared to other developmental stages. The results of this study underscore the need for further investigations to understand the mechanism of this associations seen during infancy.

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Conflict of interests

The authors declare none

Authorship

The authors' responsibilities were as follows HF, JCKW, SF, TG, RW, DY, MFO, MA, and RA designed the study; RA, BZ and BSM supervised the data collection; HF, JCKW, SF, RW, MFO, MA, and RA participated in methodology; RA analyzed the data and interpreted the findings. RA wrote the first draft. BK, BSM, DY, TG, BA, SF, HF, JCK, AAM, MFO, RW, and MA commented on the manuscript, contributed for manuscript revisions, read the final manuscript and approved it for submission.

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Table 1. Socio-demographic characteristics of children attending the 10-year follow-up [1]

Characteristics	Category	n (%)	Mean	SD
Maternal characteristics at birth				
Age at delivery (years)			24.8	4.7
Birth order	First	169 (48.6)		
	Second	94 (27.0)		
	Third and above	85 (24.4)		
Maternal education	No school	19 (5.4)		
	Primary school	214 (61.1)		
	Secondary school	66 (18.9)		
	Higher education	51 (14.6)		
Wealth index	Lowest	53 (15.3)		
	Low	62 (17.9)		
	Middle	86 (24.8)		
	Higher	80 (23.1)		
	Highest	66 (19.0)		
Child characteristics at birth				
Sex	Male	180 (51.4)		
Gestational age (weeks)			39.0	0.9
Length (cm)			49.2	2.0
Birth weight (kg)			3.1	0.4
Head circumference (cm)			34.9	2.0
Child characteristics at 10 years				
Age at 10-year visit (years)			9.8	1.0
Fat mass (kg)			5.6	3.5
Fat-free mass (kg)			21.7	3.5
Height-for-age (Z-score)			-0.7	0.9
PPVT raw score			184	40
School type (Private)		185 (65.1)		
Grade-for-age (lower)		40 (11.7)		

PPVT = Peabody Picture Vocabulary Test

[1] Values are expressed as mean (SD) for continuous variables and as n (%) for categorical variables.

Table 2. Fat mass and fat-free mass by sex and age (N=318)

	Full sample[1]	Male [1]	Female [1]	P-value [2]
		Fat mass (kg)		
Birth	0.2 (0.21, 0.22)	0.2 (0.21, 0.23)	0.2 (0.21, 0.23)	0.76
3 months	1.7 (01.69, 1.79)	1.7 (1.68, 1.81)	1.7 (1.67, 1.80)	0.90
6 months	2.1 (2.05, 2.18)	2.1 (2.02, 2.20)	2.1 (2.02, 2.21)	0.96
4 years	3.9 (3.72, 4.03)	4.0 (3.75, 4.17)	3.8 (3.56, 4.02)	0.29
5 years	4.2 (4.10, 4.38)	4.2 (4.05, 4.40)	4.3 (4.03, 4.47)	0.86
		Fat-free mass (kg)		
Birth	2.8 (2.82, 2.87)	2.9 (2.87, 2.95)	2.8 (2.74, 2.82)	< 0.001
3 months	4.4 (4.35, 4.45)	4.5 (4.46, 4.60)	4.3 (4.20, 4.33)	< 0.001
6 months	5.5(5.43, 5.55)	5.7 (5.57, 5.73)	5.3 (5.25, 5.40)	< 0.001
4 years	10.9 (10.78, 11.02)	11.0 (10.79, 11.12)	10.8 (10.68, 11.02)	0.38
5 years	12.2(12.08, 12.39)	12.4 (12.16, 12.60)	12.1 (11.90, 12.31)	0.06

[1] Data are mean (95% CI)

[2] Independent sample t-test

Legends

Figure 1. Flow diagram of the study participants. LSMEM = Linear spline mixed effect modelling, PPVT = Peabody Picture Vocabulary Test

