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Pathways Leading to Adverse Birth Outcomes in Rural Malawi

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Abstract

Background. Preterm birth and small birth size are globally important predictors of childhood morbidity, mortality, undernutrition and growth failure, and developmental loss. Maternal infections, inflammation, stress, and malnutrition are thought to cause these adverse birth outcomes, especially in low income settings. However, there is only limited information on the interaction between adverse maternal exposures and their relative importance in causing preterm birth and intrauterine growth restriction (IUGR).

Objective. To build concept maps to describe the pathways between various maternal exposures and shortened pregnancies or smaller birth length, weight, or head circumference in a rural Malawian population.

Design. We enrolled 1,391 women with uncomplicated pregnancies (<20 gestation weeks [gw]) in a randomized, controlled trial in Malawi. Nested within this trial, we carried out a prospective cohort study on the determinants of the duration of pregnancy and intrauterine growth restriction (IUGR) (i.e., neonatal weight-for-age, neonatal length-for-age, and neonatal head circumference-for-age). The tested predictors included many variables indicating maternal constitutional factors (e.g., age, parity), nutritional status (e.g., body mass index [BMI], weight gain in pregnancy, blood hemoglobin [Hb] concentration), infection (e.g., HIV, malaria, reproductive and urinary tract infections, chorioamnionitis, periodontitis, dental infections), or stress (salivary cortisol concentration).

We started the analysis by establishing associations between the stated outcome variables and the selected predictors. We then built a matrix of bivariate associations between all variables that were associated with the duration of pregnancy or neonatal weight-for-age, neonatal length-for-age, and neonatal head circumference-for-age. These analyses, including adjustments for possible confounders, allowed us to identify independent associations between various predictors and outcome variables and thus to build an initial concept map describing pathways leading to adverse pregnancy outcomes. We then refined this concept map by doing stepwise regression analyses, i.e., by adding the predictor variables into the models one by one, with the most distal variables first and most proximal ones last. Finally, we used structural equation models to estimate correlation coefficients between the variables and to create illustrations of the pathways leading to reduced duration of pregnancy or to reduced newborn length, weight, or head circumference.

Results. The duration of pregnancy was predicted by maternal malaria parasitemia at enrollment, severe chorioamnionitis, and the presence of periapical oral infections soon after birth. Additionally, pregnancy duration was predicted by maternal blood Hb concentration at enrollment, salivary cortisol concentration at 36 gw, and placental weight. All newborn size measurements were predicted by the duration of pregnancy, placental weight, and maternal inflammation. In addition, newborn length was independently associated with maternal infections, weight gain during pregnancy, primiparity and height; newborn weight was associated with maternal primiparity, maternal BMI at enrollment, weight gain during pregnancy, and newborn length-for-age z-score (LAZ); and newborn head circumference was associated with maternal BMI at enrollment and newborn LAZ. For each outcome, however, there was a complex network of proximal and more distal determinants, so that all dimensions of fetal growth were ultimately associated with both maternal nutritional status and with variables reflecting infection, inflammation, and stress, directly or indirectly.

Conclusions. Whereas maternal infections and inflammation seem to be important determinants of the duration of pregnancy and birth length in the studied cohort, the pathways to preterm birth and small birth size also include maternal undernutrition, stress, and certain constitutional factors like age and parity. Because of this complex network of adverse exposures, it is not surprising that single-pronged nutritional or infection-targeted antenatal interventions have had at best modest impacts on fetal growth or duration of pregnancy in low-income settings. For greater impact, it is likely that more-comprehensive multipronged interventions will be needed, to ensure good nutritional status for the mother both before and during pregnancy, prevention and treatment of a wide range of maternal infections, and prevention of maternal stress.

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Abbreviations and Acronyms

AGP	α -1-acid glycoprotein
BMI	body mass index
COM	University of Malawi, College of Medicine
CRP	C-reactive protein
ESRI	Environmental Systems Research Institute
FANTA	Food and Nutrition Technical Assistance III Project
g	gram(s)
GC	gas chromatography
gw	gestation weeks
Hb	hemoglobin
HCZ	head circumference-for-age z-score
HIV	human immunodeficiency virus
IFA	iron and folic acid
IGF-1	insulin like growth factor 1
iLiNS-DYAD-M	A clinical trial with the indicated name (DYAD = mother-child pair, M = Malawi)
iLiNS Project	International Lipid-Based Nutrient Supplement Project
IPTp	intermittent preventive treatment (of malaria) in pregnancy
IUGR	intrauterine growth restriction
L	liter(s)
LAZ	length-for-age z-score
LBW	low birth weight
LNS	lipid-based nutrient supplement(s)
LNS-RTI	Lipid-Based Nutrient Supplement – Reproductive Tract Infections (study)
m	meter(s)
mm	millimeter(s)
mmHg	millimeter(s) of mercury
MMN	multiple micronutrient(s)
PCR	polymerase chain reaction
RDT	rapid diagnostic testing
RMSEA	root mean square error of approximation
SAE	serious adverse event
SEM	structural equation models
SES	socioeconomic status
UCD	University of California, Davis
USAID	U.S. Agency for International Development
USDA	U.S. Department of Agriculture
UTA	University of Tampere
UTI	urinary tract infection
WAZ	weight-for-age z-score
WHO	World Health Organization

1. Introduction

Worldwide, an estimated 20 million infants are born with a low birth weight (LBW) (<2,500 g) each year, contributing to approximately 10%–15% of the global mortality of children under 5 years old and to a large share of childhood undernutrition, morbidity, and developmental loss (Black et al. 2008, Black et al. 2013, Christian et al. 2013, Espo et al. 2002, Katz et al. 2013, UNICEF/World Health Organization [WHO] 2004). Two factors determine size at birth: the rate of growth during the fetal period and the duration of pregnancy. Thus, LBW may reflect either intrauterine growth restriction (IUGR) or preterm delivery or both. While the exact molecular mechanisms leading to early onset of labor or restricted fetal growth are largely unknown, a number of risk factors have been identified for both conditions (Ergaz et al. 2005, Goldenberg et al. 2008). These factors have often been categorized into maternal conditions (e.g., maternal genetics, nutritional status or overall health), placental pathology (e.g., location in the uterus or vascularization), infant characteristics (e.g., genetics), or environmental or other factors (e.g., use of tobacco, habitat altitude, or others).

Of the identified risk factors, maternal undernutrition and infections have most consistently been associated with both IUGR and preterm birth (Ergaz et al. 2005, Goldenberg et al. 2008). Consequently, there has been wide interest in studying the efficacy of dietary supplements or presumptive treatment of pregnant women with antimicrobial agents as a means to promote fetal growth and prevent preterm birth. Indeed, a recent systematic review concluded that the incidence of IUGR could be markedly reduced by supplementing the maternal diet during pregnancy either with multiple micronutrients (MMN) or with protein and energy (Bhutta et al. 2013). In malaria-endemic areas, intermittent preventive treatment (of malaria) in pregnancy (IPTp) has also proven beneficial (Kayentao et al. 2013) and the WHO now recommends its regular use in moderate-to-high malaria transmission areas in Africa (WHO 2012). Some studies have also reported improved birth outcomes after presumptive treatment of pregnant women with antibacterial broad-spectrum antibiotics (Gray et al. 2001, Swadpanich et al. 2008, Luntamo et al. 2010).

Although there has thus been some success in increasing mean birth weight and preventing LBW through interventions targeting pregnant women, the effect size has typically been modest and many studies have reported no impact at all (Bhutta et al. 2013). One possible explanation for this limited success is narrowness of scope, i.e., that research trials have addressed only one, or at maximum a few, of the putative risk factors. This approach assumes a single dominant etiology for small birth size, but a co-causation model is arguably more plausible, especially in low-income contexts where infections, undernutrition, and other adverse exposures are common among pregnant women. So far, however, there have been few studies that would have concurrently analyzed multiple maternal risk factors and their joint contribution to birth size.

We recently conducted a controlled trial in rural Malawi, in which we tested the maternal and child health impacts of supplementing pregnant women with small-quantity lipid-based nutrient supplements (LNS) or MMN capsules, as opposed to the standard supplementation with iron and folic acid only (IFA). The trial had a large sample size and it included a very detailed clinical follow-up and frequent collection of a wide range of biological samples. Hence, it provided a unique opportunity not only to study the impact of the intervention on a number of maternal and newborn outcomes, but also to provide clues on other potential pregnancy interventions by carefully analyzing the multiple determinants of IUGR, preterm birth, and small birth size in the same dataset. To take advantage of this opportunity, the International Lipid-Based Nutrient Supplement Project (iLiNS Project) conducted a mother-child dyad trial in Malawi (iLiNS-DYAD-M), with generous support from the U.S. Agency for International Development (USAID)-funded Food and Nutrition Technical Assistance III Project (FANTA), and designed and implemented an add-on

component to the trial called the Lipid-Based Nutrient Supplement – Reproductive Tract Infections (LNS-RTI) study.

In the LNS-RTI study, we collected information on maternal, fetal, placental, and newborn health at several points of pregnancy and thereafter. Using regression analysis and structural equation models (SEM), we built concept maps to characterize and illustrate the network of pathways connecting maternal constitutional variables (infection, inflammation, nutrition, stress) to the duration of pregnancy and birth size. Because of its public health implications, we modeled newborn weight as one of the main indicators of birth size. But because attained weight is a function of both linear growth and fat and lean tissue deposition, we also built models for newborn length. Finally, to capture the third dimension of fetal growth, we modeled newborn head size, using the same techniques as for weight and length.

2. Methods

2.1 Study Design and Outcomes of Main Trial

The study was a prospective cohort study, nested within the iLiNS-DYAD-M randomized controlled trial that was carried out in Malawi. The hypothesis of the trial was that home fortification of pregnant women's diets with an LNS would increase birth size in an African community. The women were provided with one daily IFA capsule; one capsule with 18 micronutrients; or one 20 g sachet of LNS containing 118 kcal, protein, carbohydrates, essential fatty acids, and 22 micronutrients from ≤20 gestation weeks (gw) until delivery. The primary outcome measures were birth weight and child length soon after birth, and secondary outcomes included multiple maternal and child variables. The trial design and main findings are described in Ashorn et al. (2017a).

In the study sample, women who received LNS gave birth to infants whose mean birth weight and length were approximately 50 g and 4 mm greater than those of infants born to women who received IFA, respectively. However, the differences were not statistically significant (Ashorn et al. 2015). There were also no significant intergroup differences in the prevalence of maternal malaria parasitemia at various points of pregnancy or soon thereafter or of vaginal trichomoniasis and urinary tract infections (UTIs) after pregnancy. Likewise, the mean maternal saliva concentration of cortisol; the plasma concentrations of inflammation markers C-reactive protein (CRP) and α-1-acid glycoprotein (AGP); and the nutritional markers of cholesterol, triglycerides, folate, and defined fatty acids during the third trimester of pregnancy were similar in the three intervention groups. The groups also did not differ in terms of mean bacterial load in the placenta or amniotic membranes, the prevalence of chorioamnionitis in the placenta, or the development of malaria immunity during pregnancy Ashorn et al. (2017a). Thus, the data do not support a hypothesis that provision of small-quantity LNS or MMN to all pregnant women would increase the mean birth size or markedly affect other pregnancy outcomes in rural Malawi Ashorn et al. (2017a).

The trial setup was used for the presently described nested cohort study where we are interested in associations between maternal infections, inflammation, stress, and poor nutritional health status and birth outcomes.

2.2 Ethics Statement

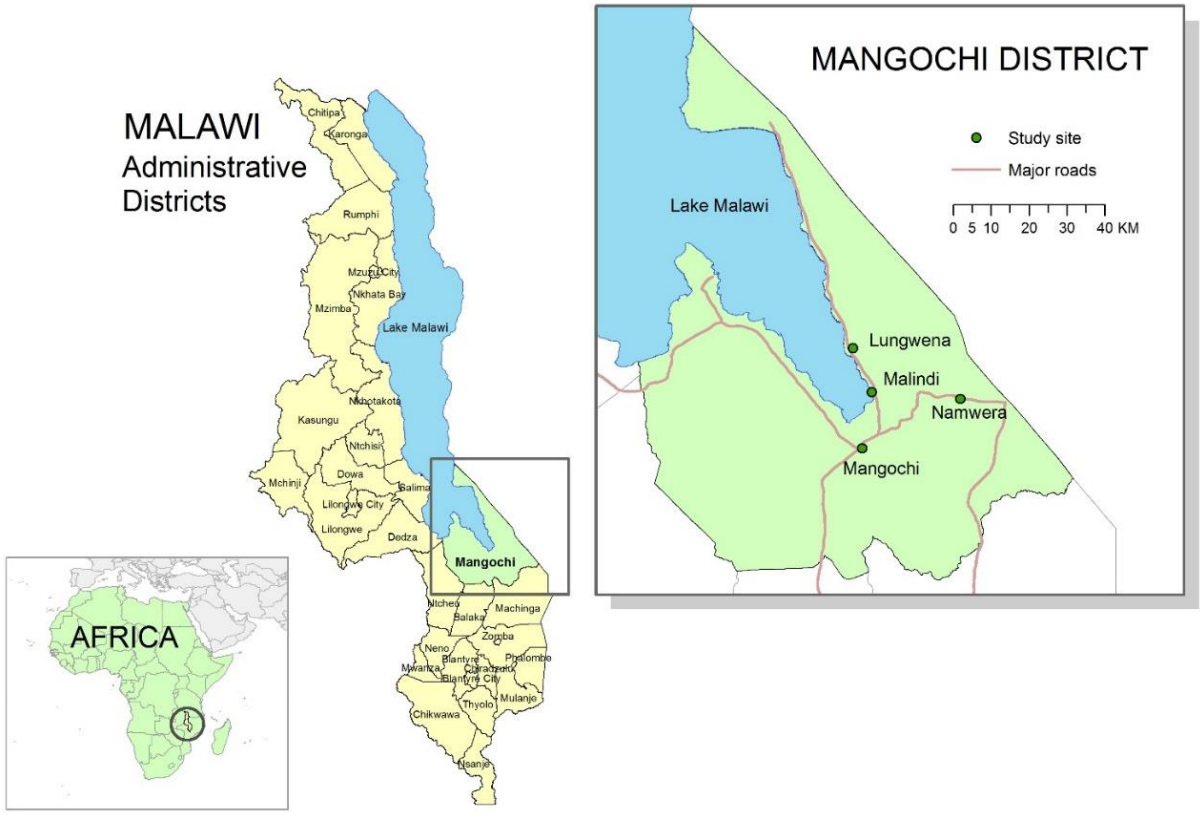
The trial was performed according to Good Clinical Practice guidelines and the ethical standards of the Helsinki Declaration. The protocol was approved by the College of Medicine (COM) Research and Ethics Committee, University of Malawi, and the Ethics Committee of Pirkanmaa Hospital District, Finland. Only participants who signed or thumb-printed an informed consent form were enrolled in the study. An independent data safety and monitoring board monitored the incidence of suspected serious adverse events (SAEs) and performed two interim analyses for safety. The data safety and monitoring board members received information about all suspected SAEs on an ongoing basis and met three times during the pregnancy part of the trial.

Key details of the protocol were published at the clinical trial registry of the National Library of Medicine, Bethesda, MD, USA (http://www.clinicaltrials.gov/ct2/show/NCT01239693?term=NCT01239693&rank=1).

2.3 Study Site and Participants

Enrollment in the study took place in one public district hospital (Mangochi), one semi-private hospital (Malindi), and two public health centers (Lungwena and Namwera) in Mangochi District of southern Malawi (Figure 2.3-1). The Mangochi Hospital outpatient clinic served a semi-urban population of 100,000; the other sites provided health care to approximately 30,000 people each. All sites were accessible by all-weather roads. The population subsisted largely on farming and fishing. Prior to commencing the trial, the study team members held numerous discussions with community leaders and organized village meetings to discuss the research objectives and procedures. Pregnant women coming to antenatal visits received further information about the trial.

Figure 2.3-1. Map of the Study Sites



Source: Data layer for Africa map downloaded from http://www.thematicmapping.org, 2015 available under a Creative Commons Attribution-Share Alike License 3.0 (borders may not be completely accurate). All other data layers downloaded from Malawi Spatial Data Portal, 2015 (http://www.masdap.mw). Map created with ArcGIS Desktop v.10.3, Environmental Systems Research Institute (ESRI) 2016, Redlands, CA.

The target population was composed of pregnant women who came for antenatal care at any of the study clinics during the enrollment period and met the following inclusion criteria: ultrasound confirmed pregnancy of no more than 20 completed gw, residence in the defined catchment area, availability during the period of the study, and signed or thumb-printed informed consent. Exclusion criteria were: age under 15 years, need for frequent medical attention due to a chronic health condition, diagnosed asthma treated with regular medication, severe illness warranting hospital referral, history of allergy to peanuts, history of anaphylaxis or serious allergic reaction to any substance, requiring emergency medical care, pregnancy complications evident at enrollment visit (moderate to severe edema, blood hemoglobin [Hb] concentration <50 g/L, systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg),

earlier participation in the iLiNS-DYAD-M trial (during a previous pregnancy), or concurrent participation in any other clinical trial.

