Relation of Body Composition at Birth with Child Development at Two Years of Age: A Prospective Cohort Study Among Ethiopian Children

Mubarek Abera[1,8*], Markos Tesfaye[1,8], Tsinuel Girma[2], Charlotte Hanlon[3,4], Gregers S. Andersen[5], Jonatan C. Wells[6], Bitiya Admassu[7,8], Rasmus Wibaek[8], Henrik Friis[8], Pernille Kæstel[8]

Email: MA:abmubarek@yahoo.com; TG:tsinuel@yahoo.com ; MT:tesmarkos@yahoo.com; CH:charlotte.hanlon@kcl.ac.uk; BA:bitiyaa@yahoo.com;GA:gregers.stig.andersen@regionh.dk; RW:rasmus.wibaek.christensen@regionh.dk; JW:jonathan.wells@ucl.ac.uk; HF:hfr@nexs.ku.dk; PK: pernille.kaestel@gmail.com

Affiliation

[1]Department of Psychiatry, College of Health Sciences, Jimma University, Jimma, Ethiopia (MA. MT)

[2]Department of Pediatrics and Child Health, College of Health Sciences, Jimma University, Jimma, Ethiopia (TG)

[3]Department of Psychiatry, School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia (CH)

[4]Centre for Global Mental Health, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK (CH)

[5]Clinical Epidemiology, Steno Diabetes Center, Gentofte, Denmark (GSA, RW)

[6]Childhood Nutrition Research Centre UCL Institute of Child Health, London WC1N 1EH, UK (JCW)

[7]Department of Population and Family Health, College of Health Sciences, Jimma University, Jimma, Ethiopia (BA)

[8]Department of Nutrition, Exercise and Sports, University of Copenhagen, Denmark (MA.MT,RW, HF,PK)

[*]Corresponding author: Mubarek Abera, Department of Psychiatry, College of Health Sciences, Jimma University, Ethiopia, PO Box 378, Jimma, Ethiopia. abmubarek@gmail.com; Mob.phone:+251 913332483

Funding Source: Danish Council for Strategic Research—Program Commission on Food and Health; Danida through the Consultative Research Committee for Development Research (104.Dan.8-1207). Funder has no any roll or involvement in the conduct and report of the study.
Conflict of Interest: None of the authors had declared conflicts of interest

ABSTRACT

Background: Birth weight, independent of socioeconomic status, has been identified as a predictor for child development. However, it is not known whether this relation is related to low birth weight per se or particularly related to a deficit in fat mass (FM) or fat free mass(FFM) at birth. This study therefore, aimed at investigating the relation between body composition at birth and child development at two years of age.

Methods: An Ethiopian birth cohort was followed-up at 2 years. Body composition was measured within 48 hours of birth using infant air-displacement plethysmography. Child development was assessed at 2 years of age using Denver Developmental Screening Test. Associations between body composition at birth and development at 2 years of age were tested using linear regression analysis.

Results: FFM but not FM at birth was positively associated with higher global developmental score at 2 years of age (β=2.48, 95% CI 0.17; 4.79) adjusted for neonatal, postnatal and parental characteristics. This association was attributable to the association with the language developmental subdomain (β=1.61, 95 CI 0.33; 2.90.

Conclusions: Among Ethiopian children, FFM at birth but not FM predicted better global and language development at 2 years of age. Higher FFM at birth mainly reflecting protein accretion, might have exerted a positive effect on the growth and differentiation of the brain and neuronal circuits for better development. This study therefore implicates the need to improve mother's nutritional status during pregnancy in ways that impact on FFM of the offspring at birth.

Key words: ‘neonatal’, ‘body composition’, ‘fat mass’, ‘fat free mass’, ‘child development’, ‘Ethiopia’

INTRODUCTION

In the 21st century, child growth and survival rate have considerably improved due to interventions targeting malnutrition and infectious diseases (1,2). As child survival improves, it becomes increasingly important to focus on functional outcomes including child development as a central focus in child health and well-being (3). More than 200 million children are at risk of failing to reach their full developmental potential in low and middle income countries (4). The first 1000 days of life from conception, is a critical window of opportunity for interventions (5) targeting most of the risk factors affecting child development (6).

A number of studies have identified birth weight (BW) as a predictor for child development (7–10). Furthermore, a recent study had reported that, variability within the normal range of BW is associated with child development (11). However, body composition of newborns, even with same weight and height might differ significantly (12–15). An Ethiopian study from the same cohort, has further shown that infants with similar birth weight have markedly different levels of fat mass (FM) and fat free mass(FFM) at birth (16). Consequently, they might be at different risk of various health outcomes.

Due to the fact that birth weight is consistently found to be a strong predictor of child development (7–10) and infant and children of same weight and height may vary in body composition (16,17), there is a growing interest in examining which component of birth weight best predicts child development (18). Therefore, this study aimed at investigating the relationship between body composition at birth and child development at two years of age among Ethiopian children. We hypothesized that FM and FFM at birth could differently predict child development at two years of age.

