# The Relationship Between Maternal and Infant Diets and Nutritional Outcomes in Sub-Saharan Africa

# The Relationship between Maternal and Infant Diets and Nutritional Outcomes in Sub-Saharan Africa

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## Abstract

Globally, 149 million children under 5 years are stunted, 13.5% are underweight, and 49 million wasted, 17 million of them severely. Low birth weight (LBW), preterm birth and small for gestational age (SGA) are also prevalent, affecting 10-15 % of all births globally, the majority in low and middle income counties (LMICs). These outcomes are significant causes of infant and child mortality, weakened immunity, increased infections, long term developmental delays and increase risk of overweight and obesity and related chronic diseases in later life.

The importance of maternal and child diets in first 1000 days of life, from conception to the first 2 years of life, and its effects on child growth and development is not well explored. This dissertation examines the role of maternal and child diet quality in preventing poor birth and child growth outcomes in LMICs countries.

**Chapter 1** examines the association of child dietary diversity with nutritional recovery, hospitalization, death, and weight and height gain among children treated for uncomplicated severe acute malnutrition (SAM), using binomial and linear regression methods. We found that eggs may be important for recovery from SAM and did not find associations with recovery or response to treatment.

**Chapter 2** evaluates the association of prenatal Minimum Diet Diversity for Women (MDD-W) and the Prime Diet Quality Score (PDQS) with birth outcomes in Tanzania, using binomial regression models. We found the PDQS was associated with lower risk of preterm, very

preterm, LBW, very low birth weight (VLBW) and fetal loss and the MDD-W was protective against SGA.

**Chapter 3** examines the association of the MDD-W during pregnancy with child growth outcomes of stunting, wasting and underweight from 3 to 12 months using Cox regression models, in a Ugandan birth cohort. We found that diversified prenatal maternal diets were associated with fewer incidences of underweight. We did not find an association with stunting and wasting.

This dissertation supports that maternal and child diet quality may be modifiable factors to improve birth and child growth outcomes in LMICs. Additional research is required to evaluate these associations, using various tools for assessing diets, in varied locations.

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**Paper I**

# The role of dietary diversity in the response to treatment of uncomplicated severe acute malnutrition among children in Niger: a prospective study

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**Abstract**

**Background.** Community-based treatment of severe acute malnutrition (SAM) has proven to be safe and cost effective, although identifying additional factors that can increase recovery and decrease treatment failure may improve program effectiveness. We examine the association of dietary diversity and clinical and program treatment outcomes among children treated for uncomplicated SAM in Niger.

**Methods.** Two thousand four hundred twelve children were enrolled in a randomized trial of routine amoxicillin in the treatment of uncomplicated SAM from 2012 to 2014. All children received ready to use therapeutic food (RUTF) and standard clinical care. Child dietary diversity was assessed using a 7-day food frequency questionnaire and 8-food group diet diversity score. We assessed the association of dietary diversity at admission with nutritional recovery, hospitalization, and death at program discharge and 12 weeks, and weight and height gain.

**Results.** Food groups most commonly consumed by children in seven days preceding SAM treatment were cereals, roots and tubers (N = 2364, 99.5%) and vitamin A rich fruits and vegetables (N = 2253, 94.8%). Egg (N = 472, 19.9%) and dairy (N = 659, 27.7%) consumption was low. Mean (SD) diet diversity score was significantly lower in the lean vs. non-lean season [2.7 (1.1) vs. 2.9 (1.0)]. There was no evidence that dietary diversity increased nutritional recovery at discharge (RR: 1.02, 95% CI: 1.00, 1.04) or 12 weeks (RR: 0.98, 95%CI: 0.94, 1.02). No significant association was found with risk of hospitalization or death, or weight and height gain. Egg consumption was protective against death at discharge (RR: 0.53, 95% CI: 0.39, 0.70) and 12 weeks (RR: 0.66, 95% CI: 0.45, 0.96). Vitamin A rich fruits and vegetable consumption

was associated with greater risk of mortality in children at discharge (RR: 1.30, 95% CI: 1.08, 1.56) and 12 weeks (RR: 1.19, 95% CI: 1.03, 1.36).

**Conclusions.** We did not find evidence that dietary diversity influenced nutrition recovery or response to treatment for children with uncomplicated SAM in Niger. It is feasible consumption of nutrient-dense foods like eggs may be important for recovery from SAM. There is need for continued research to further elucidate drivers of nutritional recovery from acute malnutrition in different settings.

## Introduction

Nearly 17 million children under 5 years of age worldwide, and 4.1 million in Africa, are affected by severe acute malnutrition (SAM) [1–3]. Approximately 7% of all deaths in children under 5 years can be attributed to SAM and children with weight-for-height Z (WHZ) score < − 3 have a 9-fold higher risk of death compared to healthy children [2]. Since 2006, SAM treatment has focused on outpatient therapy for children with no complications and appetite and reserved inpatient management for children with clinical complications [4, 5]. This community-based approach has proven to be safe and cost-effective, though treatment failure, default and mortality can reduce the potential effectiveness of programs and limit their scale-up [6–9].

Understanding the factors that drive nutritional recovery during SAM treatment could be used to improve program success. One measure of diet quality, dietary diversity (DD), has been associated with a reduced risk of wasting and stunting, as well as increased micronutrient adequacy and caloric sufficiency among children [10–13]. Dietary diversity, among other factors, can contribute to the risk of acute wasting, but its role in SAM recovery and the response to treatment is not well understood [9, 14, 15].

