Title
The Neurodevelopmental Outcomes of Preterm and Low Birth Weight Babies in Rural Kenya

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THE NEURODEVELOPMENTAL OUTCOMES OF PRETERM AND LOW BIRTH WEIGHT BABIES IN RURAL KENYA

by
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Dedication and Acknowledgments

I dedicate this thesis to my late grandfather, Dr. Harvey Sparks Jr. a professor of physiology, a teacher and a scientist, a lover of opera and ice cream, Zimbabwe, dogs, horses and Shakespeare and my fiercest and most thoughtful supporter in all pursuits.

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The Neurodevelopmental Outcomes of Low Birth Weight Babies in Rural Kenya

Aleah Sparks

Abstract

As neonatal and under-five mortality rates decrease in low- and middle-income countries (LMIC), an increased number of children may be at risk of not meeting their full developmental potential. Children born preterm and with LBW are at high risk for suboptimal neurological development. However, due to lack of accurate and available gestational dating methods, it is difficult to accurately assess prematurity in LMIC settings.

The present secondary analysis examined the neurodevelopmental outcomes of a sample (n=362) of preterm and low birth weight babies cross-sectionally sampled at 6, 12 and 18 months of adjusted age in Migori County, Kenya. Data were obtained from a large facility-based cluster randomized control trial (cRCT). The sample consisted of a majority of moderately low birth weight and late preterm babies. Of particular interest was whether birth weight was independently associated with adverse neurodevelopmental outcomes within each age category and whether neurodevelopmental outcomes were significantly different between the age categories. Neurodevelopment was evaluated using Z-scores on the Malawi Developmental Assessment Tool.

Birth weight was significantly associated with gross motor development at the 18-month stage after adjusting for gestational age, length for age and five-minute Apgar score. A significant association between neurodevelopmental outcomes and age category was also detected after controlling for birth weight, gestational age, length for age and five-minute Apgar. To conclude, the results of this analysis found associations between birth weight and neurodevelopment, and subtle developmental deviations in the12-month age category from the

population mean, based on the Z-score reference population. The implications of these findings are: 1) birth weight may be a key criterion for the allocation of resources to early child development programs, and 2) more longitudinal, long-term follow up research is needed to understand the impact of moderately low birth weight and late prematurity on the developmental trajectory and burden of developmental disability in low- and middle-income countries.

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Introduction

As the rates of neonatal and under-five mortality in low- and- middle income countries (LMICs) decline, there is an evolving understanding of adverse neurodevelopment in infancy and early childhood. It is estimated that 250 million or 44% of children under five in LMICs are at risk of not meeting their full developmental potential, and this number does not account for the estimated 50 million children with disability in LMICs (Grantham-McGregor et al. 2007; Global Research on Developmental Disabilities Collaborators 2018). The impacts of developmental difficulties are profound, intergenerational and permeate aspects of life from academic achievement, earning potential, mental and physical health to national development (Grantham-McGregor et al. 2007).

Environmental factors such as poverty, malnutrition and lack of psychosocial stimulation as well as biological and intrauterine events such as chronic illness, intrauterine growth restriction and maternal infection impact a child's risk of developmental difficulties (Ertem and WHO 2012; Grantham-McGregor et al. 2007). Risk factors clinically measurable and commonly recorded outside of a research context in the immediate neonatal period and early infancy include nutritional status and perinatal factors such as prematurity, birth weight (BW) and birth asphyxia (Grantham-McGregor et al. 2007). Neural pathways proliferate in early childhood from conception to 18-months of age and early fetal stressors can have long-terms effects on the brain's structure and function (Ackerman 1992). Low birth weight (LBW) and prematurity suggest a suboptimal intrauterine environment that may be responsible for inadequate brain growth at critical periods of development resulting in reduced overall volume, cortical gray matter volume, cortical thickness and total number of neurons (Tolsa et al. 2004; de Bie et al. 2010). However, even with significant in-utero environmental injury, brain has the capacity for

normal development, especially when circumstances are corrected in early infancy (Ackerman 1992).

The Global Burden of Disease 2016 study recognized the identification of major causes of developmental disabilities as an urgent priory in regions with the largest prevalence and burden. (Global Research on Developmental Disabilities Collaborators 2018). According to the World Health Organization (WHO), children born preterm and with LBW are at high risk for suboptimal neurological development (WHO 2014). Of all LBW births, 91% occur in LMICs, especially among the most vulnerable populations, with more than three quarters in sub-Saharan Africa and Southern Asia. (Blencowe et al. 2019). While the majority of LBW babies in Southern Asia are term, small for gestational age babies (SGA), prematurity is the most common cause of LBW in sub-Saharan Africa (Muchemi et al. 2015; WHO 2014).

Literature Review

Birth weight and neurodevelopment

There is some evidence suggesting BW regardless of gestational age (GA) is an important risk factor for adverse neurodevelopmental outcomes. A recent meta-analysis on effects of LBW in both term small for gestational age (SGA) and preterm LBW babies on cognitive and motor impairment from South Asia found that LBW children had five-point lower cognitive scores and four-point lower motor scores compared to children with normal BW with deficits persisting throughout childhood and adolescence (Upadhyay et al. 2019). A cross-sectional study of preterm and LBW babies from Rwanda found that very low birth weight (VLBW) and SGA were significantly associated with lower scores on the Ages and Stages Questionnaire 3 (ASQ-3), and term children who were SGA had the lowest ASQ-3 scores (Kirk et al. 2017). Higher rates of delay were found in children who were preterm and LBW over the

age of two, which confirms findings from Burundi, Ghana and the Central African Republic (van den Boogaard et al. 2017; Gottlieb et al. 2009). Further, in a long-term study of LBW survivors in China, differences were found between a sample of LBW and preterm babies and a normal birth weight (NBW)/term control group in both intelligence quotient (IQ) and scholastic achievement, but were more striking among those who were SGA than those who were preterm AGA (Peng et al. 2005).

Gaps in the literature

A limitation of many studies in LMICs is the use of BW as a proxy measure for GA due to a lack of accurate gestational dating techniques (Gladstone et al. 2015). While the scientific community recognizes the difference between fetal growth (size) and fetal maturation (GA), research in resource-poor settings where GA is substantially more difficult to assess than BW does not reflect this important distinction (WHO 1975). While GA defined by early prenatal ultrasound is the gold standard for gestational dating, it is infrequently available outside of the research context in LMIC settings. For this reason, studies in LMICs frequently conflate BW and prematurity. Baseline data from the cohort ultimately used for analysis suggested a poor correlation between BW and recorded GA in the maternity register (Otieno 2018). However, reliable BW alone can be typically obtained from facility deliveries in LMICs. Therefore, it is important to examine the association between BW and long-term outcomes in LMIC contexts, while efforts continue to develop scalable solutions for assessing GA.

A second limitation of recent research is a lack of generalizability to a normal population of preterm and LBW babies. The subgroups of prematurity and LBW most frequently assessed for short and long-term health and neurodevelopmental outcomes represent only a small portion of all preterm and LBW births. As survival rates increase with more advanced neonatal intensive

care, VLBW and extremely low birth weight (ELBW) infants have become the focus of studies in both LMICs and developed countries (Kirk et al. 2017; Ballot et al. 2012). However, survival of VLBW/ELBW and very preterm/extremely preterm infants is still low in LMICs, particularly in rural communities where neonatal intensive care units (NICUs) are largely unavailable, such as Migori County. For example, a related study that followed infants from Migori County and the Busoga Region of Uganda found that of infants surviving to discharge, 12.4% were preterm, but only 2.5% were between 28-32 weeks GA and 0.4% were <28 weeks GA. Approximately 12% of infants discharged alive were LBW and nearly all of these were between 1501-2500 grams (Waiswa 2020). Further, MLBW babies born between 2000 and 2499 grams account for greater than five times the number of all babies born less than 1500 grams (Stein et al. 2006). It is important to examine the relationship between BW and neurodevelopmental outcomes in a sample that is representative of a normal population of LBW and preterm babies.