SUBJECTS AND METHODS

A prospective cohort (the Infant Anthropometry and Body Composition (iABC) cohort) was established between January 2009 and October 2012 among newborns to women who gave birth at Jimma University Specialized Hospital (JUSH) and resided in Jimma town, Ethiopia. The cohort has previously been described in detail (16,19). In brief, women who gave birth at JUSH were invited to participate in the iABC study. Consenting mothers were examined together with their newborns within 48 hours after birth. Apparently healthy and term babies (identified using the New Ballard Score method (a maturational assessment of gestational age)) (20) with birth weight of ≥1500 grams and with no congenital malformation were eligible for the study. For this study a total of 617 newborns were recruited at birth. At two years of age, only 271 children were followed up successfully. For statistical comparison, we included only 227 children who have a complete data on all variables required in the analysis **(see figure 1).**

Study variables and measurements

Child development

The main outcome, developmental status of children at two years of age, was assessed using Denver-II Developmental Screening Tool (DDST-II), which was previously translated and adapted to the Ethiopian context (21). The tool is designed for children from birth to 6 years of age and has been used previously in a similar setting (22,23). This screening tool comprises 125 age-relevant test items related to global development (GD), and has four developmental sub domains: personal-social (PS) (getting along with people and caring for personal needs); fine motor/adaptive (FM) (eye-hand coordination, manipulation of small objects and problem solving); gross motor (GM) (sitting, walking, jumping, and overall large muscle movement); and language (L) – (hearing, understanding, and using language). The 125 test items are distributed across each sub-domain as follows: 25 PS, 29 FM, 39 L and 32 GM.

The training for data collectors, administration of the tool and scoring of the test result was done based on the DDST-II standard administration guidelines (24). Testing began with items that fall completely to the left of the child's 'age line' and continued to the left until the child passed three consecutive items. All items arranged to the left of three consecutive successfully performed test items on the Denver II test chart were assumed to be passed. Then the test continued to the right of the child's age line until the child failed to perform three consecutive test items. All items arranged to the right of three consecutive failures on the Denver-II test chart were recorded as failures. All successfully performed items on DDST-II coded as 1 and failures coded as 0 were added to compute a raw developmental score as a continuous outcome. The children were assessed for developmental status at the age of 2 years ± 3 months. The internal reliability (Cronbach's alpha) of the DDST-II was 0.63 for the global scale, 0.77 for the language subdomain, 0.56 for fine motor, 0.52 for gross motor subdomain and 0.31 for the personal subscale.

Body composition

Body composition (FM and FFM) at birth is the main exposure variable. We assessed FM and FFM (kg) within 48 hours of birth using an infant air-displacement plethysmograph (PeaPod LMI, Concord, CA, USA). FFM contains proteins, muscles, organs, bones, and water, while FM includes only a lipid component**.** Detailed description of the body composition assessment procedure for this study is published elsewhere (16,19).

Covariates

In addition, different set of covariates to include neonatal, postnatal and parental characteristics were collected. Sex and birth order of the baby were recorded at birth. Length (cm), weight (kg) and head circumference (cm) were all measured in duplicate at birth (16,19) and an average of the two measurements were used. The same parameters (length/height, weight and head circumference) were measured at two years of age. Caregiver's report of 7-day animal-source food intake by the child was recorded. Animal-source food consumption was classified as 'not consumed at all, consumed for 1-2 days, consumed for 3-6 days and consumed everyday' based on mothers' report of seven days' food frequency questionnaire prior to the assessment date. History of hospital admission of the study child since birth was recorded based on the mothers' recall. At enrollment to the cohort, information on maternal age, marital, educational and occupational status, and total number of under -five children living in the same household was obtained. Family socioeconomic information on household assets, utilities and housing characteristics was also collected at birth. Sex of the child, animal source food intake by the child and wealth index of the parent were considered as potential effect modifiers.

Statistical method

Data were double-entered using Epidata 3.1 (The EpiData Association, Odense, Denmark) (25) and exported to STATA version 12.1 (Texas, USA) for cleaning and analysis. Categorical variables were described using frequencies and proportions, while continuous variables were described using mean ± standard deviation (SD) for symmetric distributions, or median (interquartile range) for asymmetric distributions. *T*- tests and chi-2 tests were used to examine for differences between those followed up and lost to follow up. A wealth index score was generated from the data using Principal Components Analysis (PCA). Then the PCA scores were grouped into wealth quintiles. Ownership to car, motor cycle, electric mitad (a metallic cooking plate), electric stove, refrigerator, mobile phone, local telephone line, television, radio, access to electric city, source of drinking water, and type of latrine were considered in generating wealth index using PCA.

Univariate and multivariate linear regression analysis were used to examine the relationship between FM and FFM at birth with developmental score at two years of age. The estimate (β coefficient) and 95% Confidence Interval (CI) were reported as a measure of association. Multicollinearity among predictor variables were checked using Variance Inflation Factor (VIF) and tolerance test. The potential of effect modification was assessed by including interaction terms. Effect modification by sex, animal source food intake and wealth index were assessed by including interaction terms for both FFM and FM variables.

A series of linear regression analyses were conducted to evaluate the association between the primary exposure (FM and FFM at birth), and global developmental scores and each of the four sub-domains at two years of age. To account for the effect of different set of covariates (neonatal, postnatal, and parental characteristics) five different regression models were evaluated. Model 1: included sex of the infant and age at outcome assessment), Model 2: built on model 1 by adding length at birth. Model 3: built on model 2 by adding in additional neonatal characteristics (head circumference at birth and birth order), Model 4: built on model 3 by adding in postnatal characteristics (stunting: length-for-age z score < -2), consumption of animal-source food within 7 days prior to the study, history of hospitalization since birth), Model 5 (fully adjusted model): built on model 4 by adding in parental characteristics (maternal age, maternal and paternal education and wealth index of the family). Separate models were developed for FM and FFM at birth as exposures of child development at 2 years of age. The rationale for the different models was to observe changes in the association between the main exposure and outcome variable when different set of covariate were accounted in the model. All statistical analyses were done on 227 children who have complete data to all covariates included in the model.

Ethics statement

Ethical clearance was obtained from the ethical review board of Jimma University College of Health Sciences (reference RPO/56/2001). Written informed consent was obtained from parents of the newborn. During the study, children identified with illness requiring medical attention were linked to the pediatric clinic of JUSH. Parents were reimbursed for their transport costs.