2.4 Enrollment in the Study

At the enrollment visit, trained anthropometrists measured the participants' weight, height, and mid-upper arm circumference (MUAC). They took all measurements in triplicate, with high-quality scales (SECA 874 flat scale, Seca GmbH & Co., Hamburg, Germany), stadiometers (Harpenden stadiometer, Holtain Limited, Crosswell, Crymych, UK), and non-stretchable plastic tapes (Shorrtape, Weigh and Measure, LLC, Olney, MD, USA), with reading increments of 50 g, 1 mm, and 1 mm, respectively. Research nurses recorded participants' obstetric histories and performed antenatal examinations. They assessed the duration of pregnancy by measuring the fetal biparietal diameter, the femur length, and the abdominal circumference (all in mm, mean of two measurements), with ultrasound imagers that utilized inbuilt Hadlock tables to estimate the duration of gestation (EDAN DUS 3 Digital Ultrasonic Diagnostic Imaging System, EDAN Instruments, Inc., Shekou, Nanshan Shenzhen, China). The same nurses measured the women's peripheral blood malaria parasitemia with rapid tests (Clearview Malaria Combo, British Biocell International Ltd., Dundee, UK) and Hb concentration with on-site cuvette readers (HemoCue AB, Angelholm, Sweden). Health facility nurses gave pretest HIV counseling and tested all participants for HIV infection, except those who opted out or were already known to be HIV infected, using a whole-blood antibody rapid test (Alere Determine HIV-1/2, Alere Medical Co., Ltd., Chiba, Japan). If the result was positive, the test was repeated using another whole-blood antibody rapid test (Uni-Gold HIV, Trinity Biotech plc, Bray, Ireland). If the tests were not available at the health facility on the day of enrollment, the study team arranged the test to be performed as soon as possible thereafter. Participants with a positive test were referred to the antiretroviral clinic for treatment in accordance with Option B+ treatment guidelines for HIV-positive pregnant women.

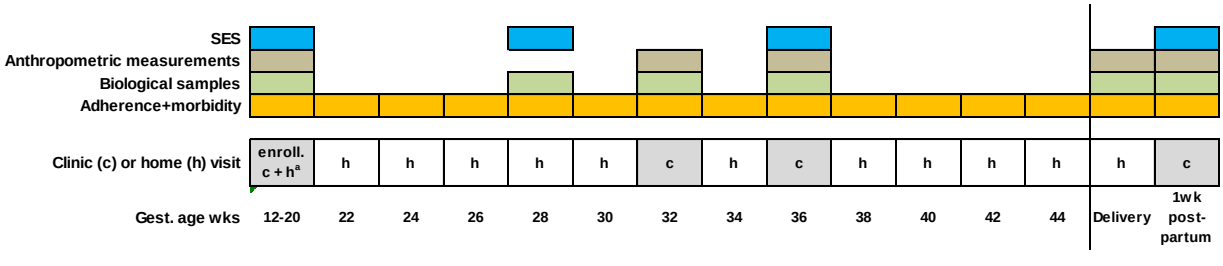
Further description on the enrollment process can be found elsewhere (Ashorn et al. 2015).

2.5 Follow-Up

After enrollment, the study team invited the participants to visits at the study clinic: at 32 gw, at 36 gw, and at approximately 1–2 weeks after delivery. Additionally, data collectors visited the participants fortnightly at their homes and soon after delivery either at their home or at the local maternity unit. Larger sets of biological samples were collected at the enrollment and at the 36 gw visits, but some samples were also collected at 28 gw, at delivery, and at 1 week after delivery.

Figure 2-5.1 shows a schematic representation of the study visits, biological sample collection, and clinical outcomes measured at each visit.

Figure 2-5.1. Study Visits, Biological Sample Collection, and Clinical Outcomes Measured at Each Visit



SES = socioeconomic status

[a] After the initial enrollment clinic visit, which took place between 12 gw and 20 gw, participants were seen regularly at home or at the clinic every 2 weeks until delivery.

During the antenatal clinical visits, study anthropometrists measured the participants' weight, height, and MUAC with the same methods as at enrollment, and study nurses carried out standardized obstetric examinations.

During the fortnightly home visits, data collectors delivered the supplements and collected information on the participant's adherence to the study intervention. As soon as possible after birth, research assistants visited the mother to record the delivery events, collect a blood sample for malaria tests, measure the placental size and collect samples from it and the amniotic membrane for histological and microbiological analyses, and measure the infant's birth weight. Other anthropometric measurements were not taken since this visit was sometimes completed at home.

A more thorough postnatal visit was completed when the infant was 1–2 weeks old and brought to the study clinic. At this visit, study nurses took anthropometric measurements for both the mother and the newborn infant. A dental therapist made an oral examination and took a panoramic x-ray from the mother's teeth.

If a participant did not come for the scheduled visit within 14 days of the appointment, data collectors made a visit to the participant's home. Information on the participants' hospitalizations and other suspected SAEs was collected actively via interviews at each fortnightly home visit. Study nurses also contacted both hospitals in the study area daily, to obtain information on any hospitalizations or deaths among study participants. Additionally, the study physicians trained health providers at all the known private and public health facilities in the area to identify the study participants from their iLiNS-DYAD-M identification cards and to record information on any nonscheduled visits on structured data collection forms that were collected and reviewed by the study team on a weekly basis. Finally, research assistants made a special home visit at 6 weeks after delivery, to verify the vital status of the participating woman and infant at the end of the primary follow-up period.

The study participants attended antenatal and under-5 clinics according to the same schedule as all other Malawian pregnant women and infants and received all normal preventive services provided by the national health system. Study nurses treated participants with documented peripheral blood malaria parasitemia with lumefantrine/artemether, the nationally recommended antimalarial drug. Other medical conditions were treated in the national health system (in either the public or the private sector). The study team reimbursed the participants for all medical costs that they incurred during the trial participation.

For the clinic visits, participants were compensated for their travel costs according to a local bicycle taxi rate. For visits taking more than 1 hour, there was also a small compensation for participant time, ranging from a reusable diaper (postnatal home visit) or 800 g of rice (antenatal clinic visits and socioeconomic background interviews) to 800 g of rice and 500 g of salt (postpartum clinic visit).

2.6 Collection of Biological Samples

As indicated above, biological samples were collected mainly at enrollment and at the 36 gw visits, but some samples were also collected at other visits. Most biological samples were placed in a −20°C freezer within 2 hours of sample collection, then transferred to −80°C within 48 hours of collection and stored at −80°C until analyzed. Placental samples used for histological analysis were fixed in formalin and stored at +4°C until embedded in paraffin and used for histology. Detailed methods used for sample collection and processing are provided in Ashorn et al. (2017a).

2.7 Quality Assurance in Data Collection

We ensured data collection quality through regular staff training and monitoring and through the use of written visit guides, instructions about the use of data collection forms, and additional standard operating procedures. Aside from birth weight, anthropometric measurements were taken only by trained personnel whose measurement reliability was verified at the start of the study and at 6-monthly intervals thereafter with methods modified from the procedures used in the WHO Multicenter Growth Reference Study (2006). Birth weight could also be measured by study nurses or study coordinators. The anthropometrists calibrated all equipment with standard weights and length rods on a daily basis. An external monitor appointed by the study team did one site monitoring visit during data collection.

2.8 Measurement of Outcome Variables and Their Predictors

General information on the methods of data collection for key outcome variables and their predictors for the LNS-RTI component of the study is provided below. Detailed information on data collection methods for each subtopic below, as well as for the full set of variables collected as part of the main iLiNS-DYAD trial, can be found in Ashorn et al. (2017a).

2.8.1 Duration of Pregnancy

Gestational age at enrollment was assessed at the enrollment visit by research nurses by measuring the fetal biparietal diameter, femur length, and abdominal circumference (all in mm, mean of two measurements), with ultrasound imagers that utilized inbuilt Hadlock tables to estimate the duration of gestation (EDAN DUS 3 Digital Ultrasonic Diagnostic Imaging System, EDAN Instruments, Inc., Shekou, Nanshan Shenzhen, China).

Duration of pregnancy at birth was calculated by adding the time interval between enrollment and miscarriage or delivery to the ultrasound-determined gestational age at enrollment.

2.8.2 Maternal and Child Anthropometrics

Trained anthropometrists measured maternal weight, height, and MUAC. They did all measurements in triplicate, with high-quality scales (SECA 874 flat scale, Seca GmbH & Co., Hamburg, Germany), stadiometers (Harpenden stadiometer, Holtain Limited, Crosswell, Crymych, UK), and non-stretchable plastic tapes (Shorrtape, Weigh and Measure, LLC, Olney, MD, USA), having reading increments of 50 g, 1 mm, and 1 mm, respectively. For measurements that were completed in triplicate, we used the mean of the first two readings if they did not differ by more than a prespecified tolerance limit. If the difference was above the limit, the third measurement was compared with the first and second measurements, and the pair of measurements that had the smallest difference was used to calculate the mean. If there were only one or two repeated measurements, the mean of those was used for the analyses.

Data on birth weight was used as such if measured within 48 hours of delivery, and back-calculated birth weight was used for data collected between 6 and 13 days after delivery using WHO z-scores. If weight was first measured between 2 and 5 days after delivery (when weight loss is typical), we calculated birth weight by multiplying the actual measured weight by a day-specific correction factor (Cheung 2014). We considered birth weight or newborn anthropometric measurements missing if they were collected more than 2 and 6 weeks after delivery, respectively.

Study anthropometrists measured the infant's length with a high-quality length board (Harpenden Infantometer, Holtain Limited, Crosswell, Crymych, UK) and recorded it to the nearest 1 mm, weight with an electronic infant weighing scale with a reading increment of 20 g (SECA 381 baby scale, Seca

GmbH & Co., Hamburg, Germany), and head and mid-upper arm circumference with the same plastic tapes that were used for maternal anthropometry.

We calculated age- and sex-standardized anthropometric indices (weight-for-age, length-for-age, and head circumference-for-age z-scores) using the WHO Child Growth Standards (WHO Multicentre Growth Reference Study Group 2006).

2.8.3 Body Mass Index and Weekly Gestational Weight Gain

We calculated body mass index (BMI) from weight and height measurements conducted at the enrollment visit for all women who enrolled in the iLiNS-DYAD-M trial. Additionally, we measured weight at 32 gw and at 36 gw to estimate weekly gestational weight gain from time of enrollment to 36 weeks gestation. (For further details on the analytic methods used to estimate weekly weight gain, refer to A2.1 in Ashorn et al. [2017a]).

2.8.4 Placental Size

Research nurses or laboratory technicians weighed the placentas as soon as possible after the delivery with dietary scales, with a reading increment of 1 g. In addition, they measured the placental diameter with a ruler from two dimensions: one at the largest diameter and the other at a 90° angle to the first one. The average of these two measures was used to calculate the radius and hence the surface area of the placenta.

2.8.5 Peripheral Blood Malaria Parasitemia during Pregnancy

Malaria was tested by rapid diagnostic testing (RDT). A finger prick sample was used for RDT at the study sites at enrollment.

2.8.6 Reproductive Tract and Urinary Tract Infections

At 1 week after delivery, the participants visited the study clinic for reproductive tract infection and UTI testing. A study nurse obtained a blind vaginal swab and immediately sent the sample to the study laboratory. The woman was also asked to provide a urine sample in a screw-top bottle. The study nurse performed a urine dipstick analysis on the urine sample.

2.8.7 Inflammatory Response; Maternal Plasma AGP Concentrations

Clinic nurses collected the blood samples at enrollment and at 36 gw. We analyzed AGP from the blood samples collected at enrollment by immunoturbidimetry on the Cobas Integra 400 system autoanalyzer (F. Hoffmann-La Roche Ltd, Basel, Switzerland) at University of California, Davis (UCD).

2.8.8 Blood Hemoglobin Concentration

Clinic nurses measured Hb concentration from whole blood collected from a finger prick at enrollment.

2.8.9 Plasma Cholesterol and Triglyceride Concentrations and Plasma Fatty Acid Status

Plasma cholesterol and triglyceride concentrations were determined at the U.S. Department of Agriculture (USDA) Western Human Nutrition Research Center (Davis, CA, USA) using a Cobas Integra 400 plus automatic analyzer (Roche Diagnostic Corp., Indianapolis, IN, USA). Plasma fatty acid composition was analyzed by gas chromatography (GC) with flame ionization detection at OmegaQuant Analytics, LLC

(Sioux Falls, SD, USA). Fatty acid composition was expressed as a percent of total identified fatty acids. Measurements were done at enrollment and 36 weeks gestation.

2.8.10 Salivary Cortisol Concentration

Saliva samples were collected at 36 weeks gestation, between 8 am and 4 pm, with a mean collection time at approximately 11 am. Women were instructed not to consume any food or drink besides water for at least 30 minutes before providing the saliva sample. Time of saliva collection, time of waking, and time of last food or drink were recorded. Saliva samples were collected at clinic sites at 36 gw when women came to provide blood and urine samples and have anthropometric measurements taken. Saliva collection occurred before any other measurements or sample collection.

Saliva was obtained by having the woman place an inert polymer cylindrical swab (10 mm x 30 mm, Salimetrics Oral Swab [Salimetrics, State College, PA, USA]) under her tongue for approximately 2 minutes, while moving her tongue and jaw as if she were chewing to stimulate saliva. The swab was then placed in a tube with a cap and refrigerated or placed on ice packs. Swabs were brought to room temperature before centrifuging for 15 minutes at 3,000 RPM. Samples were frozen and stored at −20°C within 24 hours of collection.

2.8.11 Microbial Communities in the Placenta and Fetal Membranes and in the Vagina

A sample of placenta tissue and the fetal membranes (amnion and chorion) was taken immediately after delivery, and a vaginal swab was taken 1 week after delivery. Inflammation and evidence of malaria infection were both assessed from histological slides taken from the placenta and fetal membranes at the Malawi College of Medicine. A lab technician at the Malawi-Liverpool Wellcome Trust laboratory in Blantyre extracted DNA from the placenta, fetal membranes, and vaginal swabs. The bacterial 16S rRNA gene was selectively amplified as confirmation of the presence of bacteria. Bacterial DNA underwent high-throughput sequencing at Great Ormond Street Hospital in London, UK, to elucidate the entire bacterial community that resided in each sample.

2.8.12 Oral Health

We assessed the prevalence of maternal oral diseases soon after delivery.

Two specially trained dental therapists conducted a comprehensive clinical and questionnaire-based oral health assessment and took digital radiographs at the postnatal visit at 1 week after delivery or as soon as possible at the Mangochi central site. The examiners' measurement reliability was assessed and verified at the beginning and regularly during the study. An oral and maxillofacial radiologist and an experienced dentist jointly analyzed the radiographs using structured forms.

2.8.13 HIV Infection

HIV testing and counseling was conducted at enrollment according to national guidelines. HIV testing was offered to all women attending antenatal clinics at the study sites. Pretest HIV counseling was offered to all the women during the routine antenatal health talk. For the women who expressed interest in taking part in the study and did not opt out of the test, capillary blood was drawn by a finger prick and HIV tests were performed in the study rooms. Post-test counseling was offered to all women after conducting the test. Women who tested negative or had an indeterminate result were asked to return to the clinic for repeat testing after 3 months. Those who tested positive were referred to the antiretroviral clinic for treatment in accordance with Option B+ treatment guidelines for HIV-positive pregnant women.

2.8.14 Socioeconomic and Demographic Background of the Participants

We collected information on the socioeconomic and demographic background of the mothers with structured interviews that took place at the participant's home within 2 weeks of enrollment. We asked questions about the family and household structure, the educational background of the mother and father, and the living environment. Data collectors interviewed the mother, and, if she was not available, they agreed on a later date when she would be available.

The interviews were conducted in Chichewa and Chiyao. The answers given by each respondent were written down in the language of that respondent.

2.9 Data Management

Data collection and review. Original data collection forms were developed by the researchers. Data collectors received oral instructions on how to fill out the forms from researchers and study monitors. In addition, a user guide was written for each data collection form, with information about the background of the form, specific information on how to conduct the interview and data collection, and instructions on specific form questions.

Data entry. All data were initially collected on paper forms from which they were extracted and entered into a tailor-made database through scanning and digital character recognition (TeleForm Desktop Version 10.5, Autonomy, Highland Park, IL, USA). Data entry clerks verified all critical variables or suspicious entries during the data entry process.

Database management. After data entry (TeleForm), the checked data were stored in a MySql database. From this database, the data were exported into Excel files that could be used for further data cleaning and analysis. Access to the database was organized through a custom-made access portal (iLiNS suite) with web access. Authorized researchers and personnel could access the data from there.

Data cleaning. The data in the database were cleaned by researchers and research assistants. All persons cleaning the data were blinded to the intervention each participant had received. A number of logical checks were performed on the data to identify suspicious values, which were later compared with the original research form used during data collection or after comparison with other data collected for the same participant. In case the suspicious value corresponded with the original collection form, these were mostly left in the data but marked with a cell coloring in the final dataset to be considered for revision during later analysis.

2.10 Analysis Methods

We started the analysis for the LNS-RTI component of the study by establishing bivariate associations (as reported in Ashorn et al. [2017b]) between all maternal characteristic variables that were associated ($P<0.05$) with the duration of pregnancy, newborn length-for-age z-score (LAZ), newborn weight-for-age z-score (WAZ), or newborn head circumference-for-age z-score (HCZ) (Section 3.1). As part of these analyses, we also established the bivariate association between each of the four outcomes of focus, i.e., duration of pregnancy, newborn LAZ, newborn WAZ, and newborn HCZ. Table A-2 lists and describes the variables included in this analysis.

Next, we created a series of multivariable regression models, in which we defined each of the maternal characteristic variables, one at a time, as the dependent variable and all of the remaining maternal

characteristic variables as covariates in the model. This allowed us to determine "predictors of predictors" for our pathway models (Section 3.2).

We then built a series of multivariable regression models for each birth outcome of focus by adding the predictor variables into each model one by one, with the most distal predictors entered into the model first and the most proximal predictors for that outcome entered into the model last (Section 3.3). Distal variables included variables that described maternal characteristics in early pregnancy or direct maternal exposures during the follow-up (e.g., maternal nutrition or infection), whereas the proximal variables were those that would follow from a primary exposure (e.g., maternal weight gain, plasma AGP concentration as a sign of inflammation, or duration of pregnancy). The predictor and intermediate variables were selected either based on earlier literature (Brodsky, Christou 2004) or because our own initial analyses had documented an association between them and newborn size (Harjunmaa et al. 2015, Stewart et al. 2015). By doing this, we were able to see which variables attenuated the effect of others, and this allowed us to determine the pathways though which the independent variables were associated with the dependent variables. In the final regression models, we also included the intervention that the study participants had received during the intervention trial, even if the intervention was not associated with any of the primary outcomes.