We hypothesized dietary diversity at admission, as a marker of micronutrient adequacy, may enhance a child's ability to recover from nutritional deficit by increasing micronutrient availability for recovery and repair processes and enhancing immune function, and promote nutritional recovery. Further, diversified diets may also sustain and maintain recovery from severe acute malnutrition and prevent relapse. We therefore examined the prospective association of dietary intake and dietary diversity measured before treatment for SAM with nutritional recovery, hospitalization, and death at program discharge and 12 weeks and

anthropometric outcomes of weight and height gain among children treated for uncomplicated SAM in Niger.

## Methods

### Study setting and population

The study was conducted in the Madarounfa rural health district in south-central Niger, in the Sahel region, a region affected by seasonal fluctuations in food availability, infectious illnesses and high rates of acute malnutrition among young children. The study population included 2412 children enrolled in a randomized trial of routine amoxicillin in the treatment of uncomplicated SAM conducted from 2012 to 2014 (ClinicalTrials.gov Identifier, NCT01613547) [16]. In brief, children were enrolled in the parent trial if they presented to health centers for outpatient treatment of uncomplicated SAM, resided within 15 km of study health centers, were available for 12 weeks of follow up and had no clinical complications requiring antibiotic treatment at admission. Children also could not have been admitted to a nutrition treatment program in the preceding 3 months or have congenital abnormalities. The inclusion criteria for outpatient SAM treatment were age 6 to 59 months, WHZ < −3 based on World Health Organization (WHO) growth standards, or mid-upper arm circumference (MUAC) < 115 mm. Other inclusion criteria included sufficient appetite for successful oral nutrition and absence of bipedal edema or clinical complications requiring hospitalization [16].

### Study design and interventions

The parent study was a randomized, double-blind placebo-controlled trial. Children were randomized to receive routine amoxicillin or placebo at admission, but otherwise received standard clinical care and ready-to-use therapeutic food for the outpatient treatment of SAM in line with guidelines from Médecins Sans Frontières (MSF) and the Ministry of Health of Niger [16]. Detailed descriptions of the study design and methods are provided elsewhere [16].

**Study procedures and follow-up**

At admission, study nurses interviewed caregivers and collected socio-demographic information, including child feeding practices, immunization status, child illnesses and medical history, as well as maternal characteristics and household socioeconomic status. Hemoglobin status (HemoCue Hb 301, HemoCue, Angelholm, Sweden) and malaria infection (SD Bioline Malaria Antigen P.f, Standard Diagnostics Inc., Republic of Korea) were assessed in all children at baseline.

Follow-up was conducted by study staff at health centers on a weekly basis until discharge from the nutritional program (minimum stay 3 weeks for recovery), and at 4, 8 and 12 weeks after enrollment. At each visit, anthropometric measurements were taken. Weight was measured to the nearest 100 g using a hanging Salter scale (≥ 15 kg) or SECA scale (< 15 kg), and length (standing height for children ≥24 months) using a wooden length/height measuring board. MUAC was measured to the nearest 0.1 cm using a non-stretchable MUAC tape. Study physicians conducted a physical exam and completed a medical history that included health events, medical consultations and treatments for children in the last 7 days. When a child missed a scheduled visit, home visits by a study nurse and community health agent were conducted and anthropometry and clinical condition were assessed.

**Dietary diversity**

Diet diversity (DD) has been recognized as a tool for evaluating dietary intake and quality for children in low income settings where gold standard tools such as 7 day diet records are not feasible or are limited by cost [17]. While individual foods are diverse and vary by culture, food groups are limited in number and thus are amenable to study and comparison across contexts. Dietary intake and diversity, the primary exposures of interest, were assessed at baseline using a food frequency questionnaire (FFQ) which asked caregivers if the child had eaten a list of 45 foods (in 12 food categories) in the previous 7 days, and if yes, for how many of these 7 days. As proposed by Dewey et al. [18], 8 food groups were created: grains, roots and tubers; legumes and nuts; dairy products; flesh foods; eggs; vitamin A-rich fruits and vegetables; other fruits and vegetables; fats and oils.

A diet diversity score (DDS) can be created by awarding one point for each food group consumed over the past 24 h and 0 otherwise, using a 10 g cutoff per food group for the first seven groups, and a 1 g cutoff for fats and oils. In this analysis, which used FFQ not 24-h recall data, a revised scoring algorithm was developed which awarded one point for each food group consumed at least once per day and scaled, partial points for all less frequent consumption (e.g. if eaten on 1 day in the 7-day recall, 1/7 point was awarded). DDS was computed as the sum of food groups consumed. This 8-food group DDS was selected as it has been shown to be predictive of diet quality of complementary foods for children 6–12 months of age as indicated by correlations with mean nutrient density adequacy for selected micronutrients including iron and vitamin A [18]. We also considered other measures of child dietary diversity including the WHO index to assess infant and young child feeding (2007), a 7-food group measure that included grains, roots and tubers; legumes and nuts; dairy products; flesh foods; eggs; vitamin-A

rich fruits and vegetables; and other fruits and vegetables [19]. We excluded 22 children from the analysis that were exclusively breastfed at the time of admission.

**Study outcomes**

The primary outcomes of the analysis were nutritional recovery, transfer to hospital and death at program discharge and 12 weeks of follow up. Secondary outcomes included change in child weight (g/kg/d) and height (mm/d) from baseline to weeks 1 and 2, program discharge and 12 weeks of follow up, among the children that recovered. Nutritional recovery in the program was determined at 3 weeks or beyond and was defined as WHZ $\geq -2$ on two consecutive visits and MUAC$\geq$115 mm. Recovered children had no acute complications or edema for a minimum of 7 days and had completed all antibiotic and anti-malaria treatment at program discharge. Default from the program was defined as 3 or more missed weekly visits. Non-response was defined as when a child did not meet criteria for recovery at 8 weeks. Children with weight loss greater than 5% between two consecutive visits, lack of weight gain after 2 weeks or clinical complications requiring inpatient management were transferred to hospital for inpatient management. Death was considered as all-cause mortality.