Aims

The overall goal of this analysis is to explore the relationship between BW, age at time of assessment, and neurodevelopmental outcomes defined as total MDAT score and the four domains of neurodevelopment including gross motor, fine motor & performance, language & hearing and social, in a cohort of preterm and LBW babies, cross-sectionally sampled at 6, 12 and 18 months of adjusted age in Migori County, Kenya. The aims of the analysis are outlined below.

Aim 1: Describe the overall neurodevelopmental status of this group of preterm and LBW babies in the full sample and at each age category. Aim 2: Examine the relationship between BW and neurodevelopmental outcomes within the 6, 12- and 18-month age categories. Aim 3: (Part 1) To test for differences in neurodevelopmental outcomes between the three age categories, and (Part

2) To examine the relationship between the three age categories and neurodevelopmental outcomes.

Methods

Study design

A secondary analysis was conducted using data from participants previously enrolled in the University of California, San Francisco (UCSF) East Africa Preterm Birth Initiative, Kenya (PTBi-K) study and followed up in a descriptive, cross-sectional study of long-term outcomes (Health and Neurodevelopmental Outcomes (HND) study). The PTBi-K study was a pair-matched cluster randomized control trial (cRCT) carried out in 21 public sector health facilities in the Busoga Region of Uganda (four facilities) and in Migori County, Kenya (17 facilities). The specific study regions were selected with consideration to burden of prematurity, presence of parallel studies and in-country stakeholder input. Recruited facilities were randomized into two groups: one to receive two interventions and the other to receive the full package of four interventions designed to improve care at the facility level. Detailed information on randomization and study procedures can be found in the published study (Walker 2020).

Setting and participants

The Health and Neurodevelopmental (HND) study nested within PTBi-K used a cross-sectional design to measure long-term health and neurodevelopmental outcomes of 362 preterm and LBW babies at corrected ages of 6, 12 and 18 months between October 2018 and May 2019 in Migori County, Kenya. The HND study used maternity registers from all 17 health facilities, which included both control and intervention sites, to recruit newborns who met criteria for LWB (<2500) or prematurity (<37 weeks with BW <3000g). All live infants from the HND study were used in the present secondary analysis. The sampled facilities were spread throughout

eight sub-counties, and data collection was clustered for convenient access of potential participants. Neurodevelopmental assessments were completed at the same facilities where the PTBi-K study conducted its activities.

Study procedures and data collection

Babies born alive and weighing less than 2500 grams or between 2500 grams and 2999 grams with a recorded gestational age less than 37 weeks were eligible to participate in the study. Mothers were approached to consent for follow-up at 28 days of life. For the HND study, information was taken from a list of eligible infants, generated from the PTBi-K database, who were aged 6, 12 or 18 months at the time of the study (Martin-Herz and Otieno, under preparation). Research coordinators made telephone calls to caregivers using a standard participation invitation script explaining the purpose, benefits, and risks of the study and procedures, and assessments were scheduled at the site closest to the participant's home for families who agreed to participate. Families' consent was obtained at the time of their appointment in the caregiver's preferred language (Swahili, Dholuo, or English) at an appropriate educational level. Brief health and neurodevelopmental assessments were offered to any child whose family declined to consent at the time of the visit. No data from these infants were included in the study or used in the present analysis (Martin-Herz and Otieno, under preparation).

Data on eligible participants including caregiver contact information, peripartum health records, newborn health records and caregiver contact information were obtained from the PTBi-K study database. Sociodemographic information and medical history, including prenatal information, birth, hospital-based interventions (e.g., neonatal unit admission), discharge status, feeding history and subsequent infant growth pattern, acute and chronic illness, and

hospitalizations were obtained by interview in the caregiver's preferred language (Martin-Herz and Otieno, under preparation). Local healthcare providers including a medical officer, three clinical officers and two nurses were trained as research clinicians and certified on procedures and assessment tools (Martin-Herz and Otieno, under preparation). These clinicians performed a full physical examination on each child and anthropomorphic measurements of length, weight, mid upper arm circumference (MUAC) and occipital frontal head circumference (OFC) using the standard guidelines (Cogil, 2003; Martin-Herz and Otieno, under preparation).

After evaluations were completed, caregivers received feedback on their child's neurodevelopmental status and were given the opportunity to discuss questions and concerns with a healthcare provider. All caregivers received counseling on nutrition, were taught simple developmental games to play with their child at home, educated on danger signs of common childhood illnesses and encouraged to attend preventative healthcare visits at the Child Welfare Clinics (Martin-Herz and Otieno, under preparation). If specific developmental or health concerns were identified during the course of the assessment, the child was referred to the local hospital or regional specialized clinic (e.g., audiology) for follow up. The cost of up to four subsequent necessary healthcare visits was paid for by the study (Martin-Herz and Otieno, under preparation).

Measures and Study Variables

Infant development (MDAT)

The Malawi Developmental Assessment Tool (MDAT) was used to assess infant development. The MDAT was developed as a culturally relevant assessment tool for use in children up to six years of age in Malawi (Gladstone et al. 2010). It evaluates development in four domains: gross motor, fine motor & performance, language & hearing, and social, with 34

items in each domain. Cognitive development is assessed within the fine motor & performance and the language & hearing domains. Items are scored as "pass" or "fail", or as "don't know" if the child is uncooperative (van den Heuvel et al. 2017). The MDAT was developed from the Denver Developmental Screening Tool II (DDST-II), which was formerly the most widely used test for developmental screening and was accepted globally because of its ease of use. The MDAT retains the same developmental domains and a similar scoring method as the DDST-II, but replaces assessment items with those that are more culturally appropriate in a rural African context. (Gladstone et al. 2008). The creators of MDAT used a similar method to the DDST-II to establish normal reference ranges in a large sample of Malawian children. (Gladstone et al. 2010). The MDAT takes approximately 30 minutes to administer and requires a small basket of props.

Reliability testing was conducted for all of the original 185 items in the Draft MDAT III. Inter-observer immediate reliability was measured in 56 children by assessing the same child on the same occasion by two observers. Inter-observer delayed reliability was measured in 52 children by observing the same child on the same day at different times. Intra-observer delayed reliability was measured in 124 children by the same observer assessing the same child two weeks apart. Reliability was good for the items in the final version of the tool, with 94%-100% of times scoring kappas >0.4 for interobserver immediate, delayed, and intra-observer testing.

Face and content validity of the MDAT Draft I were assessed and after two more iterations assessing nearly 1500 children, the final tool was developed. The researchers then assessed construct validity by using the MDAT to assess age-matched children with known neurodisabilities and children with delayed development as a result of malnutrition. Using the pass/fail scoring technique adapted from the DDST-II, 3% of children with neurodisabilities

passed in comparison to 82% of children with normal cognitive function, demonstrating 97% specificity and 82% sensitivity. (Gladstone et al. 2010).

For the purposes of the HND study and the present analysis, MDAT scores were categorized using two methods recommended by the developers (Martin-Herz and Otieno, under preparation; Gladstone et al. 2010). First, for any child who was unable complete two or more items in any one domain with an expected pass rate of 90% in the reference population for their age, a "fail" was recorded (Martin-Herz and Otieno, under preparation; Gladstone et al. 2010). Second, an app for MDAT scoring was used to calculate developmental Z-scores for the total and within each domain (Martin-Herz and Otieno, under preparation; Gladstone et al. 2010)). MDAT Z-scores were dichotomized as > -2 standard deviations below the mean (typical) vs. ≤ -2 standard deviations (delayed) for each participant (Martin-Herz and Otieno, under preparation; Gladstone et al. 2010). The MDAT raw score, neurodevelopmental status based on Z-score and the pass/fail based on completions per domain were all included in this analysis.