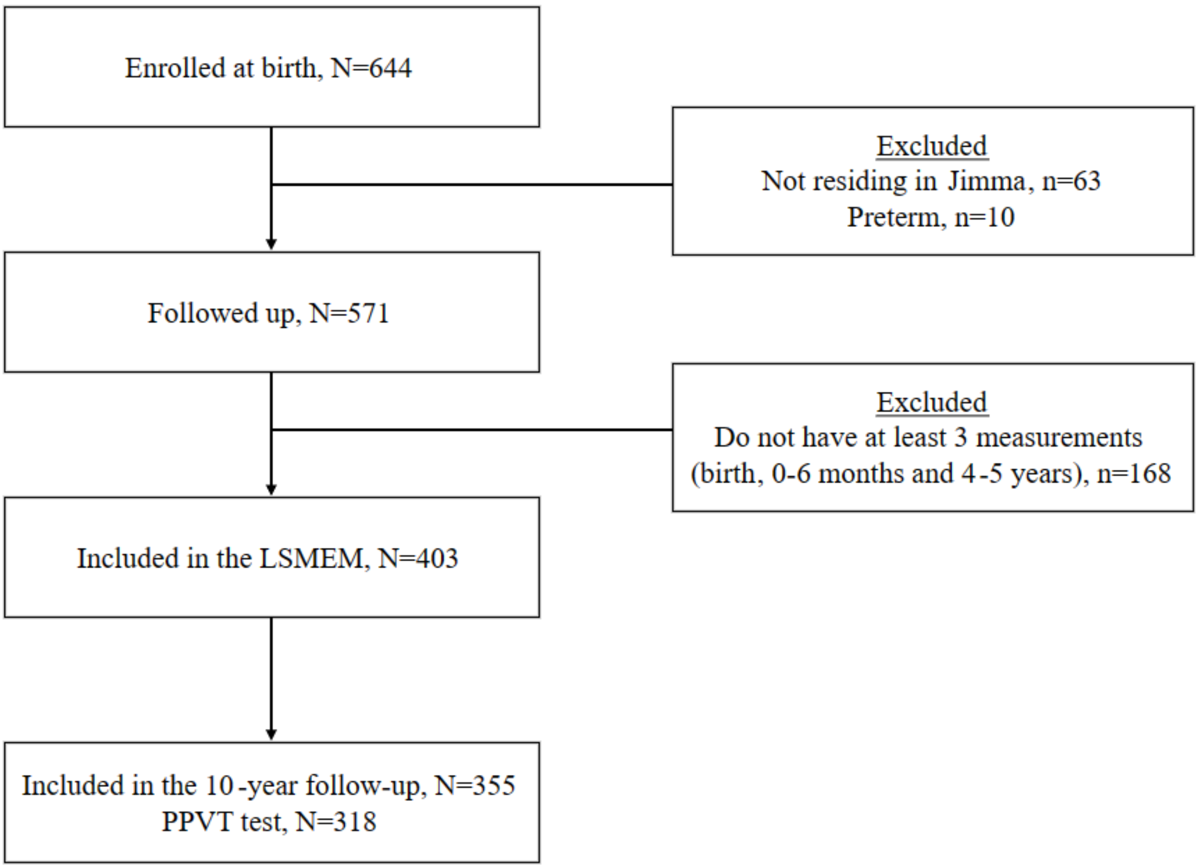
Figure 2. Association of birth fat-free mass and fat mass with cognitive function at 10 years. The Y-axis shows β coefficients from linear regression models with 95% confidence intervals. Model 1 was adjusted for age, sex and place of test. Model 2 was further adjusted for head circumference at birth, birth order, gestational age, HAZ at 10 years and academic grade at 10 years. Model 3 was further adjusted for maternal educational status, maternal age at child birth and wealth index.

Figure 3a. Association of fat-free mass accretion from 0-5 years with cognitive function at 10 years. The Y-axis shows β coefficients from linear regression models with 95% confidence intervals. Model 1 was adjusted for age, sex and place of test. Model 2 was further adjusted for head circumference at birth, birth order, gestational age, HAZ at 10 years and academic grade at 10 years. Model 3 was further adjusted for maternal educational status, maternal age at child birth and wealth index.

Figure 3b. Association of fat mass accretion from 0-5 years with cognitive function at 10 years. The Y-axis shows β coefficients from linear regression models with 95% confidence intervals. Model 1 was adjusted for age, sex and place of test. Model 2 was further adjusted for head circumference at birth, birth order, gestational age, HAZ at 10 years and academic grade at 10 years. Model 3 was further adjusted for maternal educational status, maternal age at child birth and wealth index.