**Statistical analysis**

We evaluated the socio-economic and demographic characteristics of the study children. Chi-squared tests for dichotomous variables and the Wilcoxon rank sum test for continuous variables were used to assess significant differences between levels of dietary diversity (±4 food groups/day). We described intake of individual food groups and the overall DDS, and compared differences between seasons, using chi-squared tests and the Wilcoxon rank sum test.

We calculated DDS at admission, and evaluated the associations between individual food group intake and DDS with the risk of nutritional recovery, transfer to hospital or death at program discharge and 12 weeks. Separate binomial regression models were used for individual food groups or DDS. Among recovered children, we also evaluated associations of food group intake and DDS with weight and height change using linear regression.

We adjusted for amoxicillin/placebo trial regimen, as well as potential confounders assessed at admission and selected based on univariate significance with the outcome at the level of $P < 0.20$. Covariates considered included: child characteristics (age: 6–11, 12–23 vs. 24–59 months), sex: male vs. female), breastfeeding (yes vs. no), child anthropometric status (wasting: none, moderate vs. severe, stunting: none, moderate, severe and MUAC: < 115 vs. ≥115 mm), child health status (anemia: yes vs. no, respiratory rate, and body temperature), presence of morbidity (yes/no: malaria, tachypnea, upper respiratory infection, cough, nasal discharge, diarrhea, vomiting, and ear pain), child receiving ready to use supplementary foods in the past 7 days (yes/no), vaccination status: yes/no (measles, pertussis, tetanus, and polio), previous consultation for child's health status (yes/no). We also considered household characteristics (number of children < 5 years, household size, wealth index, household food security index (HFIAS score), bednet use (yes/no)), maternal and paternal characteristics (maternal and paternal age, maternal education (none, koranic school, primary school complete, CEG complete), use of health services (yes/no) and season (lean/non-lean). Confounders were measured at admission.

Finally, to more broadly inform the identification of potential boosters of nutritional recovery, we assessed independent predictors of treatment recovery in this setting. Potential predictors identified using logistic regression models with univariate significance at $P < 0.20$ were included in a final multivariate model. All analyses were conducted using SAS version 9.4.

**Results**

The analysis population included 2377 children (Table 1.1).Most children were aged 12–23 months (n = 1058,44.3%) and were partially breastfed at the time of admission (n = 1482, 62.0%). More than one-quarter of children presented with anemia (hemoglobin < 8.5 g/dL, n = 690, 28.8%) and more than one-half with malaria infection at admission (n = 1324, 55.%). A history of recent infectious morbidity was reported in at least one-third of children at admission (31.7% = diarrhea; 55.4% = malaria).

**Table 1.1: Baseline demographic, health and anthropometric characteristics of children in SAM outpatient centers, Niger**

| Characteristic | N (%) or Mean (SD) | Low dietary diversity [a] | High dietary diversity [a] |
|---|---|---|---|
| N | 2390 | 1676(70.1) | 714(29.9)** |
| **Child characteristics** | | | |
| Age | | | |
| 6-11 months | 845 (35.6) | 637(38.0) | 208(29.1)** |
| 12- 23 months | 1058 (44.3) | 705(42.1) | 353(49.4)** |
| 24-59 months | 487 (20.4) | 334(19.9) | 153(21.4)** |
| Male sex | 1200 (50.1) | 816(48.7) | 384(53.8)* |
| Breastfeeding status | | | |
| Exclusive breastfeeding | 19 (0.8) | 12(0.7) | 7(1.0)* |
| Partial breastfeeding | 1482 (62.0) | 1074(64.1) | 408(57.1) * |
| None | 889 (37.2) | 590(35.2) | 299(41.9)* |

*Table 1.1 (Continued)*

| Characteristic | N (%) or Mean (SD) | Low dietary diversity [a] | High dietary diversity [a] |
|---|---|---|---|
| **Child nutritional status** | | | |
| Weight for length/height Z-score | -3.1 (0.6) | -3.1(0.6) | -3.1(0.6) |
| N (%) < -3SD | 1465 (61.3) | 1031(61.5) | 434(60.8) |
| Height-for-Age Z-score | | | |
| Mean (SD) | -3.0 (1.2) | -3.0(1.2) | -3.0(1.2) |
| Score below -2SD | 1891 (79.1) | 1329(79.3) | 562(78.7) |
| Mid upper arm circumference, mm | | | |
| Mean (SD) | 112 (4.5) | 112(4.5) | 113(4.4) |
| MUAC < 115 mm | 1861(77.9) | 1308(78.0) | 553(77.5) |
| **Clinical and medical history** | | | |
| Vitamin A supplementation in last 6 months | 2082 (89.6) | 1451(89.1) | 631(90.9) |
| Measles vaccination coverage | 1107 (46.8) | 753(45.3) | 354(50.4)* |
| Anemia (Haemoglobin less than <8.5 g/dL) | 690 (28.8) | 478(28.5) | 212(29.7) |
| Fever (temperature >38.5 degrees Celsius) | 112 (4.7) | 76(4.5) | 36(5.0) |
| Rapid diagnostic test positive for malaria | 1324 (55.4) | 903(53.9) | 421(59.0)* |
| Diarrhoea in the last 24 hours | 757 (31.7) | 530(31.6) | 227(31.8) |
| Vomiting in last 24 hours | 138 (5.8) | 98(5.9) | 40(5.6) |
| Cough in last 24 hours | 387 (16.2) | 277(16.5) | 110(15.4) |