RESULTS

Background characteristics

At two years of age, 271 children out of the cohort of 611 eligible children (44.4%) underwent developmental assessment, of which, only 227 children had a complete data set for all variables included in the analysis. Reasons for the lost to followed-up were, unsuccessful tracing due to change in the residence and contact address (phone number) of the parents. The mean ± SD age of children was 24.4 ± 1.2 months. The mean ± SD FFM at birth was 2.9 ± 0.3 kg while the mean ± SD FM at birth was 0.2 ± 0.2 kg. The mean ± SD maternal age at delivery of the current child was 24.1 ± 4.6 years. Only 21 (9.3%) of the mothers did not receive formal schooling **(see table 1).** There were no differences in background characteristics between those followed up compared to those not followed up (data not shown).

Developmental score

Of the total DDST-II test items, the mean ± SD developmental scores were as follows: global developmental score 79.9 ± 3.6, language 20.8 ± 2.1, fine motor 19.2 ± 1.0, gross motor 22.3± 0.8 and personal social subdomain 17.5 ± 1.4 **(See table 1).** Language domain contributed the highest variation to the global development.

Predictors of child development

Body composition

We initially found a positive association between birth weight and child development at two years of age. in the subsequent analysis, we found out that, this association was account by the FFM component of the weight. FFM at birth was positively associated with child development (global and language domains) at two years of age in both univariate **(Table 2)** and multivariable linear regression analyses **(Tables 3-4)**. In the fully adjusted model, each kg increase in FFM at birth was associated with a 2.48 points higher global developmental score (β=2.48, 95% CI 0.17; 4.79) at two years of age. The association with the global developmental score was explained by the language domains **(Table 4)**. The observed association between FFM and developmental score remained stable in all of the regression models, adjusting for potential confounders. In contrast, FM at birth was not associated with child development at two years of age. Females had higher language development (β=0.70, 95% CI 0.12; 1.20) in the final model (Model 4)**.** The effect of FM and FFM was not found to be modified by child sex, diet and wealth index (interaction $p>0,05$).

Role of the covariates

Although different models were developed to account for different set of potential confounders, the association between FFM and developmental score remained significant. The highest estimate for FFM (β=2.71, 95% CI 0.42; 5.00) was observed when FFM was adjusted for neonatal and parental characteristics, while the lowest estimate (β=2.08, 95% CI 0.04; 4.13) observed when FFM was adjusted only for sex, length and age during outcome assessment. FM was not associated with any of the developmental domains even after adjustment.

In addition to FFM, in the final model, female sex, higher wealth index, and absence of hospitalization showed positive association to the global developmental score, all attributable to the positive association with the language development score. Stunting at two years of age was negatively associated with language development.

DISCUSSION

The primary interest of this study was to examine the independent relationship of neonatal body composition with child development at two years of age. This paper, therefore, had a precised focus on the contribution of factors beyond socio-economic, demographic and other established predictors of child development such as low birth weight and other postnatal factors (26,27). When examining the relation between BC and child development at 2 years of age with simple linear regression, we found that, for each kg increase in FFM, the global development score was 2.3 points higher. This finding could be confounded by other predictors of developmental status. Then we adjusted for potential confounders including neonatal, postnatal and parental characteristics. However, in all the adjusted models, FFM persistently remained significant. On the contrary, FM at birth was not associated with developmental scores.

The finding that FFM, and not FM at birth was associated with global and language development indicate the relative importance of FFM over FM tissue accretion during fetal life for postnatal development at two years of age among Ethiopian children. Intrauterine FFM accretion occurs throughout pregnancy while fetal FM accretion is best characterized by an accelerating quadratic function, largely occurring only during the third trimester (28–30). These contrasting patterns of tissue accretion may help explain the association of fetal FFM, but not FM, with developmental outcome early in childhood. Previous literatures also indicated that higher FFM gain at birth and during neonatal period found to effect positively the development of different organ systems including brain (31). The mechanism of FFM to effect development might be attributed to its positive effect on protein accretion which intern is a basic foundation for brain development including the growth and differentiation of nerve cells (32). A study examined the relationship of body composition with speed of brain processing capacity in a preterm infant also showed that, increased FFM accretion at term found to be associated with faster neuronal processing capacity than increased accumulation of fat mass or fat mass percentage (33).

The fact that FFM was significantly associated only with the global and language subdomain was surprising. However, this might be due to variability observed in the global developmental score being largely attributable to variability in the language subdomain in this study. Other studies also reported the presence of higher degree of variation for language development at two years of age compared to other developmental subdomains (34). Furthermore, the Denver screening tool might be more sensitive to detect slight differences in the language subdomains compared to other domains specifically in this age group. This is also observed in the internal reliability (Cronbach's alpha) value of 0.77 for language subdomain, which is greater than in all other subdomains in this study.

Alternatively, using a screening tool developed in the western setting (United States) could potentially bias our results. In this regard we ascertained that the DDST-II was adapted and validated for the cultural context of Jimma, Ethiopia and has previously been used in the same study area (21). Another possibility is that the association between FFM and the global and language subdomain might be the result of confounding. However, we adjusted for several known predictors and potential confounders without changing our main finding. We therefore consider the observed association of FFM, and lack of association for FM, with child development at two years of age as a robust finding.

Although acquiring body fat may eventually benefit brain development, not least because myelination involves the deposition of fatty tissue around the nerve cells (35–37), in this study FM at birth was not associated to child development at 2 years of age. FM is mainly deposited in the last trimester of pregnancy, whereas the brain is developing throughout pregnancy (38). In this sense, FFM at birth might be a better proxy for fetal brain growth than fat mass at birth. The lack of positive association between FM and child development observed in this study may also be accounted for by the possibility that infants with higher fat at birth underwent some degree of 'catch up growth' during pregnancy, so that acts as a marker for lower levels of FFM at birth. Studies have also shown that either obesity or abnormal (both excessive and inadequate) maternal weight gain during pregnancy leads to irregular pattern of BC growth in the fetus (39,40), which could incorporate catch up of fetal FM during late pregnancy. A significant negative association of excess FM during infancy with psychomotor development of children at 2 years of age was also reported in a previous study from USA (41). However, FM deposited at birth might benefit survival or health of the newborn in other ways.