We used ordinary least squares regression and logistic regression with multiple imputed data to estimate regression coefficients for continuous variables and odds ratios for dichotomous variables, respectively, when estimating associations between variables in simple (i.e., bivariate) and multivariable regression models. For each outcome, we created pathway models based on the information from the simple and multivariable regression models.

We used multiple imputed data (50 imputations), imputed based on chained equation methods (van Buuren et al. 1999) for all ordinary least squares regression and logistic regression analyses. Of the 1,391 women who were enrolled in the study, 1,379 (99.1%) were included in the pathway analysis for duration of pregnancy and 1,179 (84.8%) were included in the pathway analysis for the newborn size outcomes. For duration of pregnancy, we excluded women with twin pregnancies. We assumed women lost to follow-up before delivery were singleton pregnancies, and we used multiple imputation to impute duration of pregnancy for all participants with singleton pregnancies with missing data. For newborn anthropometrics, we excluded twins and those who did not have 1-month measurement done. We used multiple imputation to impute values for participants who had a measurement at 1 month, but that was actually done more than 6 weeks after delivery. We included in the imputation model variables describing maternal enrollment characteristics (age, parity, height, education, household food insecurity access scale); maternal nutrition (BMI and blood Hb at enrollment, average weekly weight gain during pregnancy); maternal infections (HIV, malaria at enrollment, UTIs and vaginal trichomoniasis at 36 gw, periapical oral infections after delivery); maternal inflammation and stress (maternal AGP concentration at enrollment and at 36 gw; salivary cortisol concentration at enrollment, 28 gw, and 36 gw); placental size, infection, and inflammation (placental weight, placental malaria, severe chorioamnionitis); duration of pregnancy; newborn size (birth weight, LAZ, WAZ, HCZ, MUAC); and study intervention group. If any of the maternal characteristics had missing values, those were imputed at the same time, using all variables listed above.

We estimated coefficients for the pathway models using SEM, which allowed us to include variables as both endogenous (outcome) and exogenous (predictor) in the same model. We used the maximum likelihood method with missing values to estimate model parameters in SEM (Allison 2003). In the final SEM, we included pathways that were statistically significant at level $P<0.05$ in simple and multivariable regression models, even though some of the associations in SEM were $P\geq0.05$ (Kline 2011). We

estimated model goodness of fit index root mean square error of approximation (RMSEA), which adjusts for the number of paths estimated in the model (DiLalla 2008). An RMSEA score of 0 indicates perfect fit, scores <0.05 are considered to be a good fit, and scores <0.08 are considered to be adequate fit (Jaccard and Wan 1996). In SEM, we used only continuous endogenous variables because SEM do not allow endogenous variables to be dichotomous. This limited our models a bit because we could not estimate parameters for pathways going to maternal malaria, HIV and primiparity. We indicate this with dashed line in our pathway graphs and show the direction of association, as indicated by the corresponding simple regression model.

When trying to determine pathways between different variables, our aim was to find associations that were independent from the other measurements. When modelling the pathways to newborn LAZ, WAZ, and HCZ, we were primarily interested in fetal growth velocity and hence controlled the models for duration of pregnancy. We were interested in newborn weight as a predictor of childhood wasting and mortality (Katz et al. 2013) and length as a predictor of subsequent childhood growth stunting (Espo et al. 2002). To describe and visualize the predictors of newborn length (linear growth) and "thickness" or "robustness" (ponderal growth) separately, we included LAZ in the models for newborn WAZ. In essence, we were thus modeling newborn weight-for-length, but in a way that separated the contributions of linear and ponderal growth on newborn weight. For consistency, we also controlled for newborn LAZ when we modeled newborn HCZ.

To make it easier to interpret the results of the models, we summarized the models in illustrations showing the pathways leading to each of the four birth outcomes (Section 3.4). The arrows going to the most central variable (i.e., the main outcomes: duration of pregnancy, LAZ, WAZ, or HCZ) describe the absolute change in that outcome (weeks for duration of pregnancy, z-scores for anthropometric indices). Arrows going to any other continuous variable in the model describe the change in standardized values (mean 0, SD 1). We did not calculate the total effects (sum of direct and indirect effects) of different variables in the model. Since dichotomous variables could not be included in the SEM analysis as outcome variables, we indicated this with a dashed line in our pathway graphs and established the direction of association from regression models.

3. Results

Of the 1,391 women who were enrolled in the iLiNS-DYAD-M study, 1,379 (99.1%) were included in the analysis of duration of pregnancy and 1,179 (84.8%) in the analysis of newborn size. The reasons for exclusion were twin pregnancy (12 subjects) and missed newborn anthropometric visit (200 subjects). The included and excluded participants in the analysis of newborn size had similar baseline characteristics, except that, on average, the included participants had a lower BMI at enrollment (22.1 vs. 22.7, P=0.005), tended to be older (25 vs. 24, P=0.002), had a higher proxy for socioeconomic status (SES) (0.30 vs. −0.04, P<0.001), and a smaller proportion of them were primiparous (19.5% vs. 35.1%, P<0.001) (Table A-1).

Among the included participants for regression analyses, the number of originally missing values that were substituted with values obtained by multiple imputation ranged from 0 to 413 (0.0% to 29.9%) per variable (Table A-2).

3.1 Bivariate Associations between Various Predictor Variables

Most of the studied variables were strongly associated with each other. Table A-3 summarizes these results by listing all the individual variables that were significantly (P<0.05) or marginally (0.05≤P<0.10) associated with each of the studied predictors in bivariate analyses.

Full analysis details (with regression coefficients or odds ratios and P-values) for all bivariate associations are presented in Table A-4.

3.2 Multivariable Regression Models: Predictors of Predictors

In the series of multivariable regression models created to determine the direct and indirect predictors (i.e., "the predictors of predictors") of the duration of pregnancy, newborn LAZ, WAZ, and HCZ, most of the maternal characteristics were independently associated with several other variables, as expected.

Full results from these analyses are shown in Table A-5.

3.3 Multivariable Regression Models: Predictors of Reduced Duration of Pregnancy or Intrauterine Growth Restriction

The results from the multivariable regression models built for each birth outcome of focus (i.e., duration of pregnancy, LAZ, WAZ, and HCZ) by adding the predictor variables into the model for each outcome, one by one, with the most distal predictors entered into the model first and the most proximal predictors entered into the model last, are shown in Table A-6 through Table A-9. The results from these analyses are summarized below, by birth outcome.

3.3.1 Duration of Pregnancy

Maternal blood Hb concentration at enrollment, peripheral blood malaria parasitemia at enrollment, presence of periapical oral infections, salivary cortisol concentration at 36 gw, placental weight, and severe chorioamnionitis were all independently associated (P<0.05) with the duration of pregnancy in a model with all predictor variables included (Table A-6, Model 17).

Maternal height was associated with the duration of pregnancy in initial models with fewer explanatory variables, but the association disappeared when placental weight was included in the model (Table A-6,

Models 9–13). UTI and trichomoniasis were associated with the duration of pregnancy in earlier models, but the associations were attenuated when cortisol concentration and chorioamnionitis were added to the model. The association between weekly weight gain and duration of pregnancy became attenuated and finally disappeared when periapical oral infections, UTI, and trichomoniasis were added to the model. Maternal BMI at enrollment was associated with the duration of pregnancy only through placental weight.

Maternal age at enrollment, primiparity, HIV infection, plasma AGP concentration at enrollment, and signs of malaria infection in the placenta were not directly associated with the duration of pregnancy in any of the models, nor was the dietary intervention given to the mother during pregnancy (Table A-6).

3.3.2 Newborn Length-for-Age Z-Score

Maternal primiparity, height, weight gain during pregnancy, HIV infection (P=0.052), presence of periapical oral infections, maternal plasma AGP concentration at enrollment, placental weight, and duration of pregnancy were all independently associated with newborn LAZ (Table A-7, Model 18).

Maternal age, blood Hb concentration, and peripheral blood malaria parasitemia at enrollment were associated with newborn LAZ in initial models, but these associations disappeared when maternal primiparity or duration of pregnancy was included in the model (Table A-7, Models 2 and 17).

Maternal BMI at enrollment, UTI, trichomoniasis, salivary cortisol concentration, signs of malaria infection in the placenta, severe chorioamnionitis, and the dietary intervention given to the mother during pregnancy were not associated with newborn LAZ in any of the models (Table A-7).

3.3.3 Newborn Weight-for-Age Z-Score

Maternal primiparity, maternal BMI at enrollment, weight gain during pregnancy, maternal plasma AGP concentration at enrollment, placental weight, duration of pregnancy, and newborn LAZ were all independently associated with newborn WAZ (Table A-8, Model 19).

Maternal age was associated with newborn WAZ in initial models, but the association disappeared when maternal primiparity was included in the model (Table A-8, Model 2). Similar loss of an initially documented association with newborn WAZ was observed for many variables when new ones were entered into the models. For example, the addition of maternal plasma AGP concentration eliminated the association between newborn WAZ and maternal HIV infection (Table A-8, Model 13). The addition of the duration of pregnancy eliminated the association of newborn WAZ with maternal blood Hb concentration at enrollment and weakened that with maternal UTI (Table A-8, Model 17). The addition of newborn LAZ into the model eliminated the association of newborn WAZ with maternal height, peripheral blood malaria parasitemia at enrollment, presence of periapical oral infections, and UTI (Table A-8, Model 18).

Maternal trichomoniasis, salivary cortisol concentration at 36 gw, signs of malaria infection in the placenta, severe chorioamnionitis, and the dietary intervention given to the mother during pregnancy were not associated with newborn WAZ in any of the models (Table A-8).

3.3.4 Newborn Head Circumference-for-Age Z-Score

Maternal BMI at enrollment, plasma AGP concentration at enrollment, placental weight, duration of pregnancy, and newborn LAZ were all independently associated with newborn HCZ (Table A-9, Model 19).

Maternal age was associated with newborn HCZ in initial models, but the association disappeared when maternal primiparity was included in the model (Table A-9, Model 2). Similarly, the addition of maternal blood Hb concentration at enrollment and weight gain during pregnancy eliminated the association between newborn HCZ and primiparity (Table A-9, Models 4–6). The addition of newborn LAZ into the model eliminated the association of newborn HCZ with maternal height, maternal weight gain during pregnancy, maternal peripheral blood malaria parasitemia at enrollment, and presence of periapical oral infections (Table A-9, Model 18).

Maternal blood Hb concentration at enrollment, HIV infection, UTI, trichomoniasis, salivary cortisol concentration at 36 gw, signs of malaria infection in the placenta, severe chorioamnionitis, and the dietary intervention given to the mother during pregnancy were not associated with newborn HCZ in any of the models (Table A-9).

Table 3.3-1 provides a summary of the multivariable regression models for each of the outcomes, described above. The models were used for drawing the pathway maps presented in Section 3.4.

Table 3.3-1. Final Multivariable Regression Models for the Determinants of Pregnancy Duration and Newborn Size

	Duration of pregnancy[a]		Newborn LAZ[b]		Newborn WAZ[c]		Newborn HCZ[d]	
Predictor variable	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**
Maternal age	0.002	0.897	0.002	0.749	0.001	0.885	0.001	0.782
Maternal primiparity	−0.139	0.559	−0.280	**0.002**	−0.135	**0.027**	0.092	0.246
Maternal height	0.006	0.656	0.040	**<0.001**	0.004	0.277	−0.003	0.491
Maternal BMI at enrollment	−0.048	*0.089*	0.014	0.194	0.019	**0.009**	0.024	**0.009**
Maternal Hb at enrollment	0.017	**0.001**	0.001	0.732	0.002	0.220	−0.003	0.117
Maternal weekly weight gain	0.387	0.620	0.791	**0.007**	0.518	**0.008**	0.238	0.346
Maternal HIV infection	0.014	0.954	−0.169	*0.052*	0.044	0.459	0.105	0.171
Maternal malaria infection at enrollment	−0.433	**0.018**	−0.087	0.197	−0.078	*0.091*	−0.089	0.139
Maternal periapical infections (diagnosed after delivery)	−0.585	**0.028**	−0.230	**0.002**	−0.024	0.645	−0.058	0.366
Maternal UTI (diagnosed after delivery)	−1.151	*0.067*	−0.263	**0.183**	−0.174	0.191	0.140	0.394
Maternal trichomoniasis (diagnosed after delivery)	−0.465	0.125	−0.005	0.955	−0.077	0.235	0.001	0.989
Maternal salivary cortisol concentration at 36 gw	−0.125	**0.013**	0.017	*0.089*	0.001	0.852	−0.002	0.840
Maternal plasma AGP concentration at enrollment	−0.109	0.743	−0.393	**0.002**	−0.224	**0.009**	−0.235	**0.032**
Placental weight (g)	0.007	**<0.001**	0.002	**<0.001**	0.002	**<0.001**	0.002	**<0.001**
Placental malaria infection	0.206	0.392	−0.074	0.284	−0.009	0.858	0.028	0.662
Severe chorioamnionitis	−0.891	**0.043**	−0.090	0.365	−0.026	0.710	−0.062	0.450
Duration of pregnancy			0.221	**<0.001**	0.118	**<0.001**	0.142	**<0.001**
Newborn LAZ					0.517	**<0.001**	0.454	**<0.001**
Intervention group – MMN	0.013	0.942	0.048	0.486	−0.030	0.517	−0.007	0.906
Intervention group – LNS	0.008	0.963	0.053	0.444	0.004	0.932	0.016	0.797

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

[a] Results repeated from Table A-6, Model 17.

[b] Results repeated from Table A-7, Model 18.

[c] Results repeated from Table A-8, Model 19.

[d] Results repeated from Table A-9, Model 19.

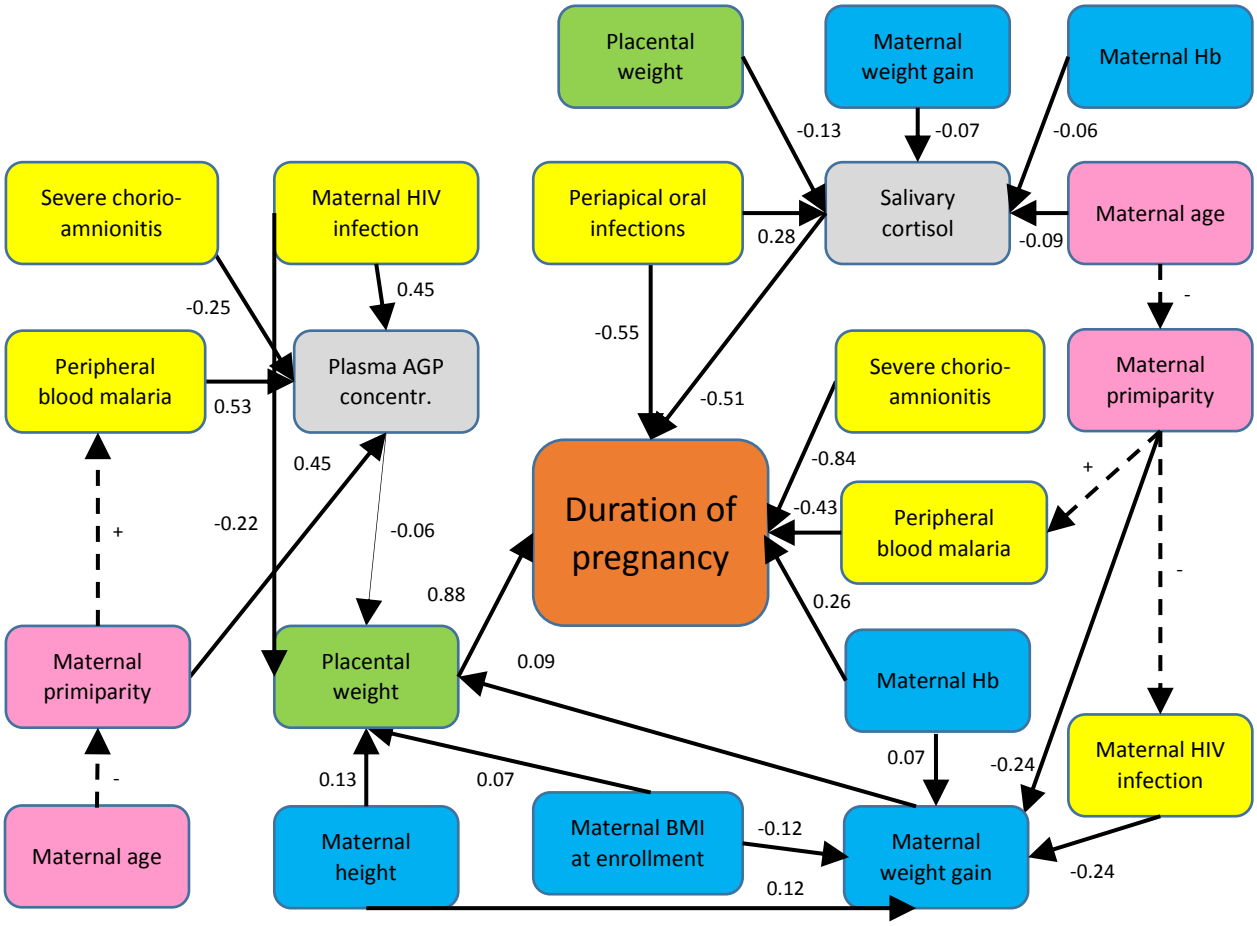
3.4 Pathway Analysis: Illustration of the Pathways Leading to Reduced Duration of Pregnancy or Intrauterine Growth Restriction

This section provides a summary and an illustration of the pathways leading to reduced duration of pregnancy, newborn LAZ, newborn WAZ, or newborn HCZ.