*Table 1.1 (Continued)*

| Characteristic | N (%) or Mean (SD) | Low dietary diversity [a] | High dietary diversity [a] |
|---|---|---|---|
| **Household Characteristics** | | | |
| Household size | 7.3 (3.8) | 7.1(3.8) | 7.4(3.9) |
| Children < 5 y | 1.9 (1.2) | 1.9(1.2) | 2.0(1.3) |
| Maternal age, years | 26.9 (6.6) | 26.9(6.6) | 26.9(6.7) |
| Maternal education: no or incomplete primary school, Koranic school | 2334 (97.9) | 1639(98.0) | 695 (97.6)* |
| Paternal education: no or incomplete primary school, Koranic school | 2191 (94.5) | 1545(95.3) | 646(92.3)* |
| **Household Socio-economic status** | | | |
| Main source of energy for cooking is wood and coal | 2389(100) | 1675(100) | 714(100) |
| Main source of household sanitation is bucket or bush | 1517 (63.5) | 1117(66.7) | 400(56.0)** |
| **Household food security score (HFIAS)[b]** | | | |
| Lean season (May to August) | 6.5 (5.9) | 7.4(6.0) | 4.0(4.9) |
| Not lean season (September to April) | 5.8 (5.6) | 6.4(5.7) | 4.6(5.2) |

***** Significant at 0.05 level; **significant at<0.001.

[a] High dietary diversity was defined intake of ≥ 4 foods groups.

[b] HFIAS score based on sum of score from 8 questions [1]. Maximum score is 24.

Table 1.2 shows the consumption of food groups and DDS at admission. Overall diets in the study population showed limited diversity and were based on consumption of staples and plant based foods. Nearly all children consumed cereals (n = 2364, 99.5%) and vitamin A rich fruits and vegetables (n = 2253, 94.8%) on a daily basis. About half of children ate legumes (n = 1582, 66.6%) and meat (n = 1199, 50.4%) in the last 7 days, but usually only 2–3 per week. Dairy was not commonly consumed among children (n = 659, 27.7%), but when available, it was consumed 4 times per week. Eggs were consumed by one in five children (n = 472, 19.9%), and only twice per week in those reporting consumption. In the lean season when household food availability and access are low and the rainy season had begun, there was significantly lower consumption of legumes, flesh foods, fruits and vegetables and fats and oils. Mean (SD) DDS in the lean season was 2.7 (1.1) food groups/day and the non-lean season it was 2.9 (1.0) food groups/day.

There was no significant association between individual food group intakes or overall DDS with treatment recovery at program discharge or 12 weeks (Table 1.3). However, the consumption of eggs was protective against death while consumption of vitamin A rich fruits and vegetables was associated with greater risk of mortality. For every additional day of egg consumption, the risk of death decreased by 47% (RR: 0.53, 95% CI: 0.39–0.70) at program discharge and 34% (RR: 0.66, 95% CI: 0.45–0.96) at 12 weeks of follow-up. Each additional day of vitamin A rich fruits and vegetables consumption was associated with a 30% increase in risk of death at program discharge (RR:1.30, 95% CI: 1.08–1.56) and a 19% (RR: 1.19, 95% CI:1.03–1.36) increase in risk at 12 weeks. There was no significant association between individual food group intakes with transfer to hospital.

**Table 1.2: Mean consumption of food groups and DD by season for children with SAM**

| | | Lean season (May-August) N=959 | | Non-lean season (September-April) N=1418 | |
|---|---|---|---|---|---|
| **Food group** | **Foods Included** | **N (%) Ever in last 7 days** | **Mean (SD) days in last 7 days** | **N (%) Ever in last 7 days** | **Mean (SD) days in last 7 days** |
| Cereal, roots &tubers | Millet, rice, sorghum, maize, cassava | 949(99.0)* | 6.7(±1.0) | 1415(99.8) | 6.7(±0.9) |
| Legumes | Cowpea, pea, lentils, peanuts, other nuts | 563(58.7)** | 3.4(± 2.0)* | 1019(71.9) | 3.7(±2.0) |
| Dairy | Milk, yogurt, cheese, other dairy products | 286(29.8) | 3.7(±2.2) | 373(26.3) | 3.8(2.3) |
| Flesh foods | Meat, poultry, fish | 427(44.5)** | 2.5(±1.6) | 772(54.4) | 2.6(±1.7) |
| Eggs | Eggs | 203(21.2) | 2.4(±1.6) | 269(19.0) | 2.1(±1.4) |
| Vitamin A rich fruits & vegetables | Pumpkin, carrots, sweet potato, dark green leaves, mango or papaya ripe | 897(93.5)* | 6.3(±2.6) | 1356(95.6) | 6.2(±2.3) |
| Other fruits &vegetables | Other vegetables (tomato, onion, cucumber, zucchini, eggplant, cabbage, okra), other fruits (banana, guava, watermelon) | 449(46.8)** | 4.1(±2.3)* | 792(55.9) | 4.4(±2.2) |

*Table 1.2 (Continued)*

| | | Lean season (May-August) N=959 | | Non-lean season (September-April) N=1418 | |
|---|---|---|---|---|---|
| **Food group** | **Foods Included** | **N (%) Ever in last 7 days** | **Mean (SD) days in last 7 days** | **N (%) Ever in last 7 days** | **Mean (SD) days in last 7 days** |
| Fats &oils | Oil, butterfat, coconut milk, butter | 600(62.6)** | 4.4(±2.2) | 1058(74.6) | 4.3(±2.1) |
| **Dietary diversity score** | Sum of 8 food groups | | 2.7 (1.1)* | | 2.9 (1.0) |

* Significant at 0.05 level; **significant at<0.001.