Birth weight

Birth weight is categorized into NBW (2500g ≤ BW <4000g), ELBW (BW ≤ 1,000g), VLBW (BW ≤ 1500-1,000g), MLBW (LBW ≤ 2499-1500g), and macrosomia (BW ≥4000g). Conditions leading to LBW include preterm birth (birth before 37 completed weeks of gestation), intrauterine growth restriction (IUGR) in full term babies leading to SGA (defined by BW less than the 10^{th} percentile for gestational age) or a combination of IUGR and prematurity (WHO 20014). Intrauterine growth restriction refers to either symmetric or asymmetric slower than typical growth and development of the fetus in-utero, and is primarily responsible for births that are SGA. It is estimated that between 15%-20% of all births worldwide are LBW representing more than 20 million births each year. (WHO 2014).

While the 2500g LBW cutoff was an arbitrary weight parameter developed in the 20th century, the INTERGROWTH-21st project developed a global standard for normal fetal growth. This project prospectively monitored fetal growth in healthy pregnancies under ideal environmental conditions in eight countries, as well as conducted a cross-sectional analysis of BW for GA that was used to create a normal reference population. With the establishment of this normal curve, accurate identification of SGA infants is increasingly possible. (Hughes et al. 2017; Papageorghiou et al. 2014).

Based on INTERGROWTH-21st standards, infants up to 3000g were included in our data collection to capture 90-97% of infants with a GA less than 34 weeks and 60-70% of infants with a GA less than 37 weeks. (Walker et al. 2020).

Covariables considered for the analysis

Gestational age

The WHO defines prematurity by GA <37 weeks. There are three primary methods of GA estimation: dating by last menstrual period (LMP), neonatal estimates such as the physical and neuromuscular maturity of the infant (Dubowitz or Ballard scoring system) and the first-trimester prenatal ultrasound, commonly regarded as the gold standard of gestational dating (Lynch and Zhang 2007). However, in LMICs where technical expertise and access to technology is limited, alternative measures including neonatal (BW) and obstetric measurements (fundal height and timing of first quickening) may be used to determine GA. (Rosenberg et al. 2009). While LMP has been found to be a feasible estimate of GA especially for infants ≤33 weeks in a clinical context to identify high risk deliveries, the implications of this imprecise measurement in a research setting are significant (Lynch and Zhang 2007; Rosenberg et al. 2009). Further, the barriers to implementing early obstetric ultrasound are complex and include

training of healthcare personnel, misuse and miscommunication especially where financial incentives may be involved, concerns surrounding legality of fetal sex determination, machine acquisition and maintenance, cost effectiveness and cultural perceptions. (Kim et al. 2018).

Gestational age estimations in the present data set relied on GA recorded in the maternity registry by a maternity unit worker at the time of delivery. Gestational age measurements were based on reported LMP, fundal height, or antenatal records carried by the mother (Waiswa 2020). A separate secondary analysis of the data revealed that recorded GA independent of BW was under-recorded and an unreliable measure of true GA (Miller et al 2020). Low birth weight term, normal BW preterm and LBW preterm babies were included in this analysis.

Apgar Score

The Apgar score assesses five components in infants immediately after birth: 1) color, 2) heart rate, 3) reflexes, 4) muscle tone, and 5) respiration, each of which is given a score of 0, 1, or 2. While Apgar alone has been determined to not be considered evidence or consequence of birth asphyxia, five-minute Apgar <7 is a frequently used covariable in studies of birth asphyxia in LMICs, where more definitive diagnostics such as umbilical cord gasses may not be available (Abdo et al. 2019; Aliyu et al. 2017; AAP & ACOG 2015). For this study, we hypothesized that a number of maternal and infant factors may result in low Apgar scores and healthy preterm infants with no insult, acidemia, or cerebral depression may receive lower Apgar scores because components of the score such as tone, color and reflex irritability reflect physiologic immaturity (Halloran et al. 2009). Therefore, five-minute Apgar score was treated as a covariable in the present analysis.

Anthropomorphic measures

Anthropomorphic measurements of length were taken and recorded using the standardized guidelines (Martin-Herz and Otieno, under preparation). Z-scores for the nutritional measurement for age (LAZ) were calculated using WHO reference data (de Onis and Branca 2016; Cogil, 2003; Martin-Herz and Otieno, under preparation). Of note, validity and reliability of length measurements is dependent on several factors including appropriate training in measurement techniques, maintenance of anthropometric equipment, behavior and cooperation of the child and accurate data collection and recording (de Onis et al. 2004; de Onis 2016). Stunting is largely recognized as the result of chronic undernutrition in-utero and throughout early childhood to age two, and is one of the best indicators of the child's overall well-being. It is defined as a LAZ measurement greater than two standard deviations below the normal reference range (de Onis and Branca 2016). Therefore, this analysis controls for the LAZ Z-score, which may indicate the presence of stunting.

Statistical Analysis

Aim 1

Descriptive statistics were generated to describe the overall neurodevelopmental status of this group of preterm and LBW babies in the full sample and in the 6, 12- and 18-month age categories. Means and standard deviations were used to describe continuous Z-score variables in MDAT total score, gross motor, fine motor & performance, language & hearing and social developmental domains. The MDAT total, gross motor, fine motor & performance, language & hearing and social scores were dichotomized into a categorical variable labeled "Delayed" and "Not delayed" when two or more items were failed (Martin-Herz and Otieno, under preparation). The categorical variable "Severe delay" was used when the Z-score was less than two deviations

from the mean. Percentages were used to describe these categorical variables (Martin-Herz and Otieno, under preparation). In the absence of a normative sample, we used the MDAT Z-score mean to compare to our sample means (Gladstone, 2015).

Aim 2

Single and multivariable linear regression modeling was used to examine the relationship between BW (continous variable) and MDAT Z-scores (continuous variable) in the total, gross motor, fine motor & performance, language & hearing and social domains of development within the 6, 12- and 18-month age categories. The single variable linear regression model examined the relationship between BW and developmental outcomes in each age category without adjusting for potential confounding variables. The multivariable model adjusted for three continuous covariables of interest including GA, LAZ and five-minute Apgar score.

Aim 3

First, an analysis of variance (ANOVA) was used to determine whether there were significant differences in the MDAT Z-scores in total, gross motor, fine motor & performance, language & hearing and social domains between the 6, 12- and 18-month age categories. Multivariable linear regression was used to examine the relationship between the 6, 12- and 18-month age categories (categorical variable) and MDAT Z-score in gross motor, fine motor & performance, language & hearing and social domains adjusting for four continuous variables of interest including BW, GA, LAZ and five-minute Apgar score.

All models were interpreted in the context of both statistical significance and clinical importance. The Bonferroni corrected alpha level for up to 15 correlation analyses on the same dependent variable is p=.003. Analysis was conducted using Stata 16.1.

Sample size

The total sample size was n=362, with three distinct groups of babies followed up at 6-months (n=155), 12-months (n=159) and 18-months (n=48). Using STATA 16.1, we determined that the most conservative minimum standardized detectable effect size of the analysis of variance (ANOVA) in the smallest group (18-month age category) for 80% power assuming alpha=.01 (to correct for tests of five phenotypes), was 0.59, or between a medium to large effect size difference (Cohen, 1988). If the 6-month or 12-month age category groups, which had substantially larger sample size, differed from the others, there would be a minimum detectable effect size of 0.4. We further determined that the most conservative minimum standardized detectable effect size of the linear regression models in the smallest group (18-month age category) for 80% power assuming alpha=.01, was 0.51. If the 6-month or 12-month age category groups, which had substantially larger sample size, differed from the others, there would be a minimum detectable effect size of 0.28, or a small to medium effect size difference (Cohen, 1988).

Results

Sample followed up

A total of 410 infants were enrolled, out of which, 28 (7.2%) died prior to study contact. The final sample consisted of 362 infants total with a unique group of babies in each of the three age categories. There were substantially fewer babies in the 18-month age group due to a prolonged national healthcare worker strike from December 2016 to November 2017 that coincided with enrollment in the parent study for babies that would be followed up in this age group (Figure 1).