3.4.1 Duration of Pregnancy

The duration of pregnancy (Figure 3.4-1) was predicted by maternal blood Hb concentration at enrollment, peripheral blood malaria parasitemia at enrollment, presence of periapical oral infections, salivary cortisol concentration at 36 gw, placental weight, and severe chorioamnionitis. Placental weight, malaria parasitemia, and salivary cortisol concentration at 36 gw had their own predictors that were indirectly associated with the duration of pregnancy. Young maternal age and primiparity were associated with increased risk of malaria but decreased risk of HIV and periapical infections (results from regression models because SEM do not allow dichotomous endogenous variables). Goodness of fit statistic RMSEA for this model was 0.013, which can be considered a good fit.

Figure 3.4-1. Pathway Model: Determinants of the Duration of Pregnancy



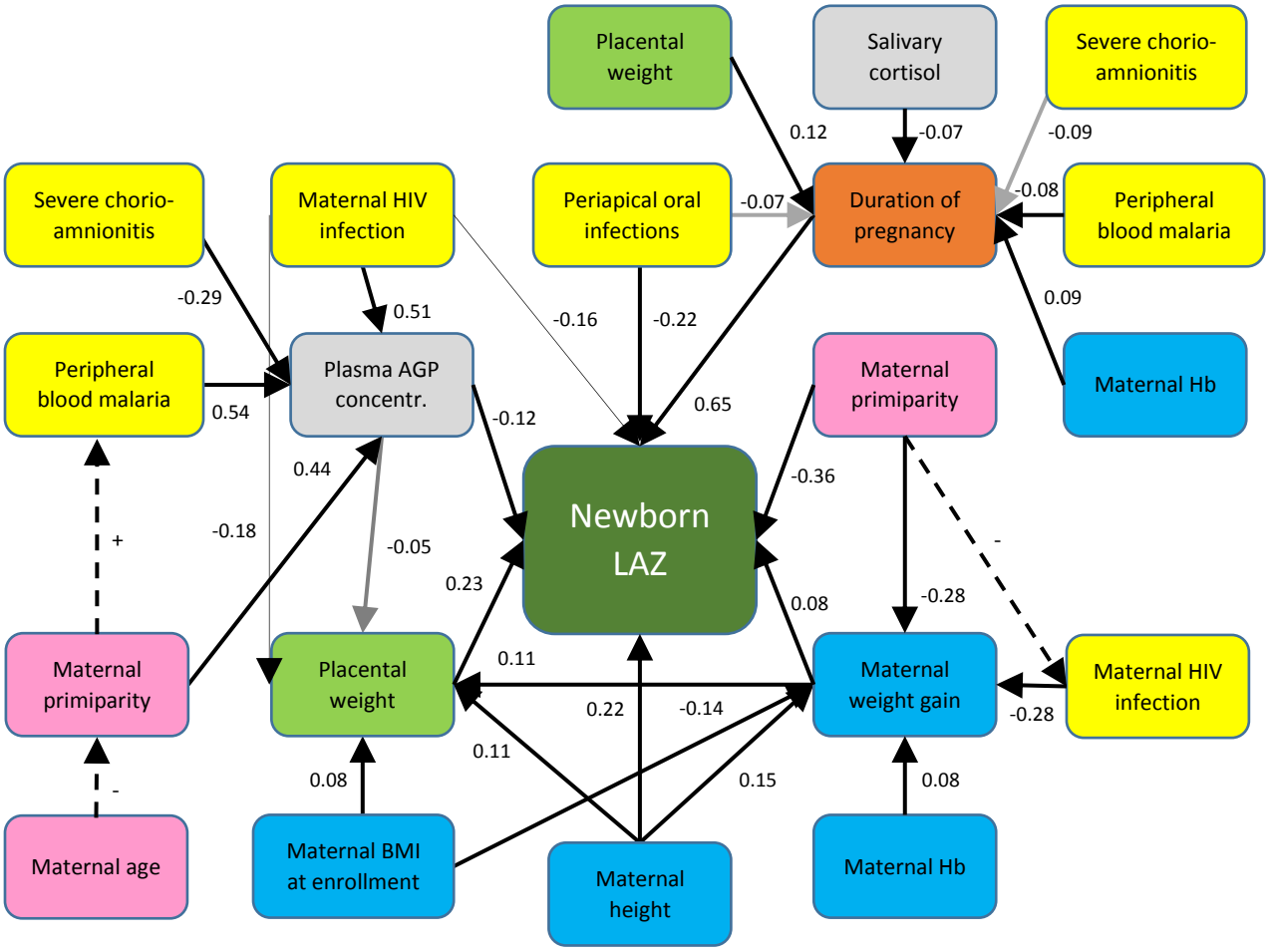
Legend: Number of observations used in the analysis: 1,379. In regression models used to define these pathways, all associations P<0.05. In SEM analyses, thick solid black lines represent P<0.05, thin solid black lines represent 0.05<P<0.1, and gray lines represent P≥0.1. Dashed lines indicate associations to dichotomous outcomes. The figures on the arrows going to the main outcome (duration of pregnancy) describe absolute change in the outcome (weeks); those on the arrows between other continuous variables describe change in standardized value (mean 0, SD 1). SEM do not allow dichotomous endogenous variables, so these associations come from regression models. ± indicates the direction of association.

Box color representation: Blue – maternal nutrition, Yellow – maternal infections, Pink – maternal constitutional variables, Gray – other variables, Green – pregnancy outcome, Orange – duration of pregnancy.

3.4.2 Newborn Length-for-Age Z-Score

Newborn LAZ (Figure 3.4-2) was predicted by the duration of pregnancy and thus also indirectly by its determinants. Additionally, newborn length was independently predicted by maternal primiparity and height, weight gain during pregnancy, HIV infection, periapical oral infections, and plasma AGP concentration at enrollment, as well as placental weight. Goodness of fit statistic RMSEA for this model was 0.036, which can be considered a good fit.

Figure 3.4-2. Pathway Model: Determinants of Newborn Length-for-Age Z-Score



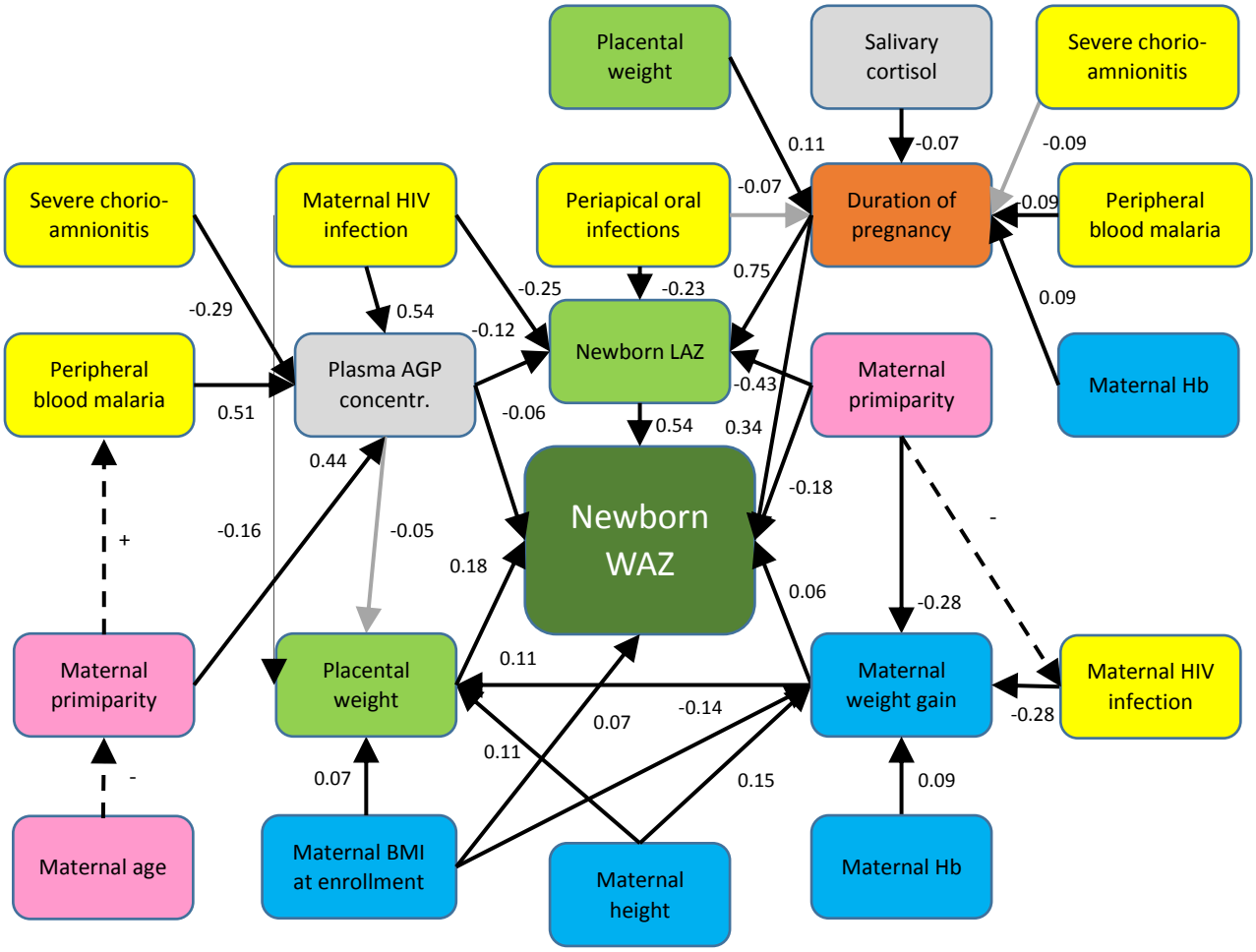
Legend: Number of observations used in the analysis: 1,179. In regression models used to define these pathways, all associations P<0.05. In SEM analyses, thick solid black lines represent P<0.05, thin solid black lines represent 0.05<P<0.1, and gray lines represent P≥0.1. Dashed lines indicate associations to dichotomous outcomes. The figures on the arrows going to the main outcome (newborn LAZ) describe absolute change in the outcome (z-score); those arrows between other continuous variables describe change in standardized value (mean 0, SD 1). SEM do not allow dichotomous endogenous variables, so these associations come from regression models. ± indicates the direction of association.

Box color representation: Blue – maternal nutrition, Yellow – maternal infections, Pink – maternal constitutional variables, Gray – other variables, Green – pregnancy outcome, Orange – duration of pregnancy, Dark green – main outcome.

3.4.3 Newborn Weight-for-Age Z-Score

Newborn WAZ (Figure **3.4-3**) was also predicted by the duration of pregnancy, maternal primiparity, weight gain during pregnancy, plasma AGP concentration at enrollment, and placental weight. Additionally, newborn weight was predicted by maternal BMI at enrollment and newborn LAZ. Maternal height, HIV infection, and periapical oral infections predicted newborn weight, but only if the model excluded newborn LAZ. When LAZ was entered into the model, these associations disappeared, i.e., maternal height, HIV infection, and periapical oral infections were associated with newborn weight only indirectly through their effect on newborn LAZ, but not directly. Goodness of fit statistic RMSEA for this model was 0.063, which can be considered an adequate fit.

Figure 3.4-3. Pathway Model: Determinants of Newborn Weight-for-Age Z-Score



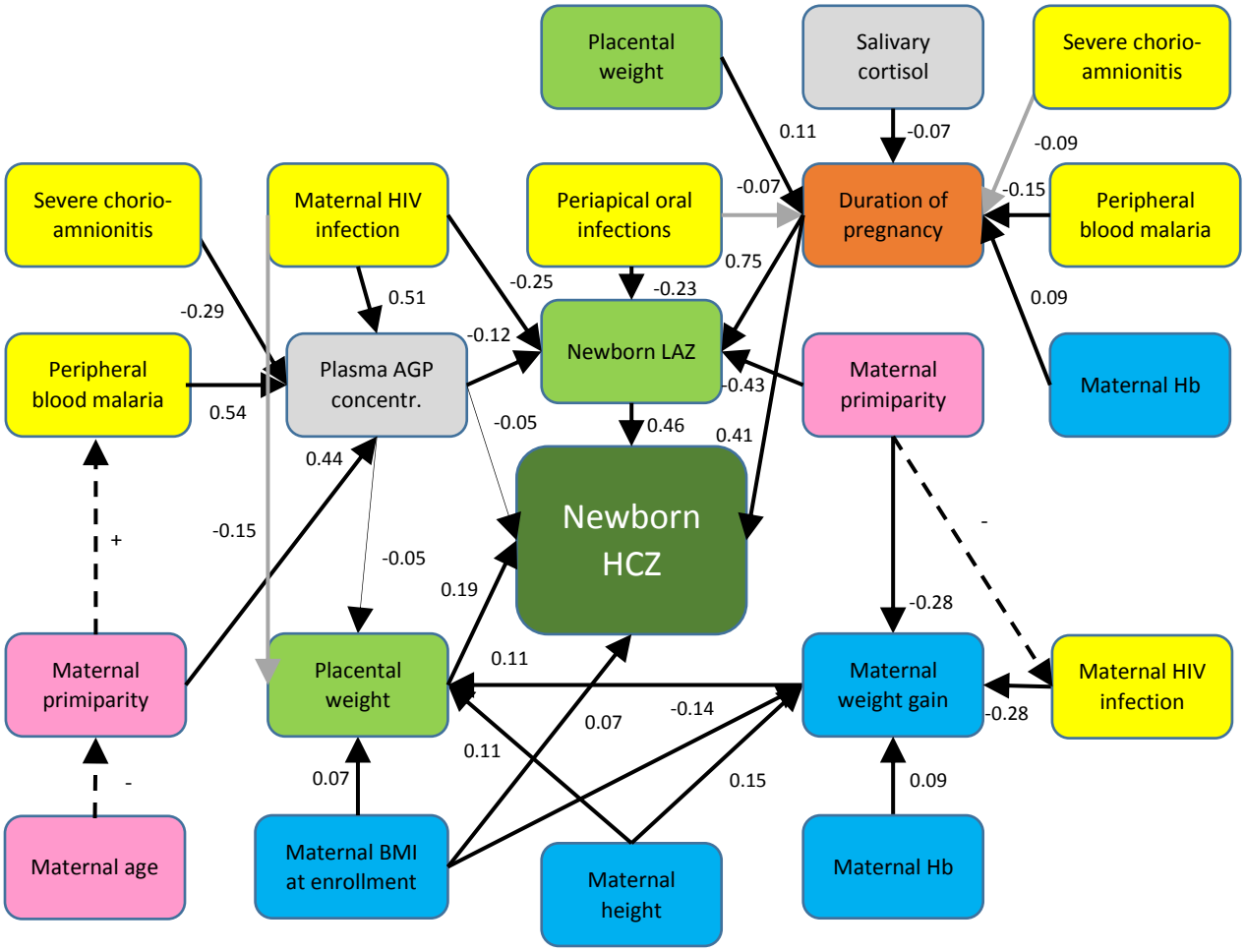
Legend: Number of observations used in the analysis: 1,179. In regression models used to define these pathways, all associations P<0.05. In SEM analyses, thick solid black lines represent P<0.05, thin solid black lines represent 0.05<P<0.1, and gray lines represent P≥0.1. Dashed lines indicate associations to dichotomous outcomes. The figures on the arrows going to the main outcome (newborn WAZ) describe absolute change in the outcome (z-score); those on the arrows between other continuous variables describe change in standardized value (mean 0, SD 1). SEM do not allow dichotomous endogenous variables, so these associations come from regression models. ± indicates the direction of association.

Box color representation: Blue – maternal nutrition, Yellow – maternal infections, Pink – maternal constitutional variables, Gray – other variables, Green – pregnancy outcome, Orange – duration of pregnancy, Dark green – main outcome.

3.4.4 Newborn Head Circumference-for-Age Z-Score

Newborn HCZ (Figure 3.4-4) was directly predicted by newborn LAZ, duration of pregnancy, maternal BMI at enrollment, plasma AGP concentration at enrollment, and placental weight. Maternal height, BMI, and weight gain during pregnancy, were associated with newborn HCZ indirectly, through their association with placental weight. Primiparity, placental AGP concentration, HIV infection, and periapical oral infections were associated with newborn HCZ through their association with newborn LAZ. Maternal peripheral malaria parasitemia at enrollment was associated with newborn HCZ indirectly through its association with the duration of pregnancy and newborn LAZ. In contrast to newborn LAZ and WAZ, newborn HCZ was not directly predicted by maternal age or primiparity or by maternal HIV infection, UTI, or vaginal trichomoniasis. Goodness of fit statistic RMSEA for this model was 0.062, which can be considered to be an adequate fit.

Figure 3.4-4. Pathway Model: Determinants of Newborn Head Circumference-for-Age Z-Score



Legend: Number of observations used in the analysis: 1,179. In regression models used to define these pathways, all associations P<0.05. In SEM analyses, thick solid black lines represent P<0.05, thin solid black lines represent 0.05<P<0.1, and gray lines represent P≥0.1. Dashed lines indicate associations to dichotomous outcomes. The figures on the arrows going to the main outcome (newborn HCZ) describe absolute change in the outcome (z-score); those on the arrows between other continuous variables describe change in standardized value (mean 0, SD 1). SEM do not allow dichotomous endogenous variables, so these associations come from regression models. ± indicates the direction of association.