Counts and means evaluated for significant difference between groups using chi-square and t-test, respectively. Consumption of food groups is calculated among children reported to consume the food group.

**Table 1.3: Association of dietary intake and DDS with outcomes at discharge and 12 weeks**

| Food group | Program discharge [a] | | 12 weeks [a] | |
|---|---|---|---|---|
| | RR Unadjusted (95% CI) | RR adjusted (95% CI) | RR Unadjusted (95% CI) | RR adjusted (95% CI) |
| **Treatment recovery** | | | | |
| Cereals, roots & tubers | 1.02(0.97, 1.08) | 1.00(0.96, 1.05) | 1.01(0.95, 1.07) | 0.98(0.94, 1.03) |
| Flesh foods | 1.00(0.96, 1.04) | 1.00(0.97, 1.03) | 1.00(0.96, 1.05) | 1.00(0.97, 1.03) |
| Legumes | 1.01(0.98, 1.04) | 1.01(0.99, 1.03) | 1.01(0.98, 1.04) | 1.01(0.98, 1.03) |
| Dairy | 1.02(0.98, 1.06) | 1.00(0.96, 1.04) | 1.01(0.97, 1.06) | 0.99(0.94, 1.04) |
| Eggs | 0.98(0.91, 1.06) | 0.98(0.93, 1.04) | 0.98(0.91, 1.07) | 0.98(0.92, 1.04) |
| Vitamin A rich fruits & vegetables | 1.01(0.99, 1.03) | 1.01(0.99, 1.02) | 1.01(0.99, 1.03) | 1.01(0.99, 1.02) |
| Other fruits & vegetables | 1.00(0.97, 1.03) | 0.99(0.97, 1.01) | 1.00(0.96, 1.02) | 0.98(0.95, 1.00) |
| Fat and oils | 1.01(0.98, 1.04) | 1.01(0.99, 1.03) | 1.01(0.98, 1.04) | 1.00(0.98, 1.03) |
| Diet diversity score | 1.06(1.03, 1.09)** | 1.02(0.98, 1.06) | 1.04(1.02, 1.08)* | 0.96(0.91, 1.02) |

*Table 1.3 (Continued)*

| Food group | Program discharge [a] | | 12 weeks [a] | |
|---|---|---|---|---|
| | **RR Unadjusted** (95% CI) | **RR adjusted** (95% CI) | **RR Unadjusted** (95% CI) | **RR adjusted** (95% CI) |
| **Death** | | | | |
| Cereals, roots & tubers | 1.08(0.56, 2.10) | 1.43(0.69, 2.99) | 0.98(0.71, 1.35) | 0.99(0.71, 1.39) |
| Flesh foods | 1.15(0.81, 1.63) | 1.16(0.88, 1.53) | 0.96(0.72, 1.28) | 0.96(0.67, 1.36) |
| Legumes | 0.94(0.69, 1.28) | 0.97(0.80, 1.18) | 0.97(0.79, 1.20) | 1.01(0.83, 1.24) |
| Dairy | 0.59(0.28, 1.26) | 0.74(0.39, 1.39) | 0.91(0.71, 1.18) | 0.70 (0.45, 1.10) |
| Eggs | 0.60(0.24, 1.48) | 0.53(0.39, 0.70)** | 0.65(0.40, 1.06) | 0.66(0.45, 0.96)* |
| Vitamin A rich fruits & vegetables | 0.91(0.72, 1.14) | 1.30(1.08, 1.56)* | 0.91(0.79, 1.04) | 1.19(1.03, 1.36)* |
| Other fruits & vegetables | 0.94(0.68, 1.29) | 1.01(0.67, 1.53) | 1.05(0.85, 1.30) | 1.06(0.79, 1.43) |
| Fat and oils | 0.72(0.51, 1.03) | 0.75(0.51, 1.10) | 0.98(0.82, 1.17) | 0.87(0.68, 1.13) |
| Diet diversity score | 1.17(0.76, 1.82) | 1.54(0.93, 2.55) | 0.86 (0.61, 1.21) | 0.80(0.54, 1.20) |

| *Table 1.3 (Continued)* | | | | |
|---|---|---|---|---|
| **Food group** | **Program discharge [a]** | | **12 weeks [a]** | |
| | **RR Unadjusted** (95% CI) | **RR adjusted** (95% CI) | **RR Unadjusted** (95% CI) | **RR adjusted** (95% CI) |
| **Transfer to hospital** | | | | |
| Cereals, roots & tubers | 0.93(0.87, 1.00) | 0.97(0.91, 1.03) | 0.98(0.91, 1.05) | 1.02(0.95, 1.10) |
| Flesh food | 1.01(0.94, 1.08) | 0.99(0.92, 1.06) | 1.00(0.94, 1.07) | 1.00(0.94, 1.06) |
| Legumes | 0.96(0.91, 1.01) | 0.96(0.91, 1.02) | 0,97(0.92, 1.03) | 0.98(0.93, 1.03) |
| Dairy | 0.96(0.90, 1.02) | 0.99(0.92, 1.06) | 0.97(0.92, 1.03) | 1.01(0.94, 1.07) |
| Eggs | 1.01(0.90, 1.13) | 1.00(0.90, 1.10) | 1.00(0.90, 1.12) | 1.09(0.97, 1.23) |
| Vitamin A rich fruits & vegetables | 0.98(0.95, 1.02) | 0.99(0.96, 1.03) | 1.00(0.97, 1.03) | 1.01(0.98, 1.04) |
| Other fruits & vegetables | 0.99(0.94, 1.04) | 1.03(0.98, 1.08) | 1.01(0.96, 1.05) | 1.04(1.00, 1.09) |
| Fat and oils | 0.99(0.94, 1.04) | 1.01(0.96, 1.05) | 0.99(0.94, 1.03) | 1.01(0.97, 1.05) |
| Diet diversity score | 0.89(0.83, 0.95) | 0.94(0.86, 1.02) | 0.95(0.89, 1.01) | 1.02(0.96, 1.09) |

Abbreviations: CI, confidence interval; RR, relative risk; * significant at 0.05 level; ** significant at <0.001.

a Analysis excludes 22 children that were exclusively breastfed as they were not expected to consume complementary foods. All food groups were modeled as continuous variables. Covariate selection based on significance in univariate models at $p < 0.20$. RR for individual food groups reflects association for a 1-day unit increase in consumption and RR for DDS reflects association for a 1 unit increase in DDS.