The sample included more females (60.2%) and consisted primarily of moderate to late preterm and term LBW infants with very few VLBW or ELBW infants. There was a total of 117 (32.6%) term SGA/LBW babies and 242 (67.4%) preterm (defined as recorded GA<37 weeks) babies in the sample (Table 1). The mean GA in the sample was 35.9 weeks. Of all preterm babies in the sample 162 (45.1%) were considered late preterm, 41 (16.9%) moderately preterm, 33 (13.6%) very preterm, and 7 (2.9%) extremely preterm. In this study, 130 (35.9%) infants were preterm and NBW, 187 infants (51.7%) were MLBW, 30 infants (8.3%) were VLBW, and 5 infants (1.4%) were ELBW. The mean BW in this sample was 2354.2 grams (*SD* = 408.18 grams) (Table 1). Over 80% of Apgar scores were >7.

Aim 1: Neurodevelopmental status of low birth weight babies at 6, 12 and 18 months of adjusted age

Infant developmental scores were below the MDAT Z-score mean within the total (-0.226) and gross motor (-0.204) domain in the 12-month age category. Infant development scores were at or above the MDAT Z-score mean in all other domains within the 6, 12- and 18-month age categories (Table 2). While the most frequent category was "Not delayed" in all domains of development, the total number of children demonstrating delay on MDAT (failing two or more items) was 23 or 6.4%, and 10 or 2.8% demonstrated severe delay (Table 3).

Aim 2: Associations between birth weight and neurodevelopmental outcomes within the 6, 12- and 18-month age categories.

Linear regression analysis was conducted to assess whether BW was significantly associated with MDAT total, gross motor, fine motor & performance, language & hearing and social Z-score within each age category.

6-month age category

The results of the unadjusted linear regression model were not significant for any developmental domains in the 6-month age category (Table 4). However, after adjustment for GA, LAZ, and five-minute Apgar, the results of the linear regression model were significant in the gross motor and social domains. In the gross motor domain ($F(4,141) = 13.29$, $p < .001$, $R^2 = 0.27$), approximately 27% of the variance in MDAT gross motor Z-score was explainable by BW, GA, LAZ and five-minute Apgar. Birth weight was significantly associated with gross motor score ($B = -0.0003$, $t(141) = -2.31$, $p = .022$) indicating an inverse linear relationship, as BW increased, gross motor Z-scores scores decreased (Table 5). The results of the linear regression model were also significant in the social domain ($F(4,141) = 3.78$, $p = .006$, $R^2 = 0.10$) indicating that approximately 10% of the variance in MDAT social Z-score score was explainable by BW, GA, LAZ and five-minute Apgar. Birth weight was significantly associated with social score ($B = -0.0004$, $t(141) = -2.13$, $p = .035$) indicating an inverse linear relationship where BW increased, social Z-scores decreased.

12-month age category

In the unadjusted model in the 12-month age group, positive significant associations were found in total score ($F = 3.89$, $p = .050$, $R^2 = 0.02$) and gross motor domain ($F= 4.63$, $p = .033$, $R^2 = 0.03$). The results indicated a direct linear relationship in that as BW increased, MDAT scores also increased (Table 4). However, after adjusting for GA, LAZ and five-minute Apgar score, BW was no longer found to be significantly associated with total MDAT score or scores in any of the four developmental domains (Table 5).

18-month age category

In the 18-month age category, the unadjusted model results for the gross motor domain were significant ($F = 5.15$, $p = .028$, $R^2 = 0.10$, $p = .028$; Table 4), with BW explaining 10% of the variation in the gross motor domain Z-scores. The results indicated a direct linear relationship in that as BW increased, gross motor scores also increased. This association remained significant in the adjusted model ($F(4,42) = 2.99$, $p = .029$, $R^2 = 0.22$), indicating that BW, GA, LAZ and five-minute Apgar explained 22% of the variance in MDAT gross motor Z-score (Table 5). Birth weight was significantly associated with gross motor score ($B = 0.001$, $t(42) = 2.51$, $p = .016$), indicating that an increase in birth weight correlated with a higher gross motor Z-score. Birth weight was not found to be associated with Z-score trends in total, fine motor & performance, language & hearing, or social domains in the 18-month age category (Table 5).

Aim 3 (Part 1): Differences in neurodevelopmental outcomes between the 6, 12- and 18-months age categories

An analysis of variance (ANOVA) was conducted to determine whether there were significant differences in MDAT total, gross motor, fine & performance motor, language & hearing, and social domain means between the 6, 12, 18-month age categories. The results of the ANOVA were significant, for total MDAT score ($F(2, 356) = 9.92$, $p < .001$), gross motor ($F(2, 356) = 57.48$, $p < .001$), and language & hearing ($F(2, 356) = 12.88$, $p < .001$) indicating there were significant differences in total MDAT score, gross motor and language & hearing among Z-scores the 6, 12 and 18 month categories (Figures 2-4). In these three developmental domains, MDAT Z-scores were significantly lower in the 12-month category than both the 6- and 18-month categories, and significantly higher in the 18-month category than both the 6- and 12-month categories. The results of the ANOVA were not significant for the fine motor &

performance, $F(2, 355) = 0.10$, $p = .905$) and social $F(2, 356) = 0.68$, $p = .510$) domains, indicating these domains among the 6, 12 and 18-month age categories were all similar.

Aim 3 (Part 2): Associations among the 6, 12 and 18-month age categories and neurodevelopmental outcomes

Multivariable regression was used to examine the relationship among the 6, 12- and 18-month age categories and Z-scores in the four domains of development and total score. The model was adjusted for BW, GA, LAZ and five-minute Apgar score. Significant associations were detected between the 6, 12 and 18-month categories and MDAT total score, gross motor and language & hearing domains.

The results of the linear regression model for MDAT total score were significant ($F(6,331) = 13.46$, $p < .001$, $R^2 = 0.20$), indicating that 20% of the variance in total Z-score is explainable by age category, BW, GA, LAZ, and five-minute Apgar. The association between the 6- and 12-month age categories and MDAT total Z-score and the 6- and 18-month age categories and MDAT total Z-score were found to be significant. Significant lower mean values of MDAT total Z-score were found in the 12-month group compared to the 6-month group, 0.032 units on average ($B = -0.32$, $t(332) = -2.52$, $p = .012$). Significant higher mean values of the Z-score were found in the 6-month group compared to the 18-month group, 0.65 units on average ($B = 0.65$, $t(331) = 3.53$, $p < .001$).

The results of the linear regression model for gross motor score were significant ($F(6,331) = 34.65$, $p < .001$, $R^2 = 0.39$), indicating that approximately 39% of the variance in gross motor Z-score is explainable by age category, BW, GA, LAZ and five-minute Apgar. The association between the 6- and 12-month age categories and MDAT gross motor Z-score and the 6- and 18-month age categories and MDAT gross motor Z-score were found to be significant. Significant lower mean values of gross motor Z-scores were found in the 12-month group

compared to the 6-month group, 0.62 units on average, (B = -0.62, t(332) = -6.24, p < .001). Significant higher mean scores in gross motor Z-scores were found in the 18-month group compared to the 6-month group, 1.08 units on average, (B = 1.08, t(332) = 7.51, p < .001).

The results of the linear regression model for language score were significant, (F(6,331) = 10.22, p < .001, R^2 = 0.16), indicating that approximately 16% of the variance in language Z-score is explainable by age category, BW, GA, LAZ and five-minute Apgar. The association between the 6- and 12-month age categories and MDAT language & hearing Z-score and the 6- and 18-month age categories and MDAT language & hearing Z-score were found to be significant. Significant lower mean values on language Z-scores were found in the 12-month age group compared to the 6-month age group, 0.36 units on average, (B = -0.36, t(331) = -2.87, p = .004). Significant lower mean values of language Z-scores were found in the 18-month age category compared to the 6-month age category, 0.6 units on average, (B = 0.60, t(331) = 3.32, p = .001).