Neonatal anthropometric measurements showed no association with our outcome variables. This is an important indication for the advantage of measuring BC over crude measure of birth weight and other anthropometric indices as a predictor of development. In previously published analyses, our cohort demonstrated varying ratios of FM and FFM at birth for the same weight of the newborn (16). Therefore, we need to be cautious when using crude birth weight as a predictor factor of health outcomes in children.

Female sex, higher wealth index, tertiary level of paternal schooling, higher maternal age, and lack of hospitalization, all previously known predictors of development (42–45), were also positively associated, while stunting was negatively associated with developmental across to the different subdomain. Although our study has a specific hypothesized objective, these additional findings are worth noting, and furthermore they are indicative of the methodological soundness of our study method including statistical power.

Considering the limited research in relation to BC and child development, the result of this study is key for extending the understanding of the relationship between birth weight and child development at two years of age. However, the relationships observed between BC and child development might be different if we had measured both the exposure and outcome longitudinally at different age during early childhood. FM deposition through infancy might potentially start playing a different role in predicting child development subsequently, as might FFM. The association of BC to the different developmental subdomains might also vary with age.

Lastly, we were able to explain about 12% of the total variance in GD and 16% for language subscales. Furthermore, our models explained lower variance for fine motor, gross motor and personal social subscales, ranging from 2-7%. In summary, the most important implication of this study is that a higher FFM at birth was associated with better development outcome during childhood, suggesting the need to improve mother's nutritional status during pregnancy in ways that impact on FFM of the offspring. It has also been indicated that maternal under-nutrition, (either in energy- or micronutrients) during pregnancy, could adversely impact development of the fetus and the newborn including via tissue accretion, organogenesis, and growth (46–48). A neonate with higher level of FFM at birth might mean that the fetus was supplied with healthier nutrition from the mother during in utero development (49).

Strengths and limitations of the study

This is the first study to investigate the relationship between BC at birth and child development from a low-/middle-income country setting. The longitudinal design of this study enabled consideration of direction of causality. Another strength of this study is that we were able to control for a range of important confounding variables. However, the study also had the following limitations: We did not assess maternal mental health (neither antenatal or postnatal) which could function as a predictor for child development. The high attrition rate and the relatively small sample size might also have contributed to the lack of association between BC and developmental subdomains except language. The lack of association between FM and development might also be due to small sample size. Absolute FM at birth is quantitatively smaller than FFM, and therefore has lower potential as a predictor of outcome. We also used history of hospital admission since birth as a proxy indicator of severe illness, therefore, we were not able to control for mild to moderate recent morbidities that could affect child development. We used a sensitive screening tool instead of a diagnostic test for developmental assessment, in which case detection of variation among those who have or do not have actual developmental problems might be compromised. This might lead to under- or over-estimation of the associations found in this study.

Conclusion

Higher FFM, not FM, at birth predicted better child developmental outcome at two years of age in a low-income setting. Fetal lean tissue accretion might play an important role in the development of children in the first two years of life. However, further similar studies are needed to confirm these findings.

ACKNOWLEDGEMENTS

We would like to acknowledge Jimma University for allowing the research to be conducted and providing logistic support. We also like to acknowledge the Jimma University and University of Copenhagen Alliance in Nutrition (JUCAN) research staff for their unreserved commitment to this research work and the study participants for their time and participation

AUTHORS' CONTRIBUTION

HF, TG, PK, GSA and JW: designed the study; MA, BA, TG, MT, GSA, RW, PK and HF: conducted the study; MA, BA, PK, JW, and HF: analyzed data and interpreted the finding; MT, TG, CH, RW, GSA: interpreted the fining and contributed in the write up; MA: wrote the first draft of the manuscript and had responsibility for the whole work. All authors reviewed the content, read and approved the final version.

None of the authors had declared conflicts of interest

REFERENCES

1. United Nation (UN). The Millennium Development Goals Report. UN. New York. 2013. Available from: http://www.un.org/millenniumgoals/pdf/report-2013/mdg-report-2013-english.pdf. [Accessed 13th November 2016].

2. You D, Hug L, Ejdemyr S, Idele P, Hogan D, & Mathers C, et al. Global, regional, and national levels and trends in under-5 mortality between 1990 and 2015, with scenario-based projections to 2030: a systematic analysis by the UN Inter-agency Group for Child Mortality Estimation. The Lancet. 2015; 386 (10010): 2275–2286. doi: 10.1016/S0140-6736(15)00120-8. Available from: https://www.ncbi.nlm.nih.gov/pubmed/26361942. [Accessed 21st January 2017].

3. Black MM, Walker SP, Fernald LCH, Andersen CT, DiGirolamo AM, Lu C, et al. Early childhood development coming of age: science through the life course. The Lancet. 2016. Available from: http://dx.doi.org/10.1016/ S0140-6736(16)31389-7. [Accessed 21st January 2017]

4. Lu C, Black MM, Richter LM. Risk of poor development in young children in low-income and middle-income countries: an estimation and analysis at the global, regional, and country level. Lancet Glob Health.2016;4(12): doi: 10.1016/S2214-109X(16)30266-2. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27717632. [Accessed 21st January 2017]

5. Maalouf-Manasseh Z, Oot L, and Sethuraman K. Giving Children the Best Start in Life: Integrating Nutrition and Early Childhood Development Programming within the First 1,000 Days. Technical Brief. Food and Nutrition Technical Assistance III Project. 2016. available from: http://www.cmamforum.org/Pool/Resources/Giving-children-best-start-intergrating-nutrition-1000days.pdf. [Accessed 21st January 2017]

6. Cusick S & Georgieff MK. Tthe first 1,000 days of life: the brain's window of opportunity: UNICEF. Office of research-Innocenti. Available from: https://www.unicef-irc.org/article/958/. [Accessed 13th November 2016].