Box color representation: Blue – maternal nutrition, Yellow – maternal infections, Pink – maternal constitutional variables, Gray – other variables, Green – pregnancy outcome, Orange – duration of pregnancy, Dark green – main outcome.

3.5 Comparison of the Associations: Differential Predictions by Exposure and Outcome

Placental size strongly predicted all the studied outcomes, i.e., the duration of pregnancy, as well as newborn LAZ, WAZ, and HCZ. Based on association analyses alone, it is of course difficult to determine the direction of causality, as placental growth could affect the duration of pregnancy and newborn size, shorter pregnancies could lead to smaller placentas at birth, and placental and newborn size could be driven by the same determinants without any causality between the two. A preliminary analysis indicated, however, that the mean placental weight remained rather constant toward the end of pregnancy, suggesting that, at least at this stage, the duration of pregnancy was not significantly influencing placental

size (Figure A-1). Hence, we have built our models on the assumption that duration of pregnancy and newborn size may be a function of placental weight, rather than the opposite.

Maternal plasma AGP concentration at enrollment, used as a proxy for the presence of an inflammatory reaction in the mother, independently predicted newborn LAZ, WAZ, and HCZ, but not the duration of pregnancy. The association was strongest with LAZ, second strongest with WAZ, and weakest with HCZ. Maternal plasma AGP concentration itself was predicted by maternal primiparity, maternal peripheral blood malaria parasitemia, HIV infection, and chorioamnionitis, but not by periapical infections.

Maternal salivary cortisol concentration at 36 gw, used as a proxy for maternal stress reaction during pregnancy, predicted the duration of pregnancy, but not directly newborn size. Maternal salivary cortisol concentration at 36 gw was predicted by maternal age, maternal blood Hb concentration, weight gain during pregnancy, placental size, and periapical infections, but not by other maternal infections.

Of the indicators of maternal nutritional status, maternal height (probably mostly a constitutional characteristic, but maybe also an indicator of maternal stunting) was associated with newborn LAZ. Maternal blood Hb concentration at enrollment was associated with the duration of pregnancy, but not directly with any of the birth size indicators. Maternal BMI at enrollment was associated with newborn WAZ and HCZ, but not with the duration of pregnancy or newborn LAZ. Maternal weight gain during pregnancy was associated with newborn LAZ and WAZ (even after adjustment for LAZ), but not with the duration of pregnancy or newborn HCZ.

Of maternal infections, periapical oral infections independently predicted both the duration of pregnancy and newborn LAZ. HIV infection predicted newborn LAZ directly and duration of pregnancy indirectly, through its association with maternal plasma AGP concentration and placental size. Maternal malaria at enrollment and severe chorioamnionitis had a direct association with the duration of pregnancy and an indirect one with newborn LAZ, through both the duration of pregnancy and maternal plasma AGP concentration. Of the infections, HIV was also associated with lower maternal weight gain, which in turn was associated with lower newborn LAZ (and WAZ).

When adjusted for newborn LAZ, none of the studied infections was associated with newborn WAZ or HCZ. There was, however, an indirect association between infections and newborn WAZ and between infections and HCZ, as these latter outcomes were predicted by newborn LAZ, which in turn was strongly associated with newborn WAZ and HCZ.

Of maternal constitutional factors, young age and primiparity were associated with lower weight gain in pregnancy and increased risk of malaria, but decreased risk of HIV infection or periapical oral infections. Because of these opposite associations with variables that were “intermediate” on the pathway to birth outcomes, young maternal age and primiparity were not associated with reduced duration of pregnancy, although primiparity was associated with newborn size.

4. Discussion

The goal of the study was to identify variables involved in the pathways leading to reduced duration of pregnancy and IUGR (i.e., LAZ, WAZ, and HCZ) in a rural Malawian setting. In a sample of 1,391 pregnant women, the duration of pregnancy was predicted by maternal peripheral malaria parasitemia at enrollment, severe chorioamnionitis, and the presence of periapical oral infections soon after birth. Additionally, pregnancy duration was predicted by maternal blood Hb concentration at enrollment, salivary cortisol concentration at 36 gw, and placental weight. All newborn size measurements were predicted by the duration of pregnancy, placental weight, and maternal inflammation. In addition, newborn LAZ was independently associated with maternal infections and weight gain during pregnancy, newborn WAZ was associated with maternal BMI at enrollment and weight gain during pregnancy, and newborn HCZ was associated with maternal BMI at enrollment. In the study sample, some differences in the pathways predicting linear, ponderal, and head growth in the fetal period were thus observed, with infections being most directly associated with length gain and the duration of pregnancy, maternal BMI and weight gain being important predictors of fetal weight gain, and fewer of the predictor variables being linked to head growth. For each outcome, however, there was a complex network of proximal and more distal determinants, so that all dimensions of fetal growth were ultimately associated both with maternal nutritional status and with variables reflecting infection, inflammation, and stress, directly or indirectly.

The methodological strengths of the study included a prospective study design, comprehensive data collection that included both clinical and laboratory variables, and rigorous quality assurance in data collection. Internal validity could have been compromised by missing data, the delay in anthropometric measurements of some participants, and the choice of modeling technique and the variables included in the pathway analyses. We believe these factors did not significantly bias our conclusions because participants with missing values typically had similar enrollment characteristics to those who provided data, we used multiple imputations to estimate the missing values in regression models, we used the maximum likelihood method in SEM to account for the missing data, and the results were robust to several sensitivity analyses. We used SEM to examine relationships among many variables simultaneously and to see how the hypothesized models of relationships from stepwise regression models fit the data (DiLalla 2008). We selected variables used in the models based on results of Ashorn et al. (2017b) and earlier knowledge. Therefore, we conclude that the findings are valid and representative and can be used to infer causal pathways to adverse pregnancy outcomes in the population from which the sample was drawn.

Maternal nutrition, reproductive tract infections, chorioamnionitis, malaria, inflammation, and stress have been associated with reduced duration of pregnancy in low-income settings in previous studies (Goldenberg et al. 2008). Determinants of IUGR, on the other hand, can be categorized into maternal, placental, and fetal factors (Brodsky and Christou 2004). Within these categories, maternal factors associated with IUGR have included vascular disorders, hypercoagulable states (such as antiphospholipid antibody syndrome), chronic hypoxia, undernutrition, and uterine malformations. Placental factors comprise various pathologies that interfere with placental function, and fetal factors include genetic aberrations; multiple gestation; and infections, such as malaria, HIV, and other congenital viral infections (Resnik 2002, Brodsky and Christou 2004, Hendrix and Berghella 2008). Our results corroborate these earlier findings and provide a concept map of pathways leading to birth outcomes in one rural population in sub-Saharan Africa. Because of the similarity in the identified determinants in our setting and those observed for earlier cohorts, it is likely that maternal nutrition, infection, inflammation, and stress form some kind of a complex network in other low-income settings as well. However, in the absence of

publications reporting similar pathway analyses, it is impossible to draw broader conclusions on whether the processes leading to adverse birth outcomes are similar or vary across settings.

There are several different possible mechanisms underlying the negative associations between maternal infections and duration of pregnancy. First, a local inflammatory response can weaken amniotic membranes and cause their premature rupture (Goldenberg et al. 2008). Additionally, inflammation typically activates prostaglandin synthesis, which may lead to increased contractibility of the uterus and softening and shortening of the cervix, thus inducing preterm labor (Challis et al. 2000). On the other hand, infection-related restriction of fetal linear growth can be potentially explained by inflammation-induced reduction in placental vascularization and function and a disturbance in growth-hormone mediated elongation of long bones (Boeuf et al. 2013, Conroy et al. 2013).

Evidence for the infection-related placental insufficiency pathway comes from both human studies and animal experiments. For instance, in a case control study of 492 pregnant Malawian women, placental transfer of selected amino acids was lower among women who had placental malaria and a local inflammatory response than women who had no malaria or no major inflammatory reaction (Boeuf et al. 2013). Women with placental malaria had also a higher mean plasma concentration of complement component C5a, which is an important mediator of human inflammatory response. Maternal plasma C5a concentration was positively associated with the risk of delivering a small-for-gestational-age baby and negatively correlated with maternal plasma concentration of several growth factors involved in the vascularization of the placenta (Conroy et al. 2013). In a murine model, placental malaria was characterized by increased C5a expression and reduced vascularization of the placenta. When C5a binding to its receptor was prevented by antibodies or genetic modification of the host receptor, the mice still developed malaria, but they exhibited fewer disturbances in fetoplacental blood vessel development, reduced placental vascular resistance, and improved fetal growth and survival (Conroy et al. 2013).

In addition to its effects on placental vascularization and function, systemic inflammation has been shown to alter a hormonal pathway that drives the elongation of long bones in human fetuses and children. In a normal situation, the pituitary gland secretes growth hormone, which stimulates the expression of a secondary hormone called insulin like growth factor 1 (IGF-1) in the liver and other target tissues (Le Roith et al. 2001). Although growth hormone also has a direct effect on bone elongation, the major share of linear growth is driven by IGF-1, which stimulates chondrocyte proliferation at the growth plates. Both animal and human studies have indicated that systemic inflammation is characterized by increased plasma concentration of cytokines IL-1, IL-6, and TNF-alpha (Klasing and Johnstone 1991, Walters and Griffiths 2009, Bolton et al. 2012). These molecules can cause chondrocyte death at the growth plates and also interrupt specific steps in the growth hormone-induced JAK/STAT signal transduction pathway in liver cells, leading to reduced expression of IGF-1 and subsequent linear growth failure (Walters and Griffiths 2009). Further evidence for the importance of IGF-1 in fetal growth and growth restriction comes from human genetic studies showing associations between IGF-1 gene polymorphism and birth size, with severe fetal growth restriction being associated with major aberrations in the IGF-1 gene (Woods et al. 1996, Klammt et al. 2011, Netchine et al. 2011). Finally, in murine and rabbit models, overexpression of the IGF-1 gene in placental tissue has prevented IUGR in the fetus (Jones et al. 2013, Keswani et al. 2015).

Whereas maternal infections and inflammation were important determinants of the duration of pregnancy and newborn LAZ in the studied cohort, the pathways to duration of pregnancy and newborn WAZ also always included maternal undernutrition, stress, and certain constitutional factors like age and parity. Because of this complex network of adverse exposures, it is not surprising that single-pronged nutritional or infection-targeted antenatal interventions have had at best modest impacts on fetal growth or duration

of pregnancy in low-income settings (Bhutta et al. 2013, Ashorn et al. 2015). For greater impact, it is likely that more-comprehensive multipronged interventions will be needed, to ensure good nutritional status for the mother both before and during pregnancy, prevention and treatment of a wide range of maternal infections, and reduction of maternal stress. For infection control, the current study suggests that maternal HIV infection, malaria, chorioamnionitis, and also oral infections should be targeted, but there is no reason to believe that this list of infections was exhaustive. Further studies should be conducted to identify other viral, parasitic, or bacterial infections that elicit systemic inflammation in pregnant women and contribute to adverse birth outcomes in low-income settings.

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Appendix

Table A-1. Comparison of the Enrollment Characteristics of Participants Who Were Included and Excluded from the Pathway Analysis

Characteristic	Included[a] (n=1179)	Excluded (n=212)	P-value[b]
Mean (SD) BMI (kg/m²)	22.1 (2.8)	22.7 (2.9)	0.005
Mean (SD) maternal age, years	25 (6)	24 (6)	0.002
Mean (SD) maternal education (completed years at school)	4.0 (3.4)	4.3 (3.7)	0.340
Mean (SD) proxy for SES	0.30 (1.17)	−0.04 (0.97)	<0.001
Percentage of anemic women (Hb <100 g/L)	19.8%	25.6%	0.055
Percentage of primiparous women	19.5%	35.1%	<0.001
Percentage of women with a BMI <18.5	5.5%	4.7%	0.667
Percentage of women with a positive HIV test	13.4 %	16.1 %	0.358
Percentage of women with positive malaria test (RDT)	22.9 %	25.0 %	0.500

[a] Those participants with singleton pregnancies who completed the 1-week postpartum visit with anthropometric data.
[b] P-values were obtained from t-test (comparison of means) or Fisher's exact test (comparison of proportions).

Table A-2. List of Variables Included in the Pathway Analyses

Category and variable	Variable type	# imputed	% imputed
Maternal enrollment characteristics			
Maternal age	continuous	0	0.0%
Maternal primiparity	dichotomous	3	0.2%
Maternal height	continuous	5	0.4%
Maternal nutrition			
Maternal BMI at enrollment	continuous	9	0.7%
Maternal blood Hb concentration at enrollment	continuous	2	0.1%
Maternal weekly weight gain (kg/week)	continuous	2	0.1%
Maternal infections			
Maternal HIV infection	dichotomous	57	4.1%
Maternal peripheral blood malaria parasitemia at enrollment	dichotomous	25	1.8%
Maternal periapical oral infection	dichotomous	353	25.6%
Maternal UTI	dichotomous	167	12.1%
Maternal vaginal trichomoniasis	dichotomous	165	12.0%
Maternal inflammation and stress			
Maternal salivary cortisol concentration at 36 gw	continuous	336	24.4%
Maternal plasma AGP concentration at enrollment	continuous	8	0.6%
Placental size, infection, and inflammation			
Placental weight (g)	continuous	413	29.9%
Placental malaria infection	dichotomous	371	26.9%
Severe chorioamnionitis	dichotomous	389	28.2%
Duration of pregnancy and newborn size			
Duration of pregnancy	continuous	84	6.1%
Newborn LAZ	continuous	80	6.8%
Newborn WAZ	continuous	90	7.6%
Newborn HCZ	continuous	88	7.5%

Table A-3. Summary of Bivariate Associations among Various Maternal Characteristic and Birth Outcome Variables

This table provides a summary listing of the maternal characteristic and birth outcome variables that were significantly associated ($P<0.05$) or marginally associated ($0.05\leq P<0.10$) with each of the studied predictors in bivariate analysis. The studied predictors include both maternal characteristic variables and the birth outcome variables (i.e., duration of pregnancy and newborn LAZ, WAZ, and HCZ). Variables associated with the predictor at $0.05\leq P<0.10$ level in bivariate analysis are indicated in parentheses.

Maternal age 1. **Positive** association with variables: Maternal (height), BMI, blood Hb, weekly weight gain, HIV infection, periapical infections, newborn LAZ, newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, maternal peripheral blood malaria parasitemia, salivary cortisol, plasma AGP, placental malaria
Maternal primiparity 1. **Positive** association with variables: Maternal peripheral blood malaria parasitemia, plasma AGP, placental malaria 2. **Negative** association with variables: Maternal age, maternal height, BMI, blood Hb, weekly weight gain, HIV infection, periapical infections, duration of pregnancy, newborn LAZ, newborn WAZ, newborn HCZ
Maternal height 1. **Positive** association with variables: Maternal (age), weekly weight gain, placental weight, duration of pregnancy, newborn LAZ, newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, trichomoniasis
Maternal BMI at enrollment 1. **Positive** association with variables: Maternal age, blood Hb, (HIV infection), placental weight, (newborn LAZ), newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, weekly weight gain, peripheral blood malaria parasitemia, plasma AGP, placental malaria
Maternal Hb concentration at enrollment 1. **Positive** association with variables: Maternal age, BMI, weekly weight gain, duration of pregnancy, newborn LAZ, newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, HIV infection, peripheral blood malaria parasitemia, salivary cortisol, plasma AGP, placental malaria
Maternal weekly weight gain during pregnancy (kg/week) 1. **Positive** association with variables: Maternal age, maternal height, blood Hb, placental weight, duration of pregnancy, newborn LAZ, newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, BMI, HIV infection, peripheral blood malaria parasitemia, (trichomoniasis), salivary cortisol, placental malaria
Maternal HIV infection 1. **Positive** association with variables: Maternal age, (BMI), periapical infections, (UTI), trichomoniasis, plasma AGP 2. **Negative** association with variables: Maternal primiparity, blood Hb, weekly weight gain, placental weight, (duration of pregnancy), newborn LAZ
Maternal peripheral blood malaria parasitemia at enrollment (positive RDT) 1. **Positive** association with variables: Maternal primiparity, trichomoniasis, plasma AGP, placental malaria 2. **Negative** association with variables: Maternal age, BMI, blood Hb, weekly weight gain, periapical infections, duration of pregnancy, newborn LAZ, newborn WAZ, newborn HCZ
Maternal periapical oral infections (diagnosed after delivery) 1. **Positive** association with variables: Maternal age, HIV infection, (trichomoniasis), salivary cortisol, (severe chorioamnionitis) 2. **Negative** association with variables: Maternal primiparity, peripheral blood malaria parasitemia, (plasma AGP), placental malaria, duration of pregnancy, newborn LAZ, (newborn HCZ)