Of note, birth weight was not significantly associated with neurodevelopmental outcomes in any of the adjusted models examining the relationship between age category and neurodevelopmental outcomes.

Discussion

The current analysis sought to examine associations between BW and neurodevelopmental outcomes of preterm and LBW babies at 6, 12 and 18 months of adjusted age in a cross-sectionally sampled cohort of babies from Migori County, Kenya. It also aimed to describe differences in neurodevelopmental outcomes between the three age categories and examine associations between the three age categories and neurodevelopmental outcomes.

Overall prevalence of poor neurodevelopment

The overall prevalence of poor neurodevelopment found in our study was 6.4%; 5.2% at 6-months, 7.6% at 12-months and 6.3% at 18-months, compared to a study with similar distribution of moderately and late preterm babies using MDAT as an assessment tool that found poor developmental outcomes in 6.7% of 12-month babies and 22.8% of 18-month babies (Gladstone 2015).

6-month age category

The negative relationship between BW and social and gross motor domains in the 6-month group observed in our study is particularly contradictory to the literature on the association between BW and neurodevelopmental outcomes. For example, a 2020 study from Wuhan, China, found that LBW results in lower neurodevelopmental in the gross motor, fine motor and adaptability domains in early infancy, with assessments at 1 to 6 months of age and after adjusting for prenatal factors (maternal active and passive smoking, and number of pregnancy tests), perinatal factors (gender of infants, delivery mode, asphyxia neonatorum and birth length) and maternal demographic factors (gestational weeks and education level of parents) (Zhang et al. 2020). However, results in the language & hearing domain are consistent with a systematic review of four studies that evaluated expressive language at 6, 9, 12 and 18 months among SGA; babies in the 6 month category showed normal performance for age until the 12th month, when there was a statistically significant difference between NBW and SGA language performance (Zerbeto et al. 2015). It is important to note that language and cognition can be difficult to assess in early infancy. The differences in results of this analysis and those of prior studies could be related to different and fewer covariates included in our model and assessment methods for all these variables.

12-month age category

While the initial models showed statistically significant associations between BW and developmental outcomes in the total, gross motor, and social domains at the 12-month age group, these relationships were no longer significant after controlling for covariables. In particular, the measure of LAZ which is indicative of stunting, was associated with neurodevelopmental outcomes. In the MDAT total domain with an $R^2 = 0.12$, LAZ was the only significant variable ($B = 0.25$, $t(140) = 3.97$, $p < .001$) and in the gross motor domain with $R^2 = 0.26$, LAZ was again the only significant variable ($B = 0.30$, $t(140) = 5.76$, $p < .001$). This is consistent with prior research demonstrating the connection between chronic malnourishment and adverse outcomes in various developmental domains in early childhood (de Onis and Branca 2016; Alam et al. 2020); Perkins et al, 2017; Grantham-McGregor 2007). However, it is important to note that the mean Z-scores in the total MDAT and gross motor domains were below the MDAT Z-score mean at 12 months of adjusted age (Gladstone et al. 2010). This finding is demonstrated in other studies that show differences in neurodevelopmental outcomes between cohorts of NBW babies and VLBW babies at 12 months of age (Boo et al. 1996; Modi et al. 2013). However, mean GA and BW was significantly higher in the present study and lack of a normal GA/BW control group makes true comparison to the population difficult.

18-month age category

At the 18-month time point, neurodevelopmental outcomes in the gross motor domain were significantly associated with BW in both the unadjusted and adjusted models. This is consistent with other findings showing the most frequent impairment to be motor development between 18 months and 2 years of age in MLBW and VLBW babies (Tavasoli et al. 2014; van den Boogaard et al. 2017).

Comparison between age categories

Compared to the 6-month group, MDAT Z-scores were significantly lower in the total, gross motor and language & hearing domains at the 12-month age category and higher at the 18-month age category. This is consistent with data from US-based study suggesting that while the effect of MLBW on motor development scores in infancy are large and statistically significant, estimates at two years become considerably smaller, suggesting "catch-up" taking place between LBW and NBW children by two years (Datar and Jacknowitz 2009). While the findings could theoretically be explained by the concept of "catch-up" growth, the 18-month cohort may have been impacted by a country-wide healthcare strike occurring during the time of data collection. Given the importance of environmental and socioeconomic factors on long-term neurodevelopmental outcomes, we hypothesized that the women who were able to access facility delivery during the healthcare strike may have had more resources (i.e. access to healthcare) than those who did not. It would stand to reason that these babies born to more more resourced families would have better overall developmental trajectories.

Relationship to prior research

This secondary analysis detected some inconsistencies with prior research on developmental outcomes of LBW babies, which overwhelmingly demonstrates an inverse relationship between BW and/or GA and the risk for neurodevelopmental impairment, wherein incidence of impairment increases as BW or GA decrease (Sutton and Darmstadt 2013). These inconsistencies were primarily found in the 6-month age category. The relationship between BW and neurodevelopmental outcomes demonstrated expected relationships in the 12-month age category overall based on prior research but did not remain significant after adjusting for

covariates. A significant linear relationship was only detected in the gross motor domain of the 18-month age category.

Explanation of findings

There are several potential explanations for these findings. First, the counter-intuitive results in the 6-month age category, could have been related to difficulties detecting delay as there are limited items that can be assessed in very young infants. However, a significant inverse linear relationship was detected in the gross motor domain and prior research has found that cultural practices in both rural Kenya and Ghana support the early onset of sitting, standing and walking without support (WHO Multicentre Growth Reference Study Group 2006; Angulo-Barroso et al. 2011; Super 1976). One observational study found that the Kipsigi people of South Eastern Kenya intentionally engaged in practices aimed at accelerating the development of gross motor skills including, sitting upright and walking, beginning in the newborn period leading to advanced milestone achievement (Super 1976). While these studies did not include LBW babies, other research has found that environmental factors such as home stimulation have a greater impact on LBW babies than their NBW counterparts (Lima et al. 2004). Further, because responsive parenting has a positive impact on early childhood development in infants who are at risk for delay (WHO 2020), research on whether parents of preterm and LBW babies are acutely responsive to their children in the first months of life would be beneficial in better understanding the phenomenon observed here.

Much of the recent literature in both high income and LMIC settings focuses on VLBW and very preterm babies (Ballot et al. 2012; Hollanders et al. 2019; Modi et al. 2013), while the current sample consists primarily of MLBW and moderately/late preterm babies. While virtually all VLBW/ELBW babies are born premature, MLBW comprise preterm/full-term and

IUGR/SGA infants. Growth restriction may be a consequence of a confluence of intrauterine (e.g. maternal infection, substance use, inadequate maternal nutrition, maternal hypertension) and extrauterine or environmental factors (sociodemographic, economic, political, postnatal growth patterns and nutrition, and parental behaviors). This makes a normal population of LBW babies, comprised of mostly moderately preterm babies, challenging to study accurately without controlling for a multitude of variables. Further in the present analysis, the early age of assessment, particularly in the 6-month age category, may be masking more subtle motor and cognitive deficits, including cognitive and language delays and deficits in visuospatial reasoning and executive functioning, which have been demonstrated among heavier LBW and later GA preterm babies between the age of two and adolescence. While these studies are primarily from developed countries, they have frequently shown a greater need for special education services at school age, poorer school readiness, and worse academic performance than peers born at term (Natarajan and Shankaran 2016; Aylward 2014; Stein et al. 2006).

Another important consideration is that all babies in this study received some level of intervention. The babies in the control group were born at facilities that received both data strengthening and implementation of the modified version of the WHO Safe Childbirth Checklist. The checklist has been used in a variety of LMIC contexts including India, Sri Lanka and Namibia, and increases in use of evidence-based practices have been consistently reported (Semrau et al. 2017; Kabongo et al. 2017). In the intervention group of the PTBi-K study, babies were born at facilities receiving a full package of interventions including provider simulation training, quality improvement, data strengthening and the modified Safe Childbirth Checklist (Otieno, 2018). While the aim of these interventions overall was to improve maternal and neonatal survival, the implementation of evidence-based practice in intrapartum and neonatal

care could theoretically impact the incidence of long-term morbidities associated with prematurity and LBW including neurodevelopmental deficits. Improvements in neonatal and obstetric care have been shown to be associated with a two-fold decline in adverse neurodevelopmental outcomes among LBW babies (Goisis et al. 2017).