7. Grantham-McGregor SM, Lira PI, Ashworth A, Morris SS, Assuncao AM. The development of low birth weight term infants and the eff ects of the environment in northeast Brazil. J Pediatr 1998; 132: 661–66. Available from: https://www.ncbi.nlm.nih.gov/pubmed/9580767. [Accessed 21st January 2017]

8. Brooks-Gunn J, Pam Kato K, Fong-Ruey L, and Donna S. "Enhancing the Development of Low-Birth-Weight, Premature Infants: Changes in Cognition and Behavior over the First Three Years." Child Development:1993; 64 (3): 736-53.

9. Boulet SL, Schieve LA, Boyle CA. Birth weight and health and developmental outcomes in US children, 1997–2005. Matern Child Health J. 2011; 15(7):836-44. doi: 10.1007/s10995-009-0538-2. Available from: https://www.ncbi.nlm.nih.gov/pubmed/19902344. [Accessed 21st January 2017].

10. Rojahn J, Aman MG, Marshburn E, Moeschberger ML, King EH, Logsdon DA, et al. Biological and environmental risk for poor developmental outcome of young children. Am J Ment Retard. 1993;97: 702–708. Available from: https://www.ncbi.nlm.nih.gov/pubmed/7686015. [Accessed 21st January 2017].

11. Wade M, Browne DT, Madigan S, Plamondon A, Jenkins JM.Normal birth weight variation and children's neuropsychological functioning: links between language, executive functioning, and theory of mind. J Int Neuropsychol Soc. 2014;20(9):909-19. Available from: https://www.ncbi.nlm.nih.gov/pubmed/25171131. [Accessed 21st January 2017].

12. Deurenberg P, Yap M, Staveren WA. Body mass index and percent body fat: a meta analysis among different ethnic groups. Int J Obes Relat Metab Disord. 1998;22:1164-71.Availbale from: https://www.ncbi.nlm.nih.gov/pubmed/9877251. [Accessed 21st January 2017].

13. Nightingale CM, Rudnicka AR, Owen CG, Cook DG, Whincup PH. Patterns of body size and adiposity among UK children of South Asian, black African-Caribbean and white European origin: Child Heart And health Study in England (CHASE Study). Int J Epidemiol:2011; 40:33–44. doi: 10.1093/ije/dyq180. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3043281/. [Accessed 21st January 2017].

14. Stanfield KM, Wells JC, Fewtrell MS, Frost C, Leon DA . Differences in body composition between infants of South Asian and European ancestry: the London Mother and Baby Study. Int J Epidemiol. 2012;41:1409–18. Available from: https://researchonline.lshtm.ac.uk/271763/1/dys139.pdf. [Accessed 21st January 2017].

15. Van SL, Karamali NS, Kanhai HH, Ariëns GA, Fall CH, Yajnik CS, et al. Neonatal anthropometry: thin-fat phenotype in fourth to fifth generation South Asian neonates in Surinam. Int J Obes (Lond). 2009;33:1326–9.Available from: http://www.nature.com/ijo/journal/v33/n11/full/ijo2009154a.html. [Accessed 21st January 2017].

16. Andersen GS, Girma T, Wells JCK, Kæstel P, Michaelsen KF, Friis H. Fat and fat-free mass at birth: air displacement plethysmography measurements on 350 Ethiopian newborns. Pediatr Res 2011; 70: 501–506.available from: http://www.nature.com/pr/journal/v70/n5/full/pr2011216a.html. [Accessed 21st January 2017].

17. Lee S, Bountziouka V, Lum S, Stocks J, Bonner R, Naik M, et al. Ethnic Variability in Body Size, Proportions and Composition in Children Aged 5 to 11 Years: Is Ethnic-Specific Calibration of Bioelectrical Impedance Required? Alemany M, ed. PLoS ONE. 2014;9(12):e113883. doi:10.1371/journal.pone.0113883.Available from: http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0113883. [Accessed 21st January 2017].

18. Wells JC, Fewtrell MS: Is body composition important for paediatricians? Arch Dis Child:2008; 93:168–172. doi: 10.1136/adc.2007.115741. available from: http://adc.bmj.com/content/93/2/168.abstract. [Accessed 21st January 2017].

19. Andersen G, Girma T, Wells J, Kaestel P, Leventi M, Hother AL, et al. Body composition from birth to 6 mo of age in Ethiopian infants: reference data obtained by air-displacement plethysmography. Am J Clin Nutr 2013; 98: 885–94. Available from: http://ajcn.nutrition.org/content/98/4/885.long. [Accessed 21st January 2017].

20. Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. J Pediatr 1991; 119:417–423. Available from: http://static.abbottnutrition.com/cms-prod/abbottnutrition.com/img/gestational_age.pdf. [Accessed 21st January 2017].

21. Gemechu T, Nigussie B, Wondafrash M, Valy J, Lemmens J, Thijs H, et al. Adaptation and standardization of a Western tool for assessing child development in non-Western low-income context. BMC Public Health (2016) 16:652. Available from: http://download.springer.com/static/pdf/300/art%253A10.1186%252Fs12889-016-3288-2.pdf?originUrl=http%3A%2F%2Fbmcpublichealth.biomedcentral.com%2Farticle%2F10.1186%2Fs1288901632882&token2=exp=1485005097~acl=%2Fstatic%2Fpdf%2F300%2Far

t%25253A10.1186%25252Fs1288901632882.pdf*~hmac=a3705324e9d45745e60ce8dadce27c76472af267ef824e1e35cdb6d0d7e9098c. [Accessed 21st January 2017].