There was no significant association of DDS with the rate of weight change among recovered children. However, each additional day of legume and nut consumption was associated with increased rate of weight gain at discharge (mean change 0.16 g/kg/day, 95% CI: 0.03–0.30) and an additional day of vitamin A rich fruits and vegetable consumption with a small increase in weight gain at 12 weeks (mean change 0.06 g/kg/day, 95% CI: 0.01–0.11) (Table 1.4).

Exploratory analyses included an assessment of any non-linear relationship between the exposures of interest (food group intake and DDS) and all outcomes using restricted cubic splines, as well as alternative categorizations of dietary diversity (e.g. binary [±4 food groups/day], defining intake as a minimum of ≥3 times in the last 7 days and using the WHO dietary diversity index for infant and young feeding [19]); all results were similar to those presented here (results not shown).

Table 1.5 shows predictors of nutritional recovery. The severity of WHZ at admission was marginally associated with the likelihood of recovery, with children with WHZ < − 3 having lower odds of recovery compared to better nourished children (OR: 0.21, 95% CI: 0.04–1.03, p = 0.05). Further, children recruited into the study in the lean months, were less likely to recover compared children treated in the non-lean season (OR: 0.51, 95% CI: 0.26–1.01, p = 0.05). Additionally, seeking health care in the last 30 days was associated with increased risk of recovery (OR: 2.29, 95% CI: 1.1–4.47, p = 0.01).

**Table 1.4: Food groups consumed by rate of weight and height gain among recovered children**

| | Mean weight gain (g/kg/day) | | | | | | | | Mean height gain (mm/day) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 week | | 2 weeks | | Discharge | | 12 weeks | | 12 weeks | |
| **Food group** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** |
| Cereals, roots and tubers | 9.38 | -0.07 (-0.47, 0.33) | 6.51 | -0.05 (-0.26, 0.17) | 4.32 | 0.05 (-0.09, 0.19) | 2.01 | -0.04 (-0.10, 0.02) | 4.96 | 0.10 (-0.12, 0.32) |
| Meats | 9.56 | -0.13 (-0.43, 0.17) | 4.81 | 0.15 (-0.07,0.37) | 4.62 | 0.03 (-0.08, 0.14) | 1.82 | 0.04 (-0.01, 0.08) | 6.86 | -0.29 (-0.29, 0.04) |
| Legumes | 8.20 | 0.02 (-0.18, 0.22) | 5.89 | -0.07 (-0.22, 0.08) | 3.61 | 0.16 (0.03, 0.30)* | 1.73 | 0.02 (-0.01, 0.05) | 5.42 | -0.05 (-0.17, 0.07) |
| Dairy | 11.56 | -0.17 (-0.51, 0.17) | 6.58 | -0.13 (-0.29, 0.04) | 4.88 | -0.02 (-0.14, 0.08) | 1.65 | -0.03 (-0.08, 0.01) | 6.36 | -0.31 (-0.65, 0.03) |
| Eggs | 7.28 | -0.02 (-0.57, 0.54) | 4.55 | -0.13 (-0.41, 0.16) | 4.01 | 0.07 (-0.13, 0.26) | 1.43 | 0.00 (-0.09, 0.09) | 4.17 | -0.15 (-0.45, 0.15) |
| Vitamin A rich fruits and vegetables | 8.67 | 0.02 (-0.13, 0.18) | 5.99 | 0.00 (-0.08, 0.09) | 4.40 | 0.03 (-0.03, 0.08) | 1.45 | 0.06 (0.01, 0.11)* | 5.61 | 0.05 (-0.04, 0.13) |

*Table 1.4 (continued)*

| | Mean weight gain (g/kg/day) | | | | | | | | Mean height gain (mm/day) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 1 week | | 2 weeks | | Discharge | | 12 weeks | | 12 weeks | |
| **Food group** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** | **Mean** | **Adj. (95% CI)** |
| Other fruits and vegetables | 7.14 | -0.05 (-0.27, 0.17) | 4.72 | -0.06 (-0.18, 0.05) | 3.87 | -0.00 (-0.08, 0.07) | 1.71 | 0.03 (-0.05, 0.10) | 5.58 | -0.03 (-0.15, 0.09) |
| Fat and oils | 8.54 | -0.12 (-0.32, 0.08) | 5.53 | -0.03 (-0.13, 0.07) | 4.21 | -0.02 (-0.09, 0.05) | 1.60 | 0.01 (-0.02, 0.04) | 6.18 | -0.05 (-0.16, 0.05) |
| Diet diversity score | 8.41 | 0.15 (-0.21, 0.51) | 6.52 | -0.13 (-0.40, 0.14) | 4.31 | 0.12 (-0.01, 0.25) | 1.64 | 0.03 (-0.02, 0.09) | 5.59 | 0.03 (-0.17, 0.23) |

Abbreviations: CI, confidence interval; Adj, Adjusted models; * Significant at 0.05 level; **Significant at <0.001

Analysis excludes 22 children that were exclusively breastfed they were not expected to consume complementary foods. Analysis modeled using linear regression.