Of note, there were statistically significant differences (p=.002) in the number of babies in each age category who were in the control group vs. the intervention group of the PTBi-K study. Significantly more babies in the 6-month age category (75%) received intervention than in the 12-month age category (62%) and the 18-month age category (60%). The very high proportion of babies who received intervention could be another potential explanation for the counter-intuitive findings in the 6-month age category. Further, although the percentage in the treatment group vs control group were comparable between the 12-month and 18-month categories, only 8% of babies in 18-month categories were born at the MRCH site, which was an intervention site known to be higher risk for preterm and LBW births, while 25% in the 12-month category and 35% in the 6-month category were born at MCRH.

Study Limitations

The sample used for this secondary analysis was from a facility-based intervention study that implemented evidence-based practices for management of labor, delivery and immediate neonatal care. The participating babies were not necessarily representative of babies born in Kenya or in LMIC contexts where neonatal care interventions are limited, and home births are common (Izugbara et al. 2009; Otieno et al. 2018). This may limit the generalizability of the findings. Further, due to the nature of the PTBi-K and ethics surrounding withholding intervention known to be beneficial, there was no true control group. Therefore, clinical significance and interpretation of results should be considered with caution.

The small sample size could have contributed to the few statistically significant findings in this analysis as well as limit generalizability to the full population of preterm and LBW babies. Further, the 18-month age category, which had a much smaller sample size than the 12- and 18-month age categories, may have been particularly vulnerable to type II error and findings should be interpreted with caution.

Although prematurity and LBW are considered risk factors for adverse neurodevelopmental outcomes, a complex interplay of factors before, during and after birth impact the risk of the individual child, especially those who are MLBW. In addition to biological factors, both sociodemographic and environmental risk and protective factors may influence individual outcomes. It should be taken into consideration that the present analysis did not control for sociodemographic, environmental or maternal risk factors.

A final limitation is the cross-sectional nature of the data. Comparisons between the 6, 12- and 18-month age categories must be interpreted carefully because it was not possible to control for all variation between cohorts. Future research should consider continuous, longitudinal study designs, in which data on developmental outcomes of the same babies is collected over an extended period of time.

Conclusion, Implications and Future Directions for Research, Practice, and Policy

With improvement of perinatal and neonatal service delivery in LMICs, there is greater survival of LBW and preterm babies in the first five years of life, raising concern for higher rates of disability in settings where resources are already scarce. This may result in substantial burden to families and society as a whole. Currently, there is no systemic global initiative that has been activated to reduce this burden among vulnerable populations. Understanding the impact of BW on neurodevelopmental outcomes is of particular importance in settings where GA assessment by

ultrasound is not available. The current analysis sought to examine the association between BW and neurodevelopment in babies at 6, 12 and 18 months of age by exploring the relationship between BW and MDAT Z-score. It also compared MDAT Z-scores between three age groups of babies to examine whether developmental risk exists after infancy.

While the present data did not overwhelmingly support the hypothesis that MDAT Z-scores would decrease with decreasing BW, there are valuable lessons to be learned from this analysis. First, studies exploring accurate gestational dating methods that are feasible in LMICs are necessary, as ultrasound-dated GA has been shown to be associated with worse neurodevelopmental outcomes in East Africa (Gladstone et al. 2011). Next, as previously noted, very preterm and VLBW babies are most often followed up in long-term outcome studies. The present sample is representative of global norms with only 16.5% of babies falling in the very or extremely preterm categories. Therefore, information on developmental outcomes from infancy to school age and beyond is crucial in order to accurately assess the burden of disease in the vast majority of LBW babies in LMICs.

Finally, subtle deviations from the MDAT Z-score reference population in neurodevelopment, especially in the 12- and 18-month age categories, were appreciated in the present analysis. The WHO Nurturing Care Framework for Early Childhood Development holds that in order to facilitate optimal early childhood development, studies and programs should prioritize the specific needs of children at high risk of developmental difficulties especially in regions with a high burden. (WHO 2018). Low birth weight should be one criterion that warrants the allocation of resources to early detection of disabilities in infancy when the brain is still sensitive to intervention, community-based programs dedicated to educating families about the expected developmental trajectory of their infant and provision of services to optimize

developmental outcomes. (Global Research on Developmental Disabilities Collaborators 2018). For the majority of babies born LBW, low-cost, accessible intervention may be adequate to improve long-term developmental outcomes. Studies have shown improvements in measures of socioemotional and cognitive/academic performance with positive parenting behaviors during early childhood (Kapri 2017). Further, the effects of responsive caregiving interventions on neurodevelopment have been shown to be particularly impactful in the gross motor domain (Jeong et al 2018). Exploring feasible, reproducible programs targeted at the overwhelming majority of LBW and preterm infants with meticulous long-term follow-up will be an important step in ensuring the developmental needs of children in LMICs are met. This analysis and the HND study will add to a growing body of evidence on health-related causes of neurodevelopmental adversity and help to establish specific indicators that can be used to improve neurodevelopment of children in low resource settings.

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Tables and Figures

Table 1. Sample Demographics adapted from "Growth and neurodevelopmental outcomes of preterm and low birth weight babies in rural Kenya," Martin-Herz and Otieno, under preparation.

Age at Assessment	6 months n (%)	12 months n (%)	18 months n (%)	All n (%)
Neonatal factors				
Gender				
Male	57 (36.8)	64 (40.3)	23 (47.9)	144 (39.8)
Female	98 (63.2)	95 (59.8)	25 (52.1)	218 (60.2)
Gestational Age (weeks)				
≥ 37	59 (38.1)	45 (28.3	10 (20.8)	114 (31.5)
33 to <37	76 (49.0)	96 (60.4)	33 (68.8)	205 (56.6)
28 to <33	17 (11.0)	12 (7.6)	5 (10.4)	34 (9.4)
22 to <28	3 (1.9)	3 (1.9)	0	6 (1.7)
Missing				
Birth Weight (grams)				
2500-2999	50 (32.3)	58 (36.5)	21 (43.8)	129 (35.6)
1500-2499	94 (60.7)	97 (61.0)	27 (56.3)	218 (60.2)
1000-1499	7 (4.5)	3 (1.9)	0	10 (2.8)
500-999	4 (2.6)	1 (0.6)	0	5 (1.4)
Apgar – one-minute				
≥5	8 (5.2)	5 (3.1)	1 (2.1)	14 (3.9)
6 to 7	12 (7.7)	14 (8.8)	3 (6.3)	29 (8.0)
>7	128 (82.6)	129 (81.1)	44 (91.7)	301 (83.2)
Apgar – 5-minute				
≥5	2 (1.3)	2 (1.3)	1 (2.1)	5 (1.4)
6 to 7	8 (5.2)	4 (2.5)	1 (2.1)	13 (3.6)
>7	138 (89.0)	142 (89.3)	46 (95.8)	326 (90.1)

Table 2. Mean MDAT Z-scores by developmental domain and age category

Domain	*M*	*SD*	*n*	*Min*	*Max*
All Age Categories					
Fine motor	0.54	1.36	358	-3.45	6.84
Total	0.30	1.19	359	-3.65	5.89
Language	0.05	1.13	359	-4.01	4.45
Gross motor	0.28	1.06	359	-2.41	4.40
Social	0.19	1.15	359	-3.88	4.67
6-month Age Category					
Fine motor	0.55	1.42	155	-3.45	5.93
Total	0.36	1.20	155	-3.45	5.89
Language	0.13	1.17	155	-4.01	3.81
Gross motor	0.44	0.82	155	-1.64	4.25
Social	0.22	1.06	155	-2.61	4.67
12-month Age Category					
Fine motor	0.05	1.07	156	-3.65	2.81
Total	-0.23	0.78	156	-3.01	2.14
Language	0.50	1.20	155	-3.41	3.41
Gross motor	-0.20	0.95	156	-2.41	2.89
Social	0.11	1.31	156	-3.88	3.01
18-month Age Category					
Fine motor	0.60	1.66	48	-2.39	6.84
Total	0.89	1.32	48	-2.15	4.13
Language	0.66	1.61	48	-3.91	4.45
Gross motor	1.38	1.14	48	-1.50	4.40
Social	0.31	0.88	48	-1.86	2.10

Table 3. All babies with developmental delay on MDAT stratified by age category Demographics adapted from "Growth and neurodevelopmental outcomes of preterm and low birth weight babies in rural Kenya," Martin-Herz and Otieno, under preparation.