22. Hadley C, Tegegn A, Tessema T, Asefa M, & Galea S. Parental symptoms of common mental disorders and children's social, motor, and language development in sub-Saharan Africa. Annals of Human Biology, May–June 2008; 35(3): 259–275.Available from: http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.527.4631&rep=rep1&type=pdf. [Accessed 21st January 2017].

23. Drewett R, Wolke D, Asefa M, Tessema F, and Kaba M. Malnutrition and Mental development: is there a sensitive period? J. Child Psychol. and Psychiat: 2001; 42(2): 181-187. Available from: https://www.cambridge.org/core/journals/journal-of-child-psychology-and-psychiatry-and-allied-disciplines/article/malnutrition-and-mental-development-is-there-a-sensitive-period-a-nested-case-control-study/35D256060B609923566CE93F87E61748. [Accessed 21st January 2017].

24. Frankenburg WK, Dobbs JB, Archer P, Shapiro H, Bresnick B. Denver II Technical Manual. In: Denver Developmental Materials. USA: Denver, CO; 1992. Available vfrom: https://www.ncbi.nlm.nih.gov/pubmed/1370185. [Accessed 21st January 2017].

25. Christiansen TB and Lauritsen JM. (Ed.) EpiData - Comprehensive Data Management and Basic Statistical Analysis System. Odense Denmark, EpiData Association, 2010. Avail;able from: http://www.epidata.dk/credit.htm. [Accessed 21st January 2017].

26. Larsson J, Aurelius G, Nordberg L, Rudelius P, & Zetterstrom R. Developmental screening at four years of age. Relation to home situation, perinatal stress, development and behaviour among Swedish children. Acta Paediatrica:1994; 83, 46–53. Available from:

http://onlinelibrary.wiley.com/doi/10.1111/j.1651-2227.1994.tb12951.x/full#references. [Accessed 21st January 2017].

27. Lawrence M, Christina P, Jane W. Income and child development Center for Research on Child Wellbeing Working Paper # 05-16-FF 2005. Available from: http://crcw.princeton.edu/workingpapers/WP05-16-FF-Paxson.pdf. [Accessed 21st January 2017].

28. Widdowson EM, Growth and Composition of the Fetus and Newborn, in: N.S. Asali (Ed.), Biology and Gestation, Academic Press, New York, 1968, pp. 1–49.

29. Sparks JW. Human intrauterine growth and nutrient accretion. Semin Perinatol: 1984;8:7.t-93. Available from; http://www.seminperinat.com/article/0146-0005(84)90022-3/abstract. [Accessed 21st January 2017].

30. Bernstein IM, Goran MI, Amini SB, Catalano PM. Differential growth of fetal tissues during the second half of pregnancy. Am J Obstet Gynecol: 1997; 176:28 –32. Available from: http://www.ajog.org/article/S0002-9378(97)80006-3/pdf. [Accessed 21st January 2017].

31. Skullerud K. Variations in the size of the human brain. Influence of age, sex, body length, body mass index, alcoholism, Alzheimer changes, and cerebral atherosclerosis. Acta Neurol Scand 1985;102: Suppl c:1– 94. Available from: https://www.ncbi.nlm.nih.gov/pubmed/3887832. [Accessed 21st January 2017].

32. Fuglestad A, Rao R, Georgieff M. The role of nutrition in cognitive devel- opment. In: Nelson CA, Luciana L, eds. Handbook of Developmental Cog- nitive Neuroscience. 2nd edn. Cambridge, MA: MIT Press, 2008:623–42.

33. Pfister KM, Gray HL, Miller NC, Demerath EW, Georgieff MK, Ramel SE. Exploratory study of the relationship of fat-free mass to speed of brain processing in preterm infants. Pediatr Res. 2013 Nov;74(5):576–83.Availbale from: http://www.nature.com/pr/journal/v74/n5/abs/pr2013138a.html. [Accessed 21st January 2017].

34. Reilly S, Wake M, Bavin EL, Prior M, Williams J, Bretherton L, et al. Predicting Language at 2 Years of Age: A Prospective Community Study. Pediatrics. 2007 Nov 30;120(6):e1441. Available from: http://pediatrics.aappublications.org/content/120/6/e1441. [Accessed 21st January 2017].

35. Thompson RA, Nelson CA. Developmental science and the media: early brain development. Am Psychol 2001;56:5–15. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11242988. [Accessed 21st January 2017].

36. Kretchmer N, Beard JL, Carlson S. The role of nutrition in the development of normal cognition. Am J Clin Nutr 1996;63(suppl):997S–1001S. Availbale from: http://ajcn.nutrition.org/content/63/6/997S.long. [Accessed 21st January 2017].

37. Georgieff MK, Innis S. Controversial nutrients in the perinatal period that potentially affect neurodevelopment: essential fatty acids and iron. Pediatr Res 2005;57:99R–103R. Available from: http://www.nature.com/pr/journal/v57/n5-2/full/pr2005138a.html. [Accessed 21st January 2017].

38. Stiles J, Jernigan TL. The Basics of Brain Development. Neuropsychology Review. 2010;20(4):327-348. doi:10.1007/s11065-010-9148-4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2989000/. [Accessed 21st January 2017].

39. Pacce S, Saure C, Mazza CS, Garcia S, Tomzig RG, Lopez AP, et al. Impact of maternal nutritional status before and during pregnancy on neonatal body composition: A cross-sectional study. Diabetes Metab Syndr. 2016;S7-S12.Available from: http://www.sciencedirect.com/science/article/pii/S187140211500082X. [Accessed 21st January 2017].