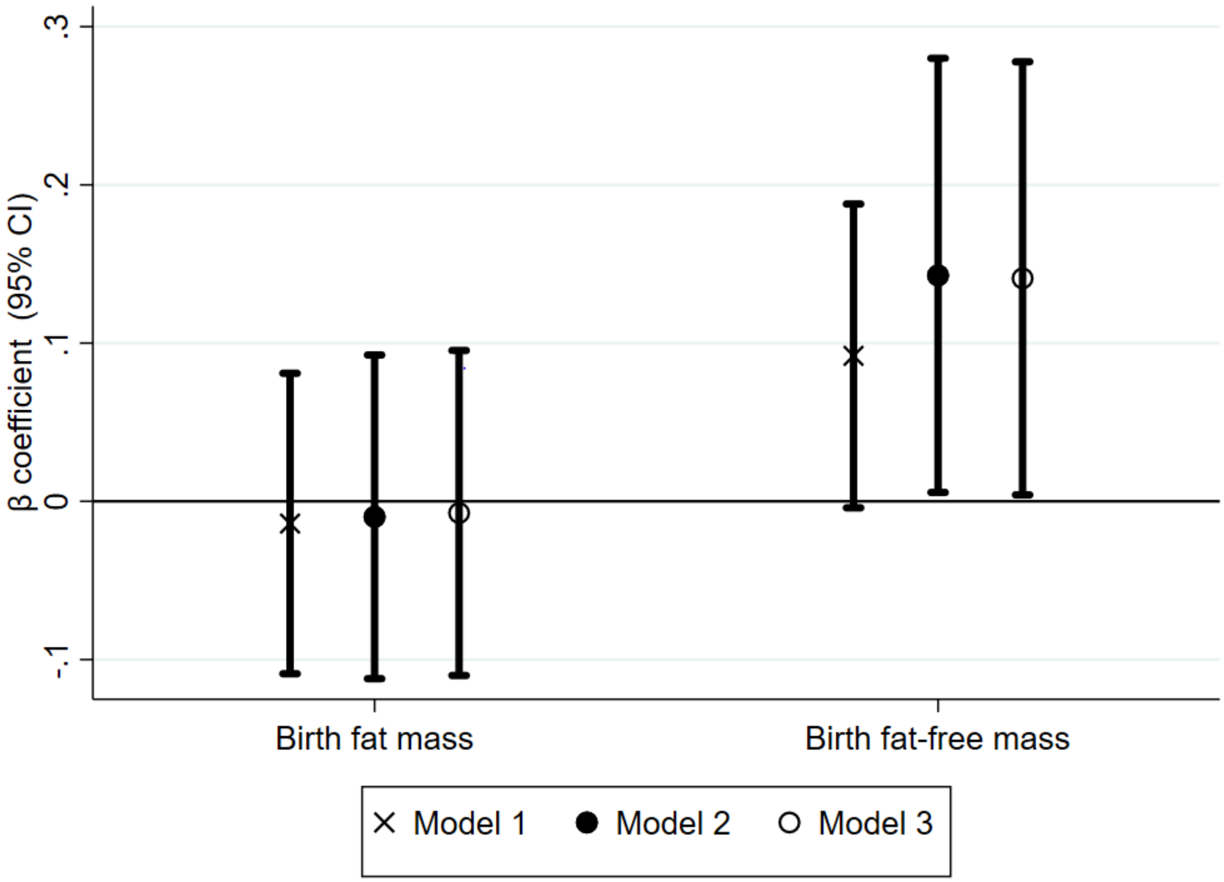
Associations of fat and fat-free mass at birth and accretion from 0-5 years with cognitive function at later childhood: The Ethiopian iABC birth cohort

Figure 1. Flow diagram of the study participants.