Age at Assessment	6 months n (%)	12 months n (%)	18 months n (%)	All n (%)
Delayed by MDAT pass/fail criteria				
Gross Motor	6 (3.9)	9 (5.7)	0	15 (4.1)
Fine Motor	1 (0.7)	2 (1.3)	1 (2.1)	4 (1.1)
Language	0	2 (1.3)	1 (2.1)	3 (0.8)
Personal Social	1 (0.7)	2 (1.3)	1 (2.1)	4 (1.1)
MDAT Total	8 (5.2)	12 (7.6)	3 (6.3)	23 (6.4)
<= -2 SD from mean				
Gross Motor	0	10 (6.3)	0	10 (2.8)
Fine Motor	6 (3.9)	4 (2.5)	1 (2.1)	11 (3.0)
Language	5 (3.2)	3 (1.9)	2 (4.2)	11 (3.)
Personal Social	3 (1.9)	15 (9.4)	0	18 (5.0)
MDAT Total	2 (1.3)	6 (3.8)	2 (4.2)	10 (2.8)

Note. MDAT fail based on Prado_Gladstone 2 item fail (Martin-Herz and Otieno under preparation)

Table 4. Univariable linear regression models for birth weight and neurodevelopmental status at 6, 12 and 18 months of adjusted age

Age Category			
6-month age category			
MDAT domain	Coefficient	P Value	95% Confidence Interval
Total	-.0003404	0.117	-.0007673, .0000865
Gross motor	-.0002809	0.056	-.0005695, 7.69e-06
Fine motor	-.0001992	0.440	-.0007077, .0003093
Language	-.0001732	0.412	-.000589, .0002426
Social	-.0002493	0.195	-.0006273, .0001287
12-month age category			
Total	.0004412	0.050	-7.15e-07, .0008832
Gross motor	.0004302	0.033	.0000354, .0008249
Fine Motor	.000054	0.833	-.0004499, .0005579
Language	.0002605	0.114	-.000063, .000584
Social	.0005386	0.051	-3.17e-06, .0010804
18-month age category			
Total	.0006431	0.241	-.0004466, .0017328
Gross motor	.0010192	0.028	.0001154, .0019231
Fine motor	-.000556	0.421	-.001935, .000823
Language	.0002416	0.720	-.0011067, .00159
Social	.0002731	0.456	-.0004575, .0010037

Table 5. Multivariable linear regression models for birth weight and neurodevelopmental status at 6, 12 and 18 months of adjusted age

Age Category			
6-month age category			
MDAT domain	Coefficient	P Value	95% Confidence Interval
Total	-.0004023	0.057	-.0008165, .0000119
Gross motor	-.0003252	0.022	-.0006039, -.0000466
Fine motor	-.000023	0.937	-.0005916, .0005457
Language	-.0001252	0.558	-.0005465, .0002962
Social	-.0004348	0.035	-.0008392, -.0000304
12-month age category			
Total	.000249	0.278	-.000203, .000701
Gross motor	.0001855	0.329	-.0001892, .0005603
Fine Motor	6.34e-06	0.982	-.0005413, .000554
Language	.0002168	0.219	-.0001305, .0005641
Social	.0004945	0.095	-.0000873, .0010763
18-month age category			
Total	.0007448	0.156	-.0002954, .0017851
Gross motor	.0010848	0.016	.0002136, .0019559
Fine motor	-.0004825	0.498	-.0019065 .0009414
Language	.0003104	0.647	-.0010475, .0016684
Social	.0003107	0.398	-.000424, .0010455

***Note*. Adjustments made for GA, LAZ and five-minute Apgar score**

Table 6. Differences in relationship between MDAT scores and birth weight among 3 age categories

Age Category

	Coefficient	P Value	95% Confidence Interval
MDAT Total Score			
12 Months	-.3210164	0.012	-.5717164, -.0703165
18 Months	.6476407	0.000	.2865387, 1.008743
Gross Motor			
12 Months	-.6236395	.000	-.8200828, -.4271963
18 Months	1.068971	.000	.7860186, 1.351922
Language			
12 Months	-.3586355	0.004	-.604439, -.1128321
18 Months	.596706	0.001	.2426569, .9507551
Fine Motor			
12 Months	-.1137155	0.485	-.4336683, .2062372
18 Months	.0219679	0.925	-.4382213, .482157
Social			
12 Months	-.1993451	0.141	-.4648323, .066142
18 Months	.1307569	0.502	-.2516441, .513158

Note. **6-month age category set to baseline**
Models control for BW, GA, LAZ, and 5-minute Agar score

Table 7. *Mean, Standard Deviation, and Sample Size for MDAT domain by age category*

Age category			
MDAT Total	*M*	*SD*	*n*
6 months	0.36	1.20	155
12 months	0.05	1.07	156
18 months	0.89	1.32	48
Gross Motor			
6 months	0.44	0.82	155
12 months	-0.20	0.95	156
18 months	1.38	1.14	48
Fine Motor			
6 months	0.55	1.42	155
12 months	0.50	1.20	156
18 months	0.60	1.66	48
Language			
6 months	0.13	1.17	155
12 months	-0.23	0.78	156
18 months	0.66	1.61	48
Social			
6 months	0.22	1.06	155
12 months	0.11	1.31	156
18 months	0.31	0.88	48

Table 8. *Analysis of Variance Table for MDAT domains by age Category*

MDAT Domain	*SS*	*df*	*F*	*p*	η_p^2
Total	26.83	2	9.92	< .001	0.05
Gross Motor	98.49	2	57.48	< .001	0.24
Fine Motor	0.38	2	0.10	.905	0.00
Language	30.78	2	12.88	< .001	0.07
Social	1.80	2	0.68	.510	0.00