**Table 1.5: Predictors of nutritional recovery among 2,377 children treated for SAM in Niger**

| Variable | Univariate OR (95% CI) | Adjusted OR (95% CI) |
|---|---|---|
| Child age | | |
| 6-11months | 0.51(0.41, 0.65) | 0.93(0.24, 3.58) |
| 12-23 months | 0.77(0.61, 0.98) | 1.68(0.54, 5.17) |
| Wasting | | |
| Moderate wasting (-3.0<=WHZ<-2.0) | 0.65(0.41, 1.01) | 0.40(0.08, 2.01) |
| Severe wasting (WHZ<-3.0 ) | 0.41(0.26, 0.63) | 0.21(0.04, 1.03) |
| Number of children under 5 years | 1.05(0.98, 1.12) | 1.23(0.92, 1.64) |
| Maternal age | 1.02(1.01, 1.04) | 1.03(0.92, 1.08) |
| Lean season at time of enrolment | 0.59(0.50, 0.70) | 0.51(0.26, 1.01) |
| Household size | 1.15(0.95, 1.40) | 0.76(0.34, 1.72) |
| Sought health care for child in the last 30 days | 1.57(1.07, 2.30) | 2.29(1.18, 4.47) |
| Positive rapid malaria test | 1.45(1.23, 1.72) | 1.89(0.93, 3.84) |
| Anti-malarial medication received in previous 7 days | 1.44(0.98, 2.12) | 1.37(0.71, 2.62) |
| Antibiotic use prior to study | 0.66(0.37, 1.17) | 0.55(0.17, 1.78) |
| Runny nose | 1.74(1.40, 2.15) | 0.53(0.22, 1.28) |
| Respiratory rate | 0.98(0.97, 1.00) | 0.96(0.88, 1.05) |
| Cough | 1.40(1.11, 1.77) | 1.10(0.36, 3.36) |
| Child anemia (hemoglobin <8.5 g/dL) | 1.46(1.21, 1.77) | 1.18(0.54, 2.60) |
| Currently breastfeeding | 0.66(0.55, 0.79) | 0.74(0.29, 1.86) |
| Drug regimen (Amoxicillin) | 1.15(0.97, 1.36) | 0.82(0.45, 1.51) |
| Male child | 0.82(0.69, 0.97) | 1.22(0.63, 2.35) |
| Consulting for child's health | 1.32(1.07, 1.63) | - |

| *Table 1.5 (Continued)* | | |
|---|---|---|
| **Variable** | **Univariate OR (95% CI)** | **Adjusted OR (95% CI)** |
| Child received Ready to use supplementary foods(RUSF) prior to study | 1.42(1.06, 1.90) | 1.17(0.41, 3.35) |

Abbreviations: CI, confidence interval; OR, odds ratio; * significant at 0.05 level; **significant at p<0.001.

Analysis excludes 22 children that were exclusively breastfed. They were not expected to consume complementary foods.

Analysis modeled using logistic regression.

## Discussion

We evaluated the relationship of dietary intake and diversity with nutritional program outcomes and response to treatment among children with uncomplicated SAM in Niger. Overall, we found that children with more diverse diets at admission did not have superior rates of nutritional recovery, decreased occurrences of hospitalization or death, nor increased rates of weight and height gain. The consumption of eggs was protective against death at program discharge and at 12 weeks of follow-up. The consumption of vitamin A rich fruits and vegetables however increased risk of mortality in children treated for uncomplicated SAM in Niger.

Poor dietary diversity has previously been associated with stunting and edema [20, 21], but to our knowledge, there has been no previous study of its potential role in SAM treatment. Our findings provide no evidence to support a role for diet diversity in SAM treatment, suggesting that other factors may more strongly contribute to recovery. Several possibilities may explain the observed lack of association in this population. During treatment, children are provided with sufficient ready to use therapeutic food (RUTF) to meet nutritional needs

during rehabilitation, and adherence to prescribed RUTF may be more influential in recovery, compared to dietary diversity at admission. Previous work by Yebyo et al. found that Ethiopian children who consumed one additional sachet of RUTF increased the likelihood of recovery by 4% (95% CI: 1.03, 1.05, $p < 0.001$) [9]. Our study collected information on reported RUTF consumption during treatment, and reported compliance was not significantly associated with recovery (results not shown).

We considered that dietary diversity may be important for treatment response through the consumption of specific food groups, such as animal-source foods previously shown to be important for improving diet quality, micronutrient status, and growth [20, 22]. Our study did not find evidence that consumption of animal-source foods, such as meats and dairy, influenced nutrition recovery or rate of weight gain, but intake of dairy and meats was low in this population. Reported diets may not have included sufficient quantities or variability of food group intake to influence recovery. Egg consumption, however, was associated with a significant reduction in the risk of death at discharge and 12 weeks. This finding is particularly important given limited consumption of eggs in the study. Eggs contain almost complete protein, B vitamins, and essential fatty acids (EFA) including the omega 6 fatty acid, arachidonic acid, and omega 3 fatty acid, docosahexanoic acid [23, 24]. EFA have been associated with increased growth and development in children [23, 24]. Ionnotti et al. further suggest that since eggs contain critical micro- and macronutrients in highly bioavailable forms, they may have value in enhancing plant-based diets for children in developing countries [23, 24]. Mosites et al. also provide evidence for the role of EFA and complete protein from egg consumption to protect against mortality in Western Kenya [25]. An unexpected finding from this study was that the consumption of vitamin A rich fruits and vegetables was associated with an increased risk of

death at discharge and 12 weeks. A potential explanation for this finding is that in poor resource areas, consumption of vitamin A rich vegetables could signify the unavailability of more nutrient dense, and more expensive, animal-source foods.