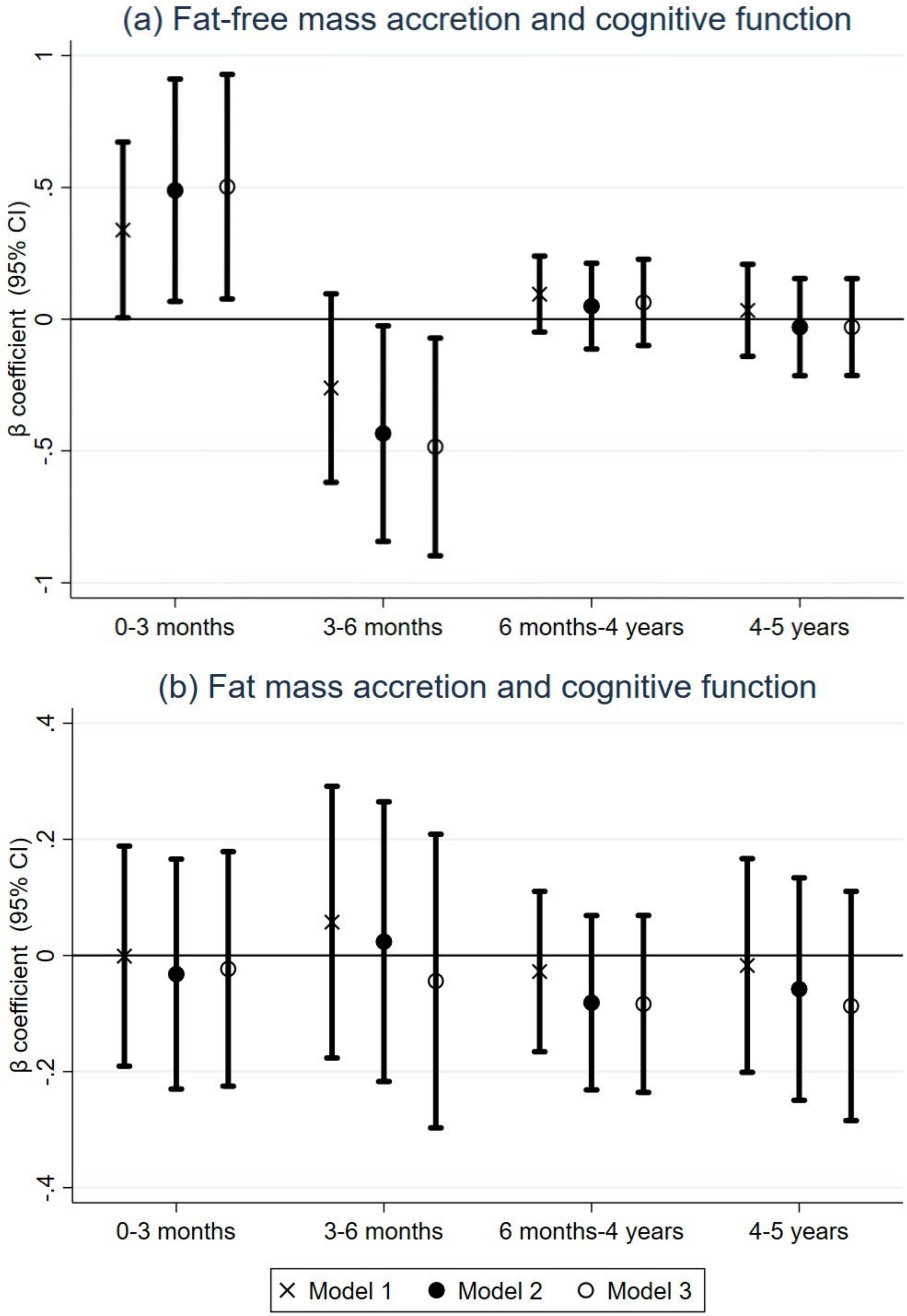
LSMEM = linear spline mixed effect modelling. PPVT = Peabody Picture Vocabulary Test.

Figure 2. Association of birth fat mass and fat-free mass with cognitive function at 10 years. Cognitive function was measured using Peabody Picture Vocabulary Test (PPVT)



PPVT was standardized so the units are standard deviation.

Figure 3. Association of fat-free mass and fat mass accretion from 0-5 years with cognitive function at 10 years. Cognitive function was measured using Peabody Picture Vocabulary Test (PPVT)



Supplementary material

Supplementary Table 1; Comparison between those included in the 10-year analysis and lost to follow-ups

Variable	Category	Lost to follow-up[1] *n*=253			Followed-up [2] *n*=318			P value [3]
		n (%)	Mean	SD	n (%)	Mean	SD	
Maternal characteristics at birth								
Maternal age (years)			23.66	0.3		24.68	0.3	0.01
BMI			12.5	0.1		12.6	0.01	0.53
Height (cm)			157.3	0.4		157.8	0.3	0.34
Wealth index	Poorest	55 (24.0)			48 (15.3)			0.05
	Poor	49 (21.4)			55 (17.5)			
	Middle	31 (13.5)			81 (25.8)			
	Rich	43 (18.8)			71 (22.6)			
	Richest	51 (22.3)			59 (18.8)			
Educational status	No education	20 (0.1)			18 (0.1)			0.61
	Primary	145 (61.7)			194 (61.2)			
	Secondary	41 (17.5)			60 (18.9)			
	Higher and above	29 (12.3)			45 (14.2)			
Child characteristics at birth								
Sex	Male	114 (48.5)			166 (52.4)			0.80
	Female	121 (51.5)			151 (47.6)			
Length (cm)			48.9	0.1		49.2	0.1	0.07
Gestational age (weeks)			39.1	0.1		39.0	0.1	0.43
Fat Mass (kg)			0.2	0.01		0.2	0.01	0.49
Fat free mass (kg)			2.8	0.02		2.8	0.2	0.14
Birth weight (kg)			3.0	0.03		3.05	0.02	0.15
Birth order	First born	140 (61.1)			151 (47.5)			0.01