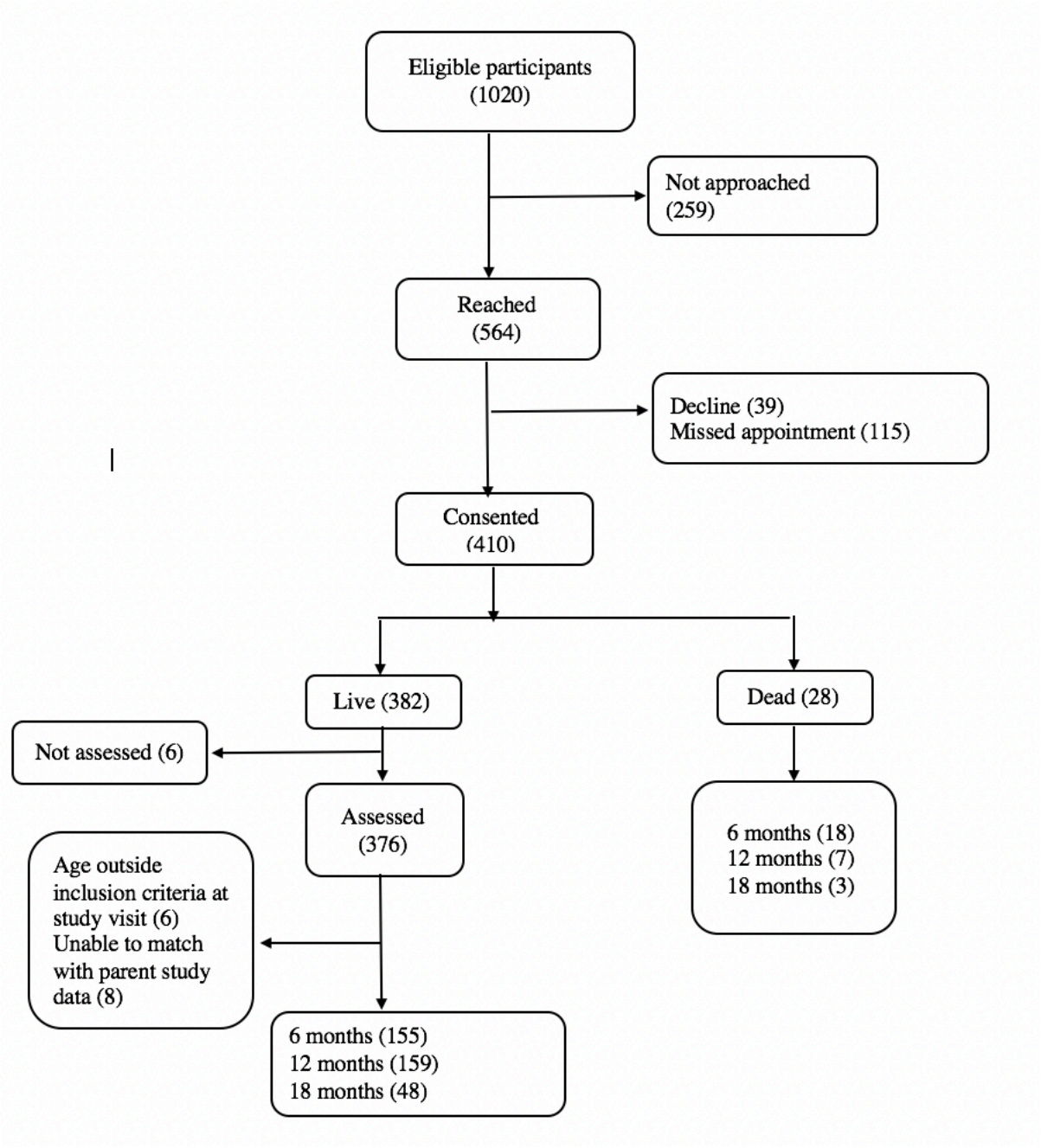

Figure 1. Study flow diagram reprinted from "Growth and neurodevelopmental outcomes of preterm and low birth weight babies in rural Kenya," Martin-Herz and Otieno, under preparation.

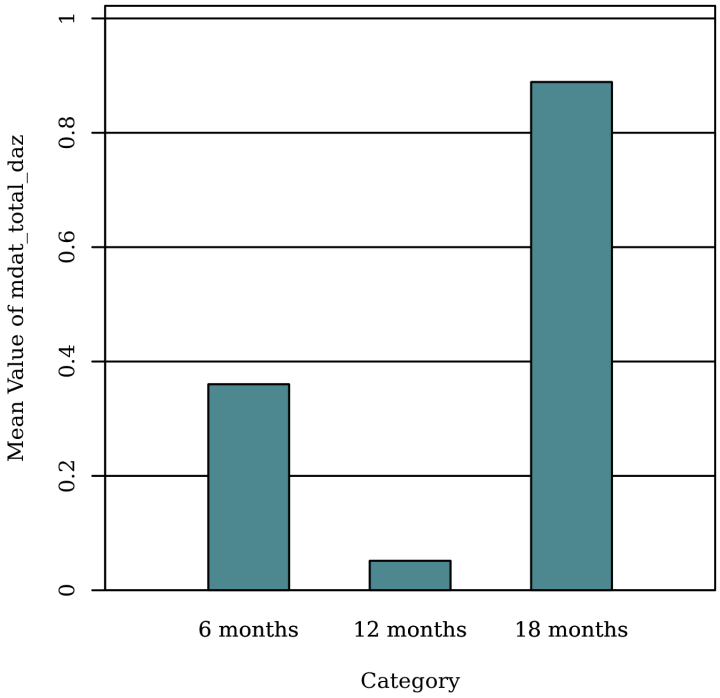

Figure 2. Means of total MDAT score by factors levels of Category
**($F(2, 356) = 9.92$, $p < .001$)

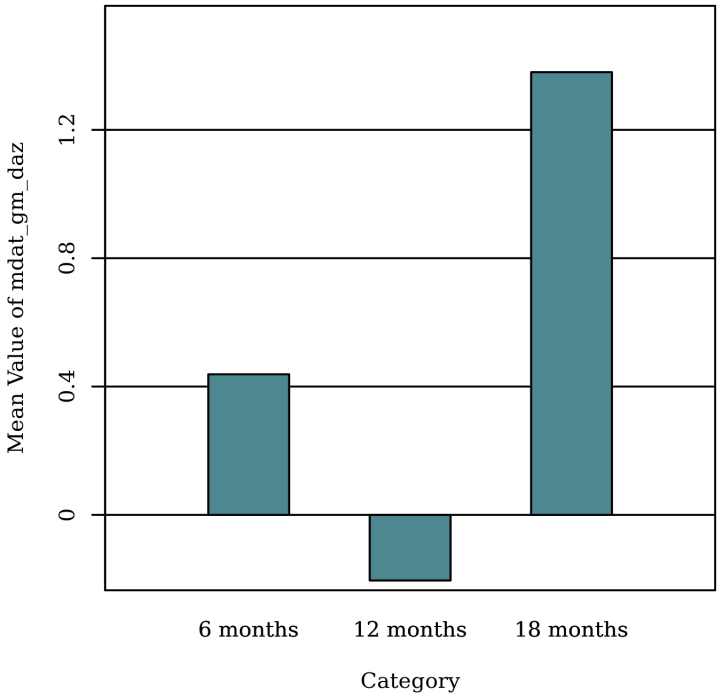

Figure 3. Means of MDAT gross motor score by factors levels of Category
**($F(2, 356) = 57.48$, $p < .001$)

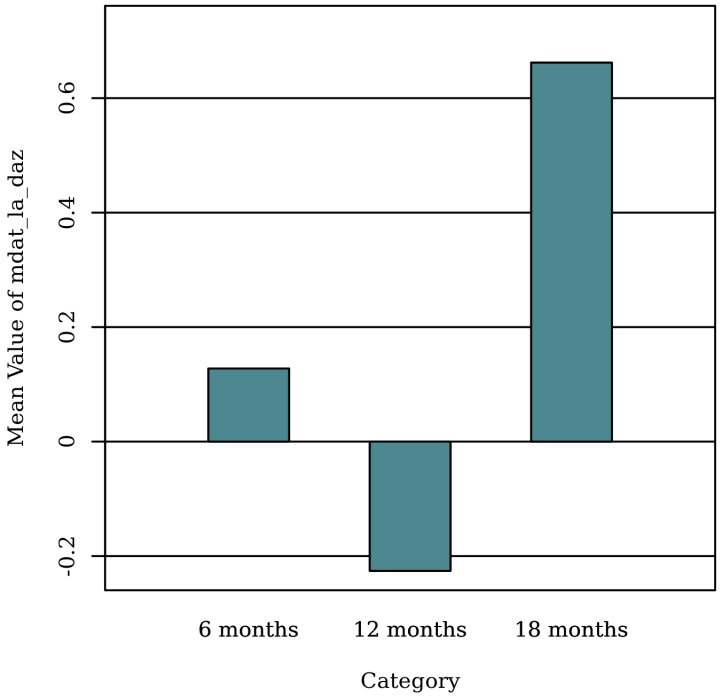

Figure 4. Means of MDAT language & hearing score by factors levels of Category
**($F(2, 356) = 12.88$, $p < .001$)

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