Maternal UTI (diagnosed after delivery) 1. **Positive** association with variables: Maternal (HIV infection), severe chorioamnionitis 2. **Negative** association with variables: Duration of pregnancy, newborn LAZ, newborn WAZ
Maternal trichomoniasis (diagnosed after delivery) 1. **Positive** association with variables: Maternal HIV infection, peripheral blood malaria parasitemia, (periapical infections), plasma AGP, placental malaria 2. **Negative** association with variables: Maternal height, (weekly weight gain), (placental weight), duration of pregnancy, newborn LAZ, newborn WAZ, (newborn HCZ)
Maternal salivary cortisol concentration at 36 gw 1. **Positive** association with variables: Maternal periapical infections, (plasma AGP) 2. **Negative** association with variables: Maternal age, blood Hb, weekly weight gain, placental weight, duration of pregnancy, newborn WAZ, newborn HCZ
Maternal plasma alpha glycoprotein (AGP) concentration at enrollment 1. **Positive** association with variables: Maternal primiparity, HIV infection, peripheral blood malaria parasitemia, trichomoniasis, (salivary cortisol), placental malaria 2. **Negative** association with variables: Maternal age, BMI, blood Hb, (periapical infections), placental weight, severe chorioamnionitis, duration of pregnancy, newborn LAZ, newborn WAZ, newborn HCZ
Placental weight (g) 1. **Positive** association with variables: Maternal height, BMI, weekly weight gain, duration of pregnancy, newborn LAZ, newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal HIV infection, (trichomoniasis), salivary cortisol, plasma AGP
Placental malaria infection 1. **Positive** association with variables: Maternal primiparity, peripheral blood malaria parasitemia, trichomoniasis, plasma AGP 2. **Negative** association with variables: Maternal age, BMI, blood Hb, weekly weight gain, periapical infections, newborn LAZ, newborn WAZ, newborn HCZ
Severe chorioamnionitis 1. **Positive** association with variables: Maternal (periapical infections), UTI 2. **Negative** association with variables: Maternal plasma AGP, duration of pregnancy
Duration of pregnancy (gestation weeks) 1. **Positive** association with variables: Maternal height, blood Hb, weekly weight gain, placental weight, newborn LAZ, newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, (HIV infection), peripheral blood malaria parasitemia, periapical infections, UTI, trichomoniasis, salivary cortisol, plasma AGP, severe chorioamnionitis
Newborn LAZ 1. **Positive** association with variables: Maternal age, maternal height, (BMI), blood Hb, weekly weight gain, placental weight, duration of pregnancy, newborn WAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, HIV infection, peripheral blood malaria parasitemia, periapical infections, UTI, trichomoniasis, plasma AGP, placental malaria
Newborn WAZ 1. **Positive** association with variables: Maternal age, maternal height, BMI, blood Hb, weekly weight gain, placental weight, duration of pregnancy, newborn LAZ, newborn HCZ 2. **Negative** association with variables: Maternal primiparity, peripheral blood malaria parasitemia, UTI, trichomoniasis, salivary cortisol, plasma AGP, placental malaria
Newborn HCZ 1. **Positive** association with variables: Maternal age, maternal height, BMI, blood Hb, weekly weight gain, placental weight, duration of pregnancy, newborn LAZ, newborn WAZ 2. **Negative** association with variables: Maternal primiparity, peripheral blood malaria parasitemia, (periapical infections), (trichomoniasis), salivary cortisol, plasma AGP, placental malaria

Table A-4. Bivariate Associations between Variables Used in the Pathway Analyses

	Maternal age		Maternal primiparity		Maternal height		Maternal BMI at enrollment	
Predictor variable	**B-coefficient**	**P-value**	**Odds ratio**	**P-value**	**B-coefficient**	**P-value**	**B-coefficient**	**P-value**
Maternal age at enrollment	NA	NA	0.583	**<0.001**	0.046	*0.064*	0.077	**<0.001**
Maternal primiparity	−7.852	**<0.001**	NA	NA	−0.764	**0.038**	−0.513	**0.005**
Maternal height at enrollment	0.054	*0.064*	0.976	**0.039**	NA	NA	0.000	0.971
Maternal BMI at enrollment	0.363	**<0.001**	0.933	**0.006**	0.002	0.971	NA	NA
Maternal blood Hb concentration at enrollment	0.054	**<0.001**	0.969	**<0.001**	−0.008	0.385	0.020	**<0.001**
Maternal weekly weight gain	4.332	**0.009**	0.079	**<0.001**	7.247	**<0.001**	−3.199	**<0.001**
Maternal HIV infection	3.151	**<0.001**	0.278	**<0.001**	−0.057	0.901	0.446	*0.058*
Maternal peripheral blood malaria parasitermia at enrollment	−3.466	**<0.001**	3.444	**<0.001**	−0.036	0.910	−0.676	**<0.001**
Maternal periapical oral infection (diagnosed after delivery)	3.682	**<0.001**	0.334	**<0.001**	−0.099	0.814	0.207	0.333
Maternal UTI (diagnosed after delivery)	−0.461	0.650	1.599	0.184	−0.875	0.359	0.600	0.212
Maternal vaginal trichomoniasis (diagnosed after delivery)	−0.539	0.353	1.021	0.931	−1.755	**0.001**	−0.132	0.616
Maternal salivary cortisol concentration at 36 gw	−0.133	**0.022**	1.028	0.252	−0.067	0.230	0.005	0.853
Maternal plasma AGP concentration at enrollment	−4.115	**<0.001**	8.291	**<0.001**	−0.635	0.296	−1.018	**0.001**
Placental weight (g)	0.002	0.341	0.999	0.119	0.007	**<0.001**	0.002	**0.034**
Placental malaria infection	−3.682	**<0.001**	5.220	**<0.001**	−0.328	0.340	−0.750	**<0.001**
Severe chorioamnionitis	0.823	0.150	0.742	0.240	−0.503	0.349	0.431	0.144
Duration of pregnancy	0.057	0.325	0.959	**0.046**	0.127	**0.018**	−0.023	0.394
Newborn LAZ	0.548	**0.001**	0.685	**<0.001**	1.343	**<0.001**	0.124	*0.096*
Newborn WAZ	0.800	**<0.001**	0.619	**<0.001**	1.202	**<0.001**	0.257	**0.001**
Newborn HCZ	0.421	**0.010**	0.816	**0.002**	0.783	**<0.001**	0.232	**0.002**

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-4. Bivariate Associations between Variables Used in the Pathway Analyses (continued)

Predictor variable	Maternal Hb at enrollment		Maternal weekly weight gain		Maternal HIV infection		Maternal malaria infection at enrollment	
	B-coefficient	P-value	B-coefficient	P-value	Odds ratio	P-value	Odds ratio	P-value
Maternal age at enrollment	0.383	**<0.001**	0.001	**0.009**	1.081	**<0.001**	0.899	**<0.001**
Maternal primiparity	−8.264	**<0.001**	−0.024	**<0.001**	0.278	**<0.001**	3.444	**<0.001**
Maternal height at enrollment	−0.068	0.385	0.002	**<0.001**	0.998	0.901	0.999	0.910
Maternal BMI at enrollment	0.676	**<0.001**	−0.004	**<0.001**	1.054	*0.057*	0.912	**<0.001**
Maternal blood Hb concentration at enrollment	NA	NA	0.000	**0.003**	0.985	**0.002**	0.969	**<0.001**
Maternal weekly weight gain	13.023	**0.003**	NA	NA	0.085	**0.002**	0.218	**0.009**
Maternal HIV infection	−4.094	**0.002**	−0.024	**0.002**	NA	NA	0.843	0.326
Maternal peripheral blood malaria parasitermia at enrollment	−8.010	**<0.001**	−0.015	**0.009**	0.843	0.326	NA	NA
Maternal periapical oral infection (diagnosed after delivery)	0.195	0.869	−0.010	0.138	1.844	**0.001**	0.468	**<0.001**
Maternal UTI (diagnosed after delivery)	−2.855	0.284	−0.025	0.103	2.132	*0.055*	1.092	0.794
Maternal vaginal trichomoniasis (diagnosed after delivery)	1.242	0.418	−0.016	*0.061*	1.870	**0.008**	1.482	**0.037**
Maternal salivary cortisol concentration at 36 gw	−0.465	**0.004**	−0.003	**0.001**	1.019	0.455	1.001	0.945
Maternal plasma AGP concentration at enrollment	−9.373	**<0.001**	0.008	0.434	3.418	**<0.001**	13.281	**<0.001**
Placental weight (g)	−0.001	0.907	0.000	**0.001**	0.998	**0.016**	1.000	0.806
Placental malaria infection	−4.460	**<0.001**	−0.020	**0.001**	0.938	0.732	3.756	**<0.001**
Severe chorioamnionitis	−0.263	0.863	−0.005	0.538	1.141	0.607	1.054	0.797
Duration of pregnancy	0.686	**<0.001**	0.003	**0.002**	0.958	*0.083*	0.944	**0.003**
Newborn LAZ	1.707	**<0.001**	0.017	**<0.001**	0.821	**0.008**	0.780	**<0.001**
Newborn WAZ	2.452	**<0.001**	0.021	**<0.001**	0.878	0.100	0.700	**<0.001**
Newborn HCZ	1.045	**0.018**	0.013	**<0.001**	0.934	0.377	0.786	**<0.001**

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-4. Bivariate Associations between Variables Used in the Pathway Analyses (continued)

Predictor variable	Maternal periapical infections (as diagnosed after delivery)		Maternal UTI (as diagnosed after delivery)		Maternal trichomoniasis (as diagnosed after delivery)		Maternal salivary cortisol concentration at 36 gw	
	Odds ratio	P-value	Odds ratio	P-value	Odds ratio	P-value	B-coefficient	P-value
Maternal age at enrollment	1.100	**<0.001**	0.987	0.643	0.985	0.353	−0.037	**0.022**
Maternal primiparity	0.334	**<0.001**	1.599	0.184	1.021	0.931	0.302	0.249
Maternal height at enrollment	0.997	0.814	0.973	0.358	0.946	**0.001**	−0.021	0.230
Maternal BMI at enrollment	1.026	0.333	1.068	0.208	0.983	0.612	0.007	0.852
Maternal blood Hb concentration at enrollment	1.001	0.868	0.990	0.283	1.005	0.417	−0.018	**0.004**
Maternal weekly weight gain	0.349	0.139	0.074	0.102	0.184	*0.062*	−3.087	**0.001**
Maternal HIV infection	1.844	**0.001**	2.132	*0.055*	1.870	**0.008**	0.209	0.452
Maternal peripheral blood malaria parasitermia at enrollment	0.468	**<0.001**	1.092	0.794	1.482	**0.037**	0.016	0.940
Maternal periapical oral infection (diagnosed after delivery)	NA	NA	1.805	0.164	1.440	*0.092*	0.714	**0.007**
Maternal UTI (diagnosed after delivery)	1.805	0.164	NA	NA	1.894	0.190	−0.104	0.864
Maternal vaginal trichomoniasis (diagnosed after delivery)	1.440	*0.092*	1.894	0.190	NA	NA	0.376	0.308
Maternal salivary cortisol concentration at 36 gw	1.067	**0.010**	0.985	0.806	1.032	0.318	NA	NA
Maternal plasma AGP concentration at enrollment	0.600	*0.094*	1.688	0.391	2.643	**0.005**	0.741	*0.062*
Placental weight (g)	1.000	0.962	1.000	0.892	0.998	*0.051*	−0.004	**0.004**
Placental malaria infection	0.617	**0.004**	1.199	0.626	1.552	**0.027**	0.338	0.139
Severe chorioamnionitis	1.589	*0.053*	2.992	**0.007**	1.416	0.245	−0.064	0.853
Duration of pregnancy	0.930	**0.008**	0.901	**0.010**	0.929	**0.009**	−0.212	**0.002**
Newborn LAZ	0.856	**0.019**	0.685	**0.013**	0.820	**0.019**	−0.159	0.133
Newborn WAZ	0.906	0.159	0.651	**0.006**	0.770	**0.003**	−0.262	**0.020**
Newborn HCZ	0.883	*0.062*	0.863	0.389	0.850	*0.061*	−0.238	**0.027**

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-4. Bivariate Associations between Variables Used in the Pathway Analyses (continued)

Predictor variable	Maternal plasma AGP concentration at enrollment		Placental weight (g)		Placental malaria infection		Severe chorioamnionitis	
	B-coefficient	P-value	B-coefficient	P-value	Odds ratio	P-value	Odds ratio	P-value
Maternal age at enrollment	−0.007	**<0.001**	0.529	0.340	0.893	**<0.001**	1.021	0.152
Maternal primiparity	0.143	**<0.001**	−13.970	0.118	5.220	**<0.001**	0.742	0.240
Maternal height at enrollment	−0.001	0.296	2.605	**<0.001**	0.990	0.340	0.984	0.349
Maternal BMI at enrollment	−0.008	**0.001**	2.500	**0.034**	0.903	**<0.001**	1.052	0.139
Maternal blood Hb concentration at enrollment	−0.002	**<0.001**	−0.024	0.907	0.983	**<0.001**	0.999	0.864
Maternal weekly weight gain	0.054	0.434	108.739	**0.001**	0.129	**0.001**	0.574	0.538
Maternal HIV infection	0.087	**<0.001**	−24.398	**0.015**	0.938	0.732	1.141	0.607
Maternal peripheral blood malaria parasitermia at enrollment	0.156	**<0.001**	−1.724	0.806	3.756	**<0.001**	1.054	0.797
Maternal periapical oral infection (diagnosed after delivery)	−0.031	*0.092*	0.466	0.963	0.617	**0.004**	1.589	*0.053*
Maternal UTI (diagnosed after delivery)	0.036	0.390	−3.346	0.897	1.199	0.626	2.992	**0.007**
Maternal vaginal trichomoniasis (diagnosed after delivery)	0.068	**0.006**	−22.567	*0.050*	1.552	**0.027**	1.416	0.245
Maternal salivary cortisol concentration at 36 gw	0.005	*0.061*	−4.117	**0.003**	1.033	0.146	0.992	0.821
Maternal plasma AGP concentration at enrollment	NA	NA	−33.006	**0.022**	4.815	**<0.001**	0.324	**0.007**
Placental weight (g)	0.000	**0.021**	NA	NA	1.000	0.946	0.999	0.394
Placental malaria infection	0.098	**<0.001**	0.502	0.945	NA	NA	0.869	0.480
Severe chorioamnionitis	−0.063	**0.006**	−10.478	0.395	0.869	0.480	NA	NA
Duration of pregnancy	−0.005	**0.025**	11.121	**<0.001**	0.996	0.882	0.906	**0.014**
Newborn LAZ	−0.033	**<0.001**	28.962	**<0.001**	0.790	**<0.001**	0.894	0.211
Newborn WAZ	−0.043	**<0.001**	39.724	**<0.001**	0.748	**<0.001**	0.907	0.305
Newborn HCZ	−0.030	**<0.001**	34.847	**<0.001**	0.860	**0.013**	0.894	0.224

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-4. Bivariate Associations between Variables Used in the Pathway Analyses (Continued)

	Duration of pregnancy		Newborn LAZ		Newborn WAZ		Newborn HCZ	
Predictor variable	**B-coefficient**	**P-value**	**B-coefficient**	**P-value**	**B-coefficient**	**P-value**	**B-coefficient**	**P-value**
Maternal age at enrollment	0.013	0.325	0.019	**0.001**	0.024	**<0.001**	0.014	**0.011**
Maternal primiparity	−0.392	**0.045**	−0.506	**<0.001**	−0.560	**<0.001**	−0.258	**0.002**
Maternal height at enrollment	0.034	**0.018**	0.054	**<0.001**	0.042	**<0.001**	0.030	**<0.001**
Maternal BMI at enrollment	−0.024	0.394	0.021	*0.096*	0.036	**0.001**	0.036	**0.002**
Maternal blood Hb concentration at enrollment	0.022	**<0.001**	0.008	**<0.001**	0.010	**<0.001**	0.005	**0.018**
Maternal weekly weight gain	2.433	**0.002**	2.051	**<0.001**	2.129	**<0.001**	1.513	**<0.001**
Maternal HIV infection	−0.416	*0.082*	−0.265	**0.007**	−0.150	0.100	−0.085	0.377
Maternal peripheral blood malaria parasitermia at enrollment	−0.507	**0.003**	−0.321	**<0.001**	−0.393	**<0.001**	−0.294	**<0.001**
Maternal periapical oral infection (diagnosed after delivery)	−0.702	**0.008**	−0.205	**0.019**	−0.112	0.159	−0.155	*0.061*
Maternal UTI (diagnosed after delivery)	−1.540	**0.024**	−0.571	**0.014**	−0.592	**0.007**	−0.195	0.389
Maternal vaginal trichomoniasis (diagnosed after delivery)	−0.811	**0.011**	−0.270	**0.019**	−0.316	**0.003**	−0.210	*0.062*
Maternal salivary cortisol concentration at 36 gw	−0.173	**0.001**	−0.020	0.132	−0.028	**0.019**	−0.028	**0.026**
Maternal plasma AGP concentration at enrollment	−0.710	**0.025**	−0.693	**<0.001**	−0.771	**<0.001**	−0.592	**<0.001**
Placental weight (g)	0.008	**<0.001**	0.003	**<0.001**	0.004	**<0.001**	0.004	**<0.001**
Placental malaria infection	−0.035	0.874	−0.300	**<0.001**	−0.317	**<0.001**	−0.184	**0.013**
Severe chorioamnionitis	−1.117	**0.019**	−0.149	0.213	−0.113	0.306	−0.142	0.226
Duration of pregnancy	NA	NA	0.270	**<0.001**	0.288	**<0.001**	0.283	**<0.001**
Newborn LAZ	0.707	**<0.001**	NA	NA	0.693	**<0.001**	0.611	**<0.001**
Newborn WAZ	0.878	**<0.001**	0.808	**<0.001**	NA	NA	0.774	**<0.001**
Newborn HCZ	0.781	**<0.001**	0.646	**<0.001**	0.703	**<0.001**	NA	NA

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-5. Factors Independently Associated with Each of the Predictor Variables Used in the Pathway Analyses: Results from Multivariable Regression Models