40. Nohr EA, VaethM, Baker JL, Sørensen T, Olsen J, Rasmussen KM. Combined associations of pre-pregnancy body mass index and gestational weight gain with the outcome of pregnancy. Am J Clin Nutr; 2008; 87:1750 –1759. Available from: http://ajcn.nutrition.org/content/87/6/1750.long. [Accessed 21st January 2017].

41. Andres A, Patrick HC, Bellando J, Mario AC, Thomas MB. Effects of Fat Mass on Motor Development During the First 2 Years of Life. ICAN: Infant, Child, & Adolescent Nutrition. 2013, vol. 5 (4), 248-254. Available from: http://journals.sagepub.com/doi/abs/10.1177/1941406413489728. [Accessed 21st January 2017].

42. Eriksson M, Marschik PB, Tulviste T, Almgren M, Pereira MP, Wehberg S. et al. Differences between girls and boys in emerging language skills: evidence from 10 language communities. British Journal of Developmental Psychology, 2012; 326-43; doi: 10.1111/j.2044-835X.2011.02042.x. available from: https://www.ncbi.nlm.nih.gov/pubmed/22550951. [Accessed 21st January 2017].

43. Kuban KC, Allred EN, O'Shea TM, Paneth N, Westra S, Miller C, et al. Developmental Correlates of Head Circumference at Birth and Two Years in a Cohort of Extremely Low Gestational Age Newborns. The Journal of Pediatrics, 155(3), 344–9.e1–3. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2803763/. [Accessed 21st January 2017].

44. Paranjothy S, Broughton H, Adappa R, Fone D. Teenage pregnancy: who suffers? Arch Dis Child. 2009;94(3):239–245. Available from: http://adc.bmj.com/content/94/3/239.full. [Accessed 21st January 2017].

45. Lejarraga H, Pascucci LC, Krupitzky S, Kelmansky D, Bianco A, Martinez E, et al. Psychomotor development in Argentina children aged 0–5 years. Paediatric and Perinatal Epidemiology: 2002; 16, 47–60. Available from: https://www.ncbi.nlm.nih.gov/pubmed/11856454. [Accessed 21st January 2017].

46. Barker DJ. The origins of the developmental origins theory. J. Intern. Med. 2007; 261(5):412–417. doi:10.1111/j.13652796.2007.01809.x. available from: https://www.ncbi.nlm.nih.gov/pubmed/17444880. [Accessed 21st January 2017].

47. Hoffman ML, Peck KN, Forella ME, Fox AR, Govoni KE, and Zinn SA. The effects of poor maternal nutrition during gestation on postnatal growth and development of lambs. J. Anim. Sci. 2016;94(2):789–799. doi:10.2527/jas.2015-9933. Available from: https://www.ncbi.nlm.nih.gov/pubmed/27065149. [Accessed 21st January 2017].

48. Hoffman ML, Rokosa MA, Zinn SA, Hoagland TA, and Govoni KE. Poor maternal nutrition during gestation in sheep reduces circulating concentrations of insulin-like growth factor-I and insulin-like growth factor binding protein-3 in offspring. Domest. Anim. Endocrinol. 2014; 49:39–48. doi:10.1016/j. domaniend.2014.05.002. Available from: http://www.sciencedirect.com/science/article/pii/S0739724014000587. [Accessed 21st January 2017].

49. Crume TL, Brinton JT, Shapiro A, Kaar J, Glueck DH, Maria AS, et al. Maternal dietary intake during pregnancy and offspring body composition: The Healthy Start Study:

American Journal of Obstetrics & Gynecology; 2016. Available from:
http://www.ajog.org/article/S0002-9378(16)30380-5/pdf. [Accessed 21st January 2017].

Table 1: Child and maternal characteristics at birth and two years of age among Ethiopian children (n=227)

Variables	Value
New born characteristics, mean ± SD / n (%)	
Female sex	118 (52.0)
Birth weight (kg)	3.1 ± 0.4
Fat free mass(kg)	2.9 ± 0.3
Fat mass (kg)	0.2 ± 0.2
Length (cm)	49.2 ± 1.9
Head circumference (cm)	34.8 ± 1.6
Birth order; n (%)	
First	110 (48.5)
Second	57 (25.1)
Third and above	60 (26.4)
Two year characteristics, mean ± SD / n (%)	
Child age (months)	24.4 ± 1.2
Height (cm)	83.1 ± 3.7
Weight (kg)	11.3 ± 1.5
Head circumference (cm)	48.5 ± 1.7
Stunted n (%)	52 (22.9)
Child ever admitted to hospital, yes? n (%)	25 (11.0)
Parental characteristics at child birth	
Maternal education, n (%)	
Illiterate	21 (9.3)
Primary school	141 (62.1)
Secondary school and above	65 (28.6)
Maternal age (years), mean ± SD	24.1 ± 4.6
Paternal education, n (%)	
Illiterate	7(3.1)
Primary school	137 (60.4)
Secondary and above	98 (36.5)
Developmental scores at 2 years, mean ± SD	
Global	79.9 ± 3.6
Language	20.8 ± 2.1
Fine motor	19.2 ± 1.0
Gross motor	22.3 ± 0.8
Personal social	17.5 ± 1.4