	Second born	46 (20.1)			86 (27.0)			
	Third born	43 (18.8)			78 (24.5)			

[1] Those who did not have PPVT data at 10 years

[2] Those who have PPVT data at 10 years

3 independent T test

Supplementary table 2; Association between fat and fat free mass at birth with PPVT test at 10 years of age

	Model I		**Model II**		**Model III**	
	β (95% CI)	**P value**	**β (95% CI)**	**P value**	**β (95% CI)**	**P value**
Fat mass	-0.01 (-0.11, 0.08)	0.77	-0.01 (-0.11, 0.09)	0.85	0.01 (-0.09, 0.11)	0.91
Fat-free mass	0.09 (-0.004, 0.19)	0.06	0.14 (0.01, 0.28)	0.04	0.14 (0.01, 0.28)	0.04

Model 1 was adjusted for age, sex and place of test. Model 2 was further adjusted for head circumference at birth, birth order, gestational age, HAZ at 10 years and academic grade at 10 years. Model 3 was further adjusted for maternal educational status, maternal age at child birth and wealth index.

Supplementary table 3; Fat mass and fat-free mass accretion from 0-5 years and PPVT test at 10 years of age

	Model I		Model II		Model III	
	β (95% CI)	**P .value**	**β (95% CI)**	**P .value**	**β (95% CI)**	**P value**
Fat free-mass						
0-3 months	0.34 (0.01, 0.67)	0.05	0.49 (0.07, 0.91)	0.02	0.50 (0.08, 0.93)	0.02
3-6 months	-0.26 (-0.62, 0.10)	0.15	-0.43 (-0.84, -0.03)	0.04	-0.48 (-0.90, -0.07)	0.02
6 months-4 years	0.09 (-0.05, 0.24)	0.20	0.05(-0.11, 0.21)	0.55	0.06 (-0.10, 0.23)	0.45
4-5 years	0.03 (-0.14, 0.21)	0.71	-0.03 (-0.22, 0.15)	0.75	-0.03 (-0.21, 0.15)	0.75
Fat mass						
0-3 months	-0.001 (-0.19, 0.19)	0.99	-0.03 (-0.23, 0.17)	0.75	-0.02 (-0.23, 0.18)	0.82
3-6 months	0.06 (-0.18, 0.29)	0.63	0.02 (-0.22, 0.26)	0.85	-0.04 (-0.30, 0.21)	0.73
6 months-4 years	-0.03 (-0.17, 0.11)	0.69	-0.08 (-0.23, 0.07)	0.29	-0.08 (-0.24, 0.08)	0.28
4-5 years	-0.02 (-0.20, 0.17)	0.85	-0.06 (-0.25, 0.13)	0.55	-0.09 (-0.28, 0.11)	0.39

Model 1 was adjusted for age, sex and place of test. Model 2 was further adjusted for head circumference at birth, birth order, gestational age, HAZ at 10 years and academic grade at 10 years. Model 3 was further adjusted for maternal educational status, maternal age at child birth and wealth index.

Supplementary table 4; Fat mass and fat-free mass accretion from 0-5 years and PPVT test at 10 years of age using observed data (sensitivity analysis)

	Model I		Model II		Model III	
	β (95% CI)	**P .value**	**β (95% CI)**	**P .value**	**β (95% CI)**	**P value**
Fat free mass						
0-3 months	0.25 (-0.18, 0.67)	0.26	0.21 (-0.22, 0.64)	0.33	0.12 (-0.33, 0.58)	0.59
3-6 months	-0.10 (-0.41, 0.21)	0.51	-0.16 (-0.47, 0.15)	0.31	-0.14(-0.47, 0.19)	0.41
6 months-4 years	0.07 (-0.06, 0.20)	0.30	0.02 (-0.13, 0.17)	0.84	0.04 (-0.11, 0.20)	0.58
4-5 years	0.08 (-0.07, 0.23)	0.29	0.03 (-0.13, 0.19)	0.68	0.07 (-0.09, 0.24)	0.38
Fat Mass						
0-3 months	-0.21 (-0.56, 0.15)	0.25	-0.22 (-0.57, 0.13)	0.21	-0.27 (-0.64, 0.09)	0.14
3-6 months	0.08 (-0.18, 0.34)	0.53	0.03 (-0.23, 0.29)	0.81	-0.02 (-0.29, 0.26)	0.89
6 months-4 years	-0.02 (-0.12, 0.09)	0.73	-0.04 (-0.14, 0.07)	0.47	-0.05 (-0.16, 0.06)	0.38
4-5 years	-0.10 (-0.26, 0.07)	0.24	-0.11 (-0.28, 0.06)	0.20	-0.16 (-0.35, 0.02)	0.08