	Maternal age		Maternal primiparity		Maternal height		Maternal BMI at enrollment	
Predictor variable	**B–coefficient**	**P-value**	**Odds ratio**	**P-value**	**B-coefficient**	**P-value**	**B-coefficient**	**P-value**
Maternal age at enrollment	NA	NA	0.616	**<0.001**	0.024	0.435	0.070	**<0.001**
Maternal primiparity	−6.228	**<0.001**	NA	NA	−0.437	0.341	0.450	**0.046**
Maternal height at enrollment	0.019	0.435	0.994	0.752	NA	NA	0.002	0.867
Maternal BMI at enrollment	0.229	**<0.001**	1.098	**0.013**	0.009	0.867	NA	NA
Maternal blood Hb concentration at enrollment	0.004	0.657	0.978	**<0.001**	−0.013	0.173	0.018	**<0.001**
Maternal weekly weight gain	1.914	0.176	0.266	0.191	6.293	**<0.001**	−3.913	**<0.001**
Maternal HIV infection	1.867	**<0.001**	0.407	**0.027**	0.217	0.653	0.347	0.147
Maternal peripheral blood malaria parasitermia at enrollment	−1.131	**<0.001**	0.944	0.789	0.276	0.448	−0.245	0.170
Maternal periapical oral infection (diagnosed after delivery)	2.366	**<0.001**	0.686	0.283	−0.082	0.855	−0.213	0.331
Maternal UTI (diagnosed after delivery)	−0.384	0.663	1.526	0.435	−0.511	0.595	0.522	0.272
Maternal vaginal trichomoniasis (diagnosed after delivery)	−0.474	0.327	0.745	0.372	−1.458	**0.006**	−0.082	0.751
Maternal salivary cortisol concentration at 36 gw	−0.118	**0.014**	0.982	0.603	−0.017	0.756	0.026	0.332
Maternal plasma AGP concentration at enrollment	−0.371	0.529	2.903	**0.007**	−0.393	0.551	−0.358	0.268
Placental weight (g)	0.000	0.776	0.999	0.486	0.006	**<0.001**	0.002	**0.007**
Placental malaria infection	−1.056	**0.002**	2.679	**<0.001**	−0.030	0.939	−0.529	**0.012**
Severe chorioamnionitis	0.189	0.691	0.832	0.606	−0.398	0.460	0.356	0.218

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-5. Factors Independently Associated with Each of the Predictor Variables Used in the Pathway Analyses: Results from Multivariable Regression Models (continued)

	Maternal Hb at enrollment		Maternal weekly weight gain		Maternal HIV infection		Maternal malaria infection at enrollment	
Predictor variable	**B-coefficient**	**P-value**	**B-coefficient**	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**
Maternal age at enrollment	0.038	0.657	0.001	0.177	1.066	**<0.001**	0.951	**<0.001**
Maternal primiparity	−6.149	**<0.001**	−0.016	**0.043**	0.258	**<0.001**	1.079	0.686
Maternal height at enrollment	−0.103	0.173	0.002	**<0.001**	1.005	0.739	1.009	0.440
Maternal BMI at enrollment	0.566	**<0.001**	−0.005	**<0.001**	1.049	0.111	0.962	0.137
Maternal blood Hb concentration at enrollment	NA	NA	0.000	**0.047**	0.978	**<0.001**	0.976	**<0.001**
Maternal weekly weight gain	8.747	**0.047**	NA	NA	0.065	**0.002**	0.236	**0.039**
Maternal HIV infection	−5.291	**<0.001**	−0.024	**0.003**	NA	NA	0.740	0.150
Maternal peripheral blood malaria parasitermia at enrollment	−5.919	**<0.001**	−0.012	*0.051*	0.806	0.287	NA	NA
Maternal periapical oral infection (diagnosed after delivery)	−1.227	0.309	−0.013	*0.082*	1.275	0.247	0.593	**0.008**
Maternal UTI (diagnosed after delivery)	−1.632	0.531	−0.014	0.369	2.119	*0.090*	0.868	0.729
Maternal vaginal trichomoniasis (diagnosed after delivery)	2.710	*0.067*	−0.008	0.362	1.684	*0.054*	1.357	0.172
Maternal salivary cortisol concentration at 36 gw	−0.407	**0.009**	−0.002	**0.027**	0.984	0.600	0.969	0.225
Maternal plasma AGP concentration at enrollment	−2.534	0.165	0.037	**0.001**	6.037	**<0.001**	8.306	**<0.001**
Placental weight (g)	−0.006	0.194	0.000	**0.008**	0.998	**0.043**	1.000	0.616
Placental malaria infection	−0.143	0.898	−0.014	**0.027**	1.263	0.281	2.479	**<0.001**
Severe chorioamnionitis	−0.842	0.574	0.002	0.858	1.038	0.894	1.434	0.126

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-5. Factors Independently Associated with Each of the Predictor Variables Used in the Pathway Analyses: Results from Multivariable Regression Models (continued)

	Maternal periapical infections (as diagnosed after delivery)		Maternal UTI (as diagnosed after delivery)		Maternal trichomoniasis (as diagnosed after delivery)		Maternal salivary cortisol concentration at 36 gw	
Predictor variable	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**	**B-coefficient**	**P-value**
Maternal age at enrollment	1.088	**<0.001**	0.986	0.715	0.979	0.302	−0.048	**0.014**
Maternal primiparity	0.727	0.290	1.759	0.264	0.716	0.267	−0.258	0.420
Maternal height at enrollment	0.998	0.903	0.981	0.537	0.954	**0.007**	−0.006	0.756
Maternal BMI at enrollment	0.974	0.369	1.072	0.245	0.989	0.753	0.035	0.332
Maternal blood Hb concentration at enrollment	0.995	0.332	0.993	0.506	1.012	*0.068*	−0.017	**0.010**
Maternal weekly weight gain	0.251	*0.091*	0.171	0.318	0.367	0.320	−2.149	**0.027**
Maternal HIV infection	1.282	0.232	1.967	0.134	1.694	**0.048**	−0.055	0.853
Maternal peripheral blood malaria parasitermia at enrollment	0.588	**0.006**	0.874	0.736	1.360	0.160	−0.310	0.195
Maternal periapical oral infection (diagnosed after delivery)	NA	NA	1.804	0.208	1.489	*0.095*	0.835	**0.003**
Maternal UTI (diagnosed after delivery)	1.800	0.207	NA	NA	1.543	0.387	−0.355	0.552
Maternal vaginal trichomoniasis (diagnosed after delivery)	1.515	*0.081*	1.527	0.401	NA	NA	0.182	0.619
Maternal salivary cortisol concentration at 36 gw	1.085	**0.005**	0.957	0.509	1.012	0.732	NA	NA
Maternal plasma AGP concentration at enrollment	1.008	0.981	1.578	0.513	2.178	**0.046**	0.567	0.185
Placental weight (g)	1.001	0.504	1.000	0.831	0.999	0.259	−0.003	**0.008**
Placental malaria infection	0.886	0.547	1.022	0.961	1.449	0.114	0.240	0.338
Severe chorioamnionitis	1.491	0.124	2.847	**0.013**	1.367	0.310	−0.126	0.708

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-5. Factors Independently Associated with Each of the Predictor Variables Used in the Pathway Analyses: Results from Multivariable Regression Models (continued)

	Maternal plasma AGP concentration at enrollment		Placental weight (g)		Placental malaria infection		Severe chorioamnionitis	
Predictor variable	**B-coefficient**	**P-value**	**B-coefficient**	**P-value**	**Odds ratio**	**P-value**	**Odds ratio**	**P-value**
Maternal age at enrollment	−0.001	0.529	−0.194	0.776	0.956	**0.002**	1.007	0.707
Maternal primiparity	0.096	**<0.001**	−14.827	0.183	2.893	**<0.001**	0.864	0.641
Maternal height at enrollment	−0.001	0.551	2.153	**<0.001**	0.999	0.937	0.987	0.464
Maternal BMI at enrollment	−0.003	0.268	3.249	**0.008**	0.926	**0.014**	1.048	0.204
Maternal blood Hb concentration at enrollment	−0.001	0.165	−0.278	0.194	1.000	0.928	0.996	0.560
Maternal weekly weight gain	0.216	**0.001**	90.135	**0.008**	0.201	**0.028**	1.171	0.868
Maternal HIV infection	0.107	**<0.001**	−22.831	**0.034**	1.298	0.224	1.025	0.927
Maternal peripheral blood malaria parasitermia at enrollment	0.121	**<0.001**	3.843	0.637	2.488	**<0.001**	1.423	0.141
Maternal periapical oral infection (diagnosed after delivery)	0.002	0.906	6.080	0.545	0.900	0.600	1.497	0.121
Maternal UTI (diagnosed after delivery)	0.023	0.559	4.355	0.860	1.022	0.960	2.786	**0.016**
Maternal vaginal trichomoniasis (diagnosed after delivery)	0.045	*0.051*	−12.905	0.250	1.398	0.152	1.341	0.345
Maternal salivary cortisol concentration at 36 gw	0.003	0.186	−3.746	**0.007**	1.025	0.320	0.985	0.670
Maternal plasma AGP concentration at enrollment	NA	NA	−25.841	0.104	1.653	0.105	0.265	**0.004**
Placental weight (g)	0.000	0.101	NA	NA	1.001	0.186	0.999	0.271
Placental malaria infection	0.028	*0.091*	10.901	0.189	NA	NA	0.974	0.902
Severe chorioamnionitis	−0.063	**0.003**	−12.446	0.281	0.976	0.910	NA	NA

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-6. Multivariable Regression Models for the Duration of Pregnancy

Predictor variable	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9	
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
Maternal age at enrollment	0.013	0.325	−0.002	0.908	−0.003	0.865	0.000	0.987	−0.002	0.898	−0.003	0.841	0.000	0.978	−0.005	0.755	0.007	0.662
Maternal primiparity			−0.406	*0.077*	−0.388	*0.090*	−0.384	*0.093*	−0.222	0.335	−0.193	0.401	−0.216	0.351	−0.167	0.472	−0.186	0.423
Maternal height at enrollment					0.032	**0.023**	0.032	**0.024**	0.034	**0.015**	0.030	**0.032**	0.030	**0.032**	0.031	**0.030**	0.030	**0.034**
Maternal BMI at enrollment							−0.029	0.324	−0.041	0.158	−0.033	0.263	−0.032	0.278	−0.035	0.227	−0.038	0.192
Maternal blood Hb concentration at enrollment									0.022	**<0.001**	0.021	**<0.001**	0.020	**<0.001**	0.018	**<0.001**	0.018	**0.001**
Maternal weekly weight gain											1.766	**0.028**	1.670	**0.039**	1.602	**0.047**	1.399	*0.083*
Maternal HIV infection													−0.311	0.205	−0.309	0.207	−0.265	0.276
Maternal peripheral blood malaria parasitemia at enrollment															−0.344	*0.053*	−0.405	**0.024**
Maternal periapical oral infection (diagnosed after delivery)																	−0.778	**0.005**
Maternal UTI (diagnosed after delivery)																		
Maternal vaginal trichomoniasis (diagnosed after delivery)																		
Maternal salivary cortisol concentration at 36 gw																		
Maternal plasma AGP concentration at enrollment																		
Placental weight (g)																		
Placental malaria infection																		
Severe chorioamnionitis																		
Intervention group – MMN																		
Intervention group – LNS																		

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-6. Multivariable Regression Models for the Duration of Pregnancy (continued)

	Model 10		Model 11		Model 12		Model 13		Model 14		Model 15		Model 16		Model 17	
Predictor variable	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**
Maternal age at enrollment	0.006	0.686	0.005	0.752	−0.003	0.871	−0.003	0.863	−0.001	0.970	0.001	0.939	0.002	0.898	0.002	0.897
Maternal primiparity	−0.160	0.491	−0.169	0.467	−0.181	0.435	−0.165	0.480	−0.075	0.746	−0.126	0.597	−0.138	0.560	−0.139	0.559
Maternal height at enrollment	0.029	**0.039**	0.026	*0.067*	0.024	*0.088*	0.024	*0.090*	0.007	0.595	0.007	0.592	0.006	0.656	0.006	0.656
Maternal BMI at enrollment	−0.035	0.235	−0.036	0.219	−0.033	0.255	−0.033	0.248	−0.056	**0.047**	−0.053	*0.060*	−0.048	*0.089*	−0.048	*0.089*
Maternal blood Hb concentration at enrollment	0.017	**0.001**	0.018	**<0.001**	0.015	**0.003**	0.015	**0.003**	0.017	**0.001**	0.017	**0.001**	0.017	**0.001**	0.017	**0.001**
Maternal weekly weight gain	1.340	*0.096*	1.281	0.111	0.920	0.249	0.949	0.237	0.302	0.698	0.366	0.640	0.386	0.620	0.387	0.620
Maternal HIV infection	−0.227	0.351	−0.181	0.459	−0.164	0.497	−0.148	0.547	0.020	0.933	0.010	0.967	0.013	0.956	0.014	0.954
Maternal peripheral blood malaria parasitemia at enrollment	−0.404	**0.024**	−0.374	**0.037**	−0.405	**0.023**	−0.387	**0.034**	−0.428	**0.015**	−0.469	**0.011**	−0.433	**0.018**	−0.433	**0.018**
Maternal periapical oral infection (diagnosed after delivery)	−0.746	**0.007**	−0.719	**0.009**	−0.595	**0.033**	−0.595	**0.033**	−0.632	**0.017**	−0.628	**0.017**	−0.584	**0.029**	−0.585	**0.028**
Maternal UTI (diagnosed after delivery)	−1.271	*0.065*	−1.229	*0.072*	−1.287	*0.053*	−1.285	*0.053*	−1.301	**0.040**	−1.301	**0.040**	−1.149	*0.067*	−1.151	*0.067*
Maternal vaginal trichomoniasis (diagnosed after delivery)			−0.633	**0.045**	−0.590	*0.059*	−0.583	*0.063*	−0.488	0.104	−0.502	*0.096*	−0.465	0.124	−0.465	0.125
Maternal salivary cortisol concentration at 36 gw					−0.152	**0.005**	−0.151	**0.006**	−0.123	**0.015**	−0.124	**0.014**	−0.125	**0.012**	−0.125	**0.013**
Maternal plasma AGP concentration at enrollment							−0.146	0.665	0.029	0.929	0.008	0.981	−0.110	0.741	−0.109	0.743
Placental weight (g)									0.007	**<0.001**	0.007	**<0.001**	0.007	**<0.001**	0.007	**<0.001**
Placental malaria infection											0.208	0.388	0.206	0.392	0.206	0.392
Severe chorioamnionitis													−0.891	**0.042**	−0.891	**0.043**
Intervention group – MMN															0.013	0.942
Intervention group – LNS															0.008	0.963

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-7. Multivariable Regression Models for Newborn Length-for-Age Z-Score

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9	
Predictor variable	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**
Maternal age at enrollment	0.019	**0.001**	0.002	0.700	0.002	0.758	0.001	0.935	0.000	0.976	−0.001	0.889	0.002	0.753	0.000	0.985	0.004	0.504
Maternal primiparity			−0.486	**<0.001**	−0.452	**<0.001**	−0.456	**<0.001**	−0.405	**<0.001**	−0.379	**<0.001**	−0.402	**<0.001**	−0.368	**<0.001**	−0.373	**<0.001**
Maternal height at enrollment					0.052	**<0.001**	0.052	**<0.001**	0.053	**<0.001**	0.049	**<0.001**	0.049	**<0.001**	0.049	**<0.001**	0.049	**<0.001**
Maternal BMI at enrollment							0.017	0.162	0.012	0.296	0.020	*0.090*	0.021	*0.076*	0.019	0.108	0.018	0.132
Maternal blood Hb concentration at enrollment									0.006	**0.002**	0.005	**0.009**	0.005	**0.021**	0.004	*0.059*	0.004	*0.076*
Maternal weekly weight gain											1.499	**<0.001**	1.405	**<0.001**	1.361	**<0.001**	1.289	**<0.001**
Maternal HIV infection													−0.294	**0.002**	−0.295	**0.002**	−0.281	**0.003**
Maternal peripheral blood malaria parasitemia at enrollment															−0.176	**0.015**	−0.196	**0.007**
Maternal periapical oral infection (diagnosed after delivery)																	−0.264	**0.002**
Maternal UTI (diagnosed after delivery)																		
Maternal vaginal trichomoniasis (diagnosed after delivery)																		
Maternal salivary cortisol concentration at 36 gw																		
Maternal plasma AGP concentration at enrollment																		
Placental weight (g)																		
Placental malaria infection																		
Severe chorioamnionitis																		
Duration of pregnancy																		
Intervention group – MMN																		
Intervention group – LNS																		

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-7. Multivariable Regression Models for Newborn Length-for-Age Z-Score (continued)