Table 2: Univariate linear regression analysis modelled to examine the association of new born measurements to child development at 2 years of age in Ethiopian healthy children (n=227)

variables	Global development	Language	Fine motor	Gross motor	Personal and social
Birth weight (kg)	1.61 (0.33, 2.88)	1.02 (0.34, 1.71)	0.25 (-0.06, 0.56)	0.26(-0.03, 0.55)	0.18 (-0.14, 0.49)
Fat free mass(kg)	2.34 (0.81, 3.88)	1.41 (0.59, 2.24)	0.33 (-0.04, 0.69)	0.29(0.08, 0.66)	0.31 (-0.029 0.92)
Fat mass (kg)	0.81 (-2.26, 3.88)	0.83 (-0.94, 2.59)	0.32 (-0.42, 1.05)	-0.01(-0.71, 0.69)	-0.36(-1.51, 0.86)
Length at birth (cm)	0.34 (0.06, 0.61)	0.15 (0.02, 0.29)	0.08 (0.03, 0.14)	0.04(-0.03, 0.11)	0.06 (-0.05, 0.17)
Female sex	0.62 (-0.32, 1.56)	0.41 (-0.13, 0.96)	-0.02 (-0.24, 0.28)	0.04(-0.16, 0.24)	0.15 (-0.21, 0.51)
Head circumference at birth (cm)	0.28 (-0.058 0.64)	0.21 (-0.01, 0.43)	0.06 (-0.01, 0.13)	0.01(-0.04 0.07)	-0.01 (-0.15, 0.12)
Birth order					
1st	Ref.	Ref.	Ref.	Ref.	Ref.
2nd	-0.46 (-1.58,0.67)	-0.48 (-1.15, 0.18)	0.08 (-0.25, 0.41)	-0.14 (-0.39, 0.10)	0.09 (-0.32, 0.51)
3rd and above	0.18 (-1.33,0.96)	0.09 (-0.56, 0.74)	0.04 (-0.26, 0.34)	0.02 (-0.26, 0.21)	-0.29 (-0.74, 0.16)

Data given are B-coefficients (95% Confidence interval)

Table 3: Multivariable linear regression analysis modelled to examine the independent effect of fat free mass (FFM) to child development at 2 years of age in Ethiopian healthy children (n=227)

	Global development	Language	Fine motor	Gross motor	Personal and social
FFM at birth (kg)					
Model 1[a]	2.63** (1.04, 4.22)	1.60*** (0.73, 2.46)	0.27 (-0.11, 0.66)	0.34 (-0.06, 0.74)	0.42 (-0.22, 1.06)
adj. R^2	0.06	0.07	0.02	0.00	-0.00
Model 2[b]	2.08* (0.04, 4.13)	1.70** (0.54, 2.87)	0.22 (-0.22, 0.66)	-0.10 (-0.68, 0.49)	0.26 (-0.62, 1.13)
adj. R^2	0.06	0.06	0.02	0.01	-0.00
Model 3[c]	2.39* (0.11, 4.66)	1.53* (0.23, 2.84)	0.35 (-0.17, 0.86)	-0.12 (-0.75, 0.52)	0.62 (-0.32, 1.56)
adj. R^2	0.05	0.06	0.02	0.01	0.00
Model 4[d]	2.43* (0.22, 4.63)	1.57* (0.27, 2.87)	0.31 (-0.23, 0.84)	-0.14 (-0.78, 0.51)	0.69 (-0.22, 1.60)
adj. R^2	0.08	0.09	0.02	0.00	0.03
Model 5[e]	2.48* (0.17, 4.79)	1.61* (0.33, 2.90)	0.36 (-0.21, 0.94)	-0.17 (-0.85, 0.50)	0.68 (-0.21, 1.57)
adj. R^2	0.12	0.16	0.07	-0.02	0.03
N	227	227	227	227	227

a) FFM adjusted for sex & age at developmental assessment
b) Model 1 and length at birth
c) Model 2 and head circumference at birth and birth order
d) Model 3 and postnatal characteristics (stunning, hospitalization, one week animal protein intake)
e) Model 4 and parental characteristics (maternal age, maternal school, paternal school, parental wealth index)

Data given are B-coefficients (95% Confidence interval)

*** $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$**

Table 4: Multivariable linear regression analysis modelled to examine the independent effect of fat mass (FM) to child development at 2 years of age in Ethiopian healthy children (n=227)

	Global development	Language	Fine motor	Gross motor	Personal and social
FM at birth (kg)					
Model 1[a]	0.80 (-2.22, 3.82)	0.82 (-0.90, 2.54)	0.01 (-0.70, 0.73)	0.33 (-0.40, 1.06)	-0.38 (-1.43, 0.67)
adj. R^2	0.01	0.01	0.03	0.00	-0.01
Model 2[b]	-1.37 (-4.70, 1.96)	-0.11 (-2.04, 1.82)	-0.23 (-0.96, 0.50)	-0.15 (-0.92, 0.61)	-0.89 (-2.20, 0.43)
adj. R^2	0.04	0.03	0.02	0.01	0.00
Model 3[c]	-1.42 (-4.80, 1.97)	-0.24 (-2.14, 1.65)	-0.21 (-0.96, 0.55)	-0.15 (-0.94, 0.63)	-0.81 (-2.13, 0.50)
adj. R^2	0.04	0.04	0.01	0.01	0.00
Model 4[d]	-2.01 (-5.34, 1.31)	-0.57 (-2.40, 1.27)	-0.14 (-0.89, 0.61)	-0.18 (-0.97, 0.60)	-1.13 (-2.44, 0.19)
adj. R^2	0.07	0.07	0.01	0.00	0.03
Model 5[e]	-2.93 (-6.32, 0.46)	-1.25 (-3.03, 0.54)	-0.31 (-1.09, 0.47)	-0.23 (-1.02, 0.57)	-1.14 (-2.47, 0.19)
adj. R^2	0.11	0.14	0.07	-0.02	0.03
N	227	227	227	227	227

a) FM adjusted for sex & age at developmental assessment
b) Model 1 and length at birth
c) Model 2 and head circumference at birth and birth order
d) Model 3 and postnatal characteristics (stunning, hospitalization, one week protein intake)
e) Model 4 and parental characteristics (maternal age, maternal school, paternal school, parental wealth index)

Data given are B-coefficients (95% Confidence interval)

Figure 1: Flowchart diagram showing how the final sample size was reached