Model 1 was adjusted for age, sex and place of test. Model 2 was further adjusted for head circumference at birth, birth order, gestational age, HAZ at 10 years and academic grade at 10 years. Model 3 was further adjusted for maternal educational status, maternal age at child birth and wealth index.

Supplementary table 5; Fat mass and fat-free mass accretion from 0-5 years and PPVT test at 10 years of age (sensitivity analysis after adjusting school type in model 2 and 3)

	Model I		**Model II**		**Model III**	
	β (95% CI)	**P value**	**β (95% CI)**	**P value**	**β (95% CI)**	**P value**
At birth						
Fat mass	-0.01 (-0.11, 0.08)	0.77	-0.06 (-0.16, 0.05)	0.27	-0.04 (-0.14, 0.06)	0.45
Fat-free mass	0.09 (-0.004, 0.19)	0.06	0.17 (0.03, 0.31)	0.02	0.18 (0.04, 0.32)	0.01
Fat-free mass accretion						
0-3 months	0.34 (0.01, 0.67)	0.05	0.48 (-0.17, 0.83)	0.10	0.46 (0.09, 0.10)	0.04
3-6 months	-0.26 (-0.62, 0.10)	0.15	-0.45 (-0.43, 0.70)	0.24	-0.38 (-0.95, -0.08)	0.03
6 months-4 years	0.09 (-0.05, 0.24)	0.20	0.17 (-0.02, 0.35)	0.08	0.16 (-0.02, 0.35)	0.09
4-5 years	0.03 (-0.14, 0.21)	0.71	-0.18 (0.44, 0.09)	0.19	-0.15 (-0.42, 0.11)	0.26
Fat mass accretion						
0-3 months	-0.001 (-0.19, 0.19)	0.99	-0.03 (-0.47, 0.42)	0.89	-0.13 (-0.57, 0.31)	0.56
3-6 months	0.06 (-0.18, 0.29)	0.63	0.11 (-0.34, 0.56)	0.63	0.14 (-0.31, 0.60)	0.53
6 months-4 years	-0.03 (-0.17, 0.11)	0.69	-0.06 (-0.16, 0.05)	0.29	-0.06 (-0.17, 0.04)	0.21
4-5 years	-0.02 (-0.20, 0.17)	0.85	-0.05 (-0.19, 0.10)	0.54	-0.08 (-0.23, 0.07)	0.31

Model 1 was adjusted for age, sex and place of test. Model 2 was further adjusted for head circumference at birth, birth order, gestational age, HAZ at 10 years, academic grade at 10 years and school type. Model 3 was further adjusted for maternal educational status, maternal age at child birth and wealth index.

Supplementary table 6: Fat mass and fat-free mass accretion from 0-5 years and PPVT test at 10 years of age (sensitivity analysis after adjusting breast feeding status at 6 months in model 3)

	Model I	
	β (95% CI)	**P value**
At birth		
Fat-free mass	0.10 (-0.02, 0.19)	0.13
Fat mass	-0.03 (-0.14, 0.08)	0.61
Fat free-mass		
0-3 months	0.49 (-0.04, 0.98)	0.06
3-6 months	-0.57 (-2.01, 0.08)	0.07
6 months-4 years	0.10 (-0.12, 0.33)	0.37
4-5 years	-0.02 (-0.44, 0.41)	0.94
Fat mass		
0-3 months	-0.11 (-0.33, 0.11)	0.34
3-6 months	-0.08 (-0.22, 0.37)	0.61
6 months-4 years	-0.12 (-0.29, 0.05)	0.15
4-5 years	-0.15 (-0.37, 0.08)	0.21

Model was adjusted for age, sex, place of test, head circumference at birth, birth order, gestational age, HAZ at 10 years, academic grade at 10 years, maternal educational status, maternal age at child birth, wealth index and breast-feeding status at 4.5-6 months of child's age.