	Model 10		Model 11		Model 12		Model 13		Model 14		Model 15		Model 16		Model 17		Model 18	
Predictor variable	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**
Maternal age at enrollment	0.004	0.518	0.004	0.533	0.004	0.566	0.003	0.644	0.004	0.519	0.003	0.601	0.003	0.588	0.002	0.749	0.002	0.749
Maternal primiparity	−0.368	**<0.001**	−0.369	**<0.001**	−0.370	**<0.001**	−0.331	**0.001**	−0.307	**0.001**	−0.283	**0.004**	−0.287	**0.004**	−0.279	**0.002**	−0.280	**0.002**
Maternal height at enrollment	0.049	**<0.001**	0.048	**<0.001**	0.048	**<0.001**	0.048	**<0.001**	0.042	**<0.001**	0.042	**<0.001**	0.042	**<0.001**	0.040	**<0.001**	0.040	**<0.001**
Maternal BMI at enrollment	0.018	0.132	0.018	0.137	0.018	0.136	0.017	0.163	0.007	0.536	0.006	0.616	0.007	0.576	0.014	0.191	0.014	0.194
Maternal blood Hb concentration at enrollment	0.004	*0.079*	0.004	*0.073*	0.004	*0.082*	0.003	*0.098*	0.004	**0.024**	0.004	**0.025**	0.004	**0.026**	0.001	0.727	0.001	0.732
Maternal weekly weight gain	1.272	**<0.001**	1.264	**<0.001**	1.250	**<0.001**	1.332	**<0.001**	1.015	**0.001**	0.986	**0.002**	0.989	**0.002**	0.789	**0.007**	0.791	**0.007**
Maternal HIV infection	−0.274	**0.004**	−0.267	**0.005**	−0.267	**0.005**	−0.215	**0.027**	−0.164	*0.082*	−0.160	*0.090*	−0.160	*0.091*	−0.172	**0.048**	−0.169	*0.052*
Maternal peripheral blood malaria parasitemia at	−0.196	**0.007**	−0.193	**0.008**	−0.194	**0.007**	−0.144	*0.051*	−0.163	**0.023**	−0.145	**0.047**	−0.139	*0.057*	−0.086	0.201	−0.087	0.197
Maternal periapical oral infection (diagnosed after	−0.258	**0.002**	−0.254	**0.002**	−0.250	**0.003**	−0.254	**0.003**	−0.283	**0.001**	−0.284	**0.001**	−0.279	**0.001**	−0.228	**0.003**	−0.230	**0.002**
Maternal UTI (diagnosed after delivery)	−0.354	0.106	−0.353	0.106	−0.357	0.103	−0.333	0.127	−0.365	*0.097*	−0.363	*0.098*	−0.347	0.115	−0.259	0.188	−0.263	0.183
Maternal vaginal trichomoniasis (diagnosed after delivery)			−0.091	0.404	−0.090	0.410	−0.070	0.524	−0.050	0.638	−0.042	0.694	−0.038	0.722	−0.008	0.933	−0.005	0.955
Maternal salivary cortisol concentration at 36 gw					−0.006	0.653	−0.004	0.740	0.004	0.712	0.005	0.683	0.004	0.705	0.017	*0.093*	0.017	*0.089*
Maternal plasma AGP concentration at enrollment							−0.394	**0.005**	−0.322	**0.019**	−0.312	**0.023**	−0.332	**0.015**	−0.394	**0.002**	−0.393	**0.002**
Placental weight (g)									0.003	**<0.001**	0.003	**<0.001**	0.003	**<0.001**	0.002	**<0.001**	0.002	**<0.001**
Placental malaria infection											−0.092	0.213	−0.091	0.217	−0.074	0.277	−0.074	0.284
Severe chorioamnionitis													−0.137	0.216	−0.093	0.350	−0.090	0.365
Duration of pregnancy															0.222	**<0.001**	0.221	**<0.001**
Intervention group – MMN																	0.048	0.486
Intervention group – LNS																	0.053	0.444

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-8. Multivariable Regression Models for Newborn Weight-for-Age Z-Score

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9	
Predictor variable	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**
Maternal age at enrollment	0.024	**<0.001**	0.007	0.264	0.006	0.285	0.003	0.545	0.003	0.588	0.002	0.735	0.004	0.519	0.001	0.807	0.004	0.458
Maternal primiparity			−0.508	**<0.001**	−0.482	**<0.001**	−0.490	**<0.001**	−0.429	**<0.001**	−0.399	**<0.001**	−0.413	**<0.001**	−0.372	**<0.001**	−0.375	**<0.001**
Maternal height at enrollment					0.040	**<0.001**	0.040	**<0.001**	0.040	**<0.001**	0.036	**<0.001**	0.036	**<0.001**	0.036	**<0.001**	0.036	**<0.001**
Maternal BMI at enrollment							0.031	**0.005**	0.026	**0.017**	0.035	**0.001**	0.035	**0.001**	0.033	**0.003**	0.032	**0.003**
Maternal blood Hb concentration at enrollment									0.008	**<0.001**	0.007	**<0.001**	0.006	**0.001**	0.005	**0.007**	0.005	**0.009**
Maternal weekly weight gain											1.689	**<0.001**	1.630	**<0.001**	1.576	**<0.001**	1.526	**<0.001**
Maternal HIV infection													−0.183	**0.037**	−0.185	**0.034**	−0.175	**0.044**
Maternal peripheral blood malaria parasitemia at															−0.217	**0.001**	−0.231	**<0.001**
Maternal periapical oral infection (diagnosed after																	−0.185	**0.014**
Maternal UTI (diagnosed after delivery)																		
Maternal vaginal trichomoniasis (diagnosed after																		
Maternal salivary cortisol concentration at 36 gw																		
Maternal plasma AGP concentration at enrollment																		
Placental weight (g)																		
Placental malaria infection																		
Severe chorioamnionitis																		
Duration of pregnancy																		
Newborn LAZ																		
Intervention group – MMN																		
Intervention group – LNS																		

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-8. Multivariable Regression Models for Newborn Weight-for-Age Z-Score (continued)

Predictor variable	Model 10		Model 11		Model 12		Model 13		Model 14		Model 15		Model 16		Model 17		Model 18		Model 19	
	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value	Beta	P-value
Maternal age at enrollment	0.004	0.473	0.004	0.504	0.003	0.598	0.002	0.695	0.004	0.513	0.003	0.580	0.003	0.568	0.001	0.757	0.001	0.887	0.001	0.885
Maternal primiparity	−0.369	**<0.001**	−0.372	**<0.001**	−0.374	**<0.001**	−0.331	**<0.001**	−0.301	**<0.001**	−0.284	**0.001**	−0.287	**0.001**	−0.280	**<0.001**	−0.135	**0.027**	−0.135	**0.027**
Maternal height at enrollment	0.036	**<0.001**	0.035	**<0.001**	0.035	**<0.001**	0.034	**<0.001**	0.027	**<0.001**	0.027	**<0.001**	0.027	**<0.001**	0.024	**<0.001**	0.004	0.269	0.004	0.277
Maternal BMI at enrollment	0.032	**0.003**	0.032	**0.004**	0.032	**0.003**	0.031	**0.005**	0.019	*0.063*	0.018	*0.079*	0.019	*0.070*	0.027	**0.004**	0.019	**0.009**	0.019	**0.009**
Maternal blood Hb concentration at enrollment	0.005	**0.009**	0.005	**0.007**	0.005	**0.011**	0.005	**0.014**	0.006	**0.001**	0.006	**0.001**	0.006	**0.001**	0.002	0.235	0.002	0.221	0.002	0.220
Maternal weekly weight gain	1.506	**<0.001**	1.489	**<0.001**	1.452	**<0.001**	1.543	**<0.001**	1.153	**<0.001**	1.133	**<0.001**	1.135	**<0.001**	0.925	**<0.001**	0.517	**0.008**	0.518	**0.008**
Maternal HIV infection	−0.167	*0.055*	−0.155	*0.077*	−0.153	*0.079*	−0.096	0.279	−0.033	0.695	−0.030	0.719	−0.029	0.724	−0.043	0.561	0.046	0.433	0.044	0.459
Maternal peripheral blood malaria parasitemia at	−0.232	**<0.001**	−0.225	**0.001**	−0.229	**0.001**	−0.173	**0.010**	−0.196	**0.002**	−0.184	**0.004**	−0.178	**0.006**	−0.123	**0.032**	−0.079	*0.090*	−0.078	*0.091*
Maternal periapical oral infection (diagnosed after	−0.179	**0.018**	−0.172	**0.023**	−0.161	**0.034**	−0.165	**0.029**	−0.201	**0.007**	−0.202	**0.006**	−0.197	**0.008**	−0.144	**0.032**	−0.026	0.628	−0.024	0.645
Maternal UTI (diagnosed after delivery)	−0.400	*0.050*	−0.398	*0.050*	−0.408	**0.044**	−0.382	*0.058*	−0.421	**0.033**	−0.420	**0.034**	−0.405	**0.040**	−0.313	*0.065*	−0.179	0.178	−0.174	0.191
Maternal vaginal trichomoniasis (diagnosed			−0.173	*0.083*	−0.170	*0.089*	−0.147	0.139	−0.122	0.190	−0.117	0.211	−0.113	0.225	−0.082	0.311	−0.078	0.229	−0.077	0.235
Maternal salivary cortisol concentration at 36 gw					−0.015	0.188	−0.013	0.240	−0.003	0.783	−0.002	0.811	−0.003	0.785	0.010	0.213	0.002	0.813	0.001	0.852
Maternal plasma AGP concentration at enrollment							−0.439	**0.001**	−0.351	**0.004**	−0.343	**0.005**	−0.361	**0.003**	−0.425	**<0.001**	−0.222	**0.010**	−0.224	**0.009**
Placental weight (g)									0.004	**<0.001**	0.004	**<0.001**	0.004	**<0.001**	0.003	**<0.001**	0.002	**<0.001**	0.002	**<0.001**
Placental malaria infection											−0.066	0.321	−0.065	0.327	−0.048	0.424	−0.009	0.852	−0.009	0.858
Severe chorioamnionitis													−0.119	0.212	−0.073	0.381	−0.025	0.715	−0.026	0.710
Duration of pregnancy															0.233	**<0.001**	0.118	**<0.001**	0.118	**<0.001**
Newborn LAZ																	0.517	**<0.001**	0.517	**<0.001**
Intervention group – MMN																			−0.030	0.517
Intervention group – LNS																			0.004	0.932

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-9. Multivariable Regression Models for Newborn Head Circumference-for-Age Z-Score

	Model 1		Model 2		Model 3		Model 4		Model 5		Model 6		Model 7		Model 8		Model 9		Model 10	
Predictor variable	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**
Maternal age at enrollment	0.014	**0.011**	0.007	0.272	0.007	0.289	0.004	0.544	0.004	0.562	0.003	0.664	0.004	0.565	0.001	0.820	0.005	0.474	0.005	0.476
Maternal primiparity			−0.203	**0.038**	−0.183	*0.058*	−0.192	**0.047**	−0.166	*0.091*	−0.142	0.145	−0.150	0.126	−0.109	0.267	−0.113	0.249	−0.112	0.254
Maternal height at enrollment					0.029	**<0.001**	0.029	**<0.001**	0.029	**<0.001**	0.026	**<0.001**	0.026	**<0.001**	0.026	**<0.001**	0.026	**<0.001**	0.026	**<0.001**
Maternal BMI at enrollment							0.033	**0.005**	0.031	**0.009**	0.038	**0.002**	0.038	**0.002**	0.036	**0.003**	0.035	**0.004**	0.035	**0.004**
Maternal blood Hb concentration at enrollment									0.003	0.116	0.002	0.233	0.002	0.279	0.001	0.546	0.001	0.607	0.001	0.609
Maternal weekly weight gain											1.324	**<0.001**	1.293	**<0.001**	1.241	**<0.001**	1.186	**<0.001**	1.182	**<0.001**
Maternal HIV infection													−0.097	0.320	−0.098	0.312	−0.088	0.365	−0.086	0.374
Maternal peripheral blood malaria parasitemia at															−0.210	**0.004**	−0.225	**0.002**	−0.225	**0.002**
Maternal periapical oral infection (diagnosed after																	−0.203	**0.015**	−0.202	**0.016**
Maternal UTI (diagnosed after delivery)																			−0.069	0.751
Maternal vaginal trichomoniasis (diagnosed																				
Maternal salivary cortisol concentration at 36 gw																				
Maternal plasma AGP concentration at enrollment																				
Placental weight (g)																				
Placental malaria infection																				
Severe chorioamnionitis																				
Duration of pregnancy																				
Newborn LAZ																				
Intervention group – MMN																				
Intervention group – LNS																				

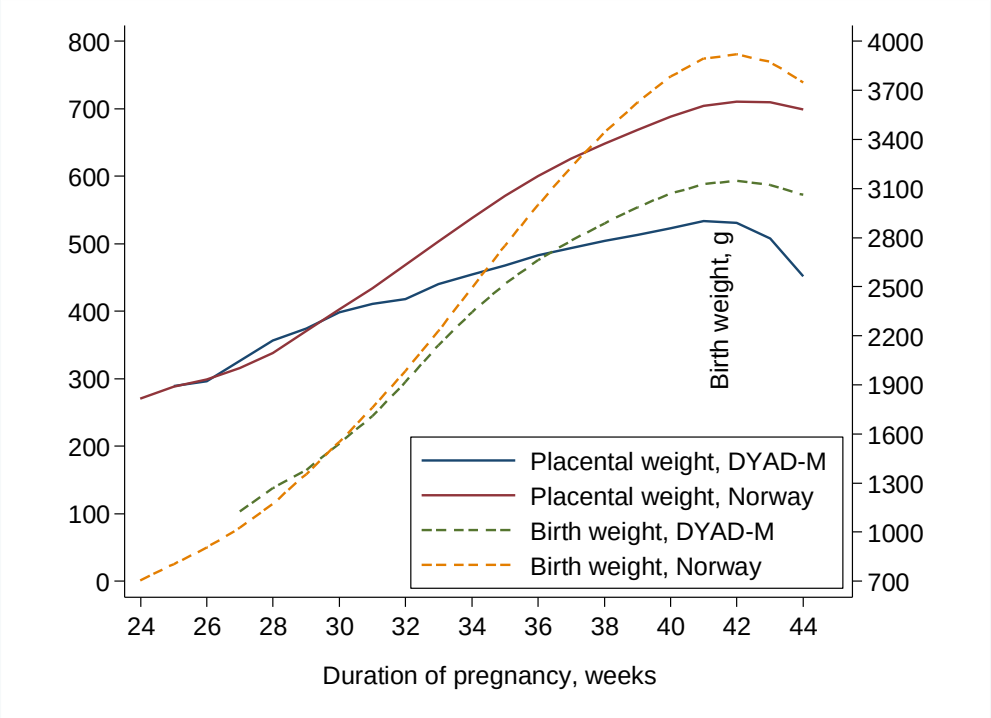
Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Table A-9. Multivariable Regression Models for Newborn Head Circumference-for-Age Z-Score (continued)

	Model 11		Model 12		Model 13		Model 14		Model 15		Model 16		Model 17		Model 18		Model 19	
Predictor variable	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**	**Beta**	**P-value**
Maternal age at enrollment	0.004	0.490	0.003	0.597	0.003	0.679	0.004	0.519	0.004	0.544	0.004	0.530	0.002	0.695	0.001	0.783	0.001	0.782
Maternal primiparity	−0.114	0.248	−0.117	0.235	−0.076	0.442	−0.046	0.629	−0.039	0.690	−0.043	0.662	−0.035	0.695	0.092	0.245	0.092	0.246
Maternal height at enrollment	0.026	**<0.001**	0.025	**<0.001**	0.025	**<0.001**	0.018	**0.002**	0.018	**0.002**	0.017	**0.002**	0.015	**0.004**	−0.003	0.491	−0.003	0.491
Maternal BMI at enrollment	0.035	**0.004**	0.035	**0.004**	0.034	**0.005**	0.022	*0.055*	0.022	*0.061*	0.022	*0.053*	0.031	**0.003**	0.024	**0.009**	0.024	**0.009**
Maternal blood Hb concentration at enrollment	0.001	0.583	0.001	0.692	0.001	0.765	0.002	0.336	0.002	0.337	0.002	0.349	−0.002	0.218	−0.003	0.117	−0.003	0.117
Maternal weekly weight gain	1.173	**<0.001**	1.125	**0.001**	1.211	**<0.001**	0.820	**0.009**	0.811	**0.010**	0.814	**0.010**	0.595	**0.038**	0.237	0.348	0.238	0.346
Maternal HIV infection	−0.080	0.413	−0.078	0.421	−0.024	0.809	0.040	0.675	0.040	0.668	0.041	0.663	0.027	0.749	0.105	0.166	0.105	0.171
Maternal peripheral blood malaria parasitemia at	−0.222	**0.003**	−0.227	**0.002**	−0.174	**0.021**	−0.197	**0.006**	−0.193	**0.009**	−0.186	**0.011**	−0.128	*0.055*	−0.089	0.139	−0.089	0.139
Maternal periapical oral infection (diagnosed after	−0.199	**0.018**	−0.184	**0.029**	−0.188	**0.025**	−0.224	**0.007**	−0.224	**0.007**	−0.218	**0.008**	−0.162	**0.029**	−0.058	0.363	−0.058	0.366
Maternal UTI (diagnosed after delivery)	−0.068	0.754	−0.081	0.711	−0.056	0.796	−0.096	0.647	−0.095	0.650	−0.076	0.715	0.020	0.915	0.137	0.400	0.140	0.394
Maternal vaginal trichomoniasis (diagnosed after delivery)	−0.093	0.402	−0.089	0.420	−0.067	0.542	−0.043	0.688	−0.040	0.704	−0.036	0.734	−0.004	0.969	0.000	1.000	0.001	0.989
Maternal salivary cortisol concentration at 36 gw			−0.019	0.122	−0.018	0.154	−0.007	0.533	−0.007	0.540	−0.008	0.513	0.006	0.524	−0.002	0.852	−0.002	0.840
Maternal plasma AGP concentration at enrollment					−0.414	**0.003**	−0.325	**0.016**	−0.322	**0.017**	−0.345	**0.011**	−0.412	**0.001**	−0.233	**0.033**	−0.235	**0.032**
Placental weight (g)							0.004	**<0.001**	0.004	**<0.001**	0.004	**<0.001**	0.003	**<0.001**	0.002	**<0.001**	0.002	**<0.001**
Placental malaria infection									−0.026	0.730	−0.025	0.741	−0.007	0.924	0.027	0.667	0.028	0.662
Severe chorioamnionitis											−0.153	0.150	−0.105	0.263	−0.063	0.447	−0.062	0.450
Duration of pregnancy													0.243	**<0.001**	0.142	**<0.001**	0.142	**<0.001**
Newborn LAZ−score															0.454	**<0.001**	0.454	**<0.001**
Intervention group – MMN																	−0.007	0.906
Intervention group – LNS																	0.016	0.797

Green cells with bold font indicate a regression coefficient with P<0.05; yellow cells with italic font indicate 0.05≤P<0.10.

Figure A-1. Association between the Duration of Pregnancy and Placental Weight and Birth Weight in the Study Cohort (including comparison to a Norwegian reference population)



Source for Norway data (Thompson et al. 2007).