We sought to determine independent predictors of treatment recovery aside from dietary intake and diversity. We found that WHZ severity had a trend towards independently decreasing the odds of recovery. This finding was in line with Gebremichael et al., who showed that weight at recruitment lower than the mean increased nutritional recovery time for severely malnourished children [26]. James et al. also found that WHZ less than − 3.5 was associated with lower odds for recovery among children in Myanmar [27]. Similarly, in an inpatient program of non-edematous children aged 6–59 months in Uganda, low WHZ at admission was a significant risk factor for mortality [28]. This association is supported by the mechanism in which acute malnutrition impairs a child's ability to respond to infection and environmental stressors [29]. We also found a marginal association with season (P = 0.05), as children recruited in the lean months (May to August) were less likely to recover compared children treated in the non-lean season. Although RUTF is provided in quantities sufficient to meet nutrient needs for recovery, lower food availability during the lean season may increase sharing within the household or sales of RUTF intended for the index child [30]. Season may therefore be predictive of recovery. Finally we also found that seeking health care in the last 30 days was associated with increased recovery. This is plausible given the interaction between malnutrition and infection [31] . Recent consultation at a health service may also be a proxy for positive health care and dietary behaviors. A study in Malawi found poorer nutritional recovery in younger children,

those with marasmic kwashiorkor, stunting, infection, and cough at enrolment [32]. Another program in Ethiopia found that diarrhea, vomiting, average weight gain, amoxicillin and de-worming medication were positively associated with recovery [9]. Differences in predictors of nutritional recovery may be due to the contextual nature of malnutrition and SAM, with the relative importance of determinants differing based on the local context.

This study has several strengths and limitations. To our knowledge, this study provides the first evidence related to the possible role of dietary intake and diversity in the nutritional recovery of severely malnourished children. Other strengths of the study include a large study population, and an in-depth assessment of clinical and socio-economic factors associated with SAM in this setting. A key limitation of the study is that dietary intake for children was measured at baseline only, prior to the start of treatment.

Further, we could not apply a minimum amount of food intake in the DDS calculation. Studies have shown that when minimum amounts of consumption are considered (eg at least 10 g or 15 g of food consumed for it contribute to food groups), the association of DDS with nutrient adequacy and sensitivity of the DDS indicator are improved [10, 17, 33]. Incorporation of portion sizes may help DDS identify children with low dietary diversity, [33] although consideration of a cut-off of consumption of food groups at least 3 times did not substantially change the results (data not shown).

## Conclusion

In this study, neither dietary intake nor diversity were associated with nutrition recovery or response to treatment of children with uncomplicated SAM. It is feasible that beyond dietary diversity, the consumption of energy dense foods like eggs may be more important for recovery

from SAM. There is need for continued research to further elucidate the drivers of nutritional recovery from acute malnutrition in different settings to inform recommendations to support nutritional recovery and response to treatment.

## Abbreviations

CI: Confidence interval; DDS: Diet diversity score; EFA: Essential fatty acids; FFQ: Food frequency questionnaire; MSF: Médecins Sans Frontières; MUAC: Mid-upper arm circumference; OR: Odds ratio; RR: Relative risk; RUTF: Ready to use therapeutic food; SAM: Severe acute malnutrition; WHO: World Health Organization; WHZ: Weight-for-height Z score

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## Conflict of interest

The authors have nothing to disclose.

## Authors' contributions

I.M. conceived the study, conducted the data analysis, and drafted the article. S.I. was the principal investigator for the parent study, conceived the study, contributed to study design, interpreted the data, and guided revisions of the manuscript. C.D. contributed to study design, interpreted the data, and guided revisions of the draft manuscript. F.B. and R.G where co-principal investigators for the parent study, participated in the study implementation and field supervision, interpreted the data, and guided revisions of the manuscript. All authors contributed to the editing of the final version of the manuscript. All authors read and approved the final manuscript.

**Ethics approval and consent to participate**

The study was approved by the ethics committees of the Comité Consultatif National d'Éthique, Niger and the Comité de Protection des Personnes, Îlede-France XI, Paris. Written informed consent was obtained from the parent or legal guardian of all participating children.

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**Paper II**

# Maternal dietary diversity and dietary quality scores in relation to adverse birth outcomes in Tanzanian women

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**Abstract**

**Background:** Preterm birth, small for gestational age (SGA) and low birth weight (LBW) are risk factors for morbidity and mortality among infants. High-quality maternal diets during pregnancy may protect against these adverse birth outcomes.

**Objective:** To examine the association of maternal dietary diversity and diet quality during pregnancy with poor birth outcomes among women in Dar es Salaam, Tanzania.

**Design:** We analyzed data from 7,553 HIV-negative pregnant women enrolled in a multivitamin trial at 12-27 weeks gestation. Dietary intake was assessed using 24-hour dietary recalls. Log binomial regression methods were used to assess associations of Minimum Dietary Diversity for Women (MDD-W) and Prime Diet Quality Score (PDQS) with preterm, SGA, LBW, fetal loss, very preterm, severe SGA and very low birth weight (VLBW).

**Results:** In the previous 24 hours, 99.9% of women reported consuming grains, roots and tubers, 57.9% meats, 4.7 % eggs and 0.5% nuts and seeds. Median MDD-W score was 3.0±1.0. For the PDQS, women consumed at least 4 servings/week of green leafy vegetables (100%) and other vegetables (64.7%) and consumption of refined grains was high (99.6%). Higher MDD-W scores were associated with lower risk of SGA (RR highest vs. lowest quintile 0.74, 95% CI: 0.62, 0.89). Higher PDQS scores were associated with lower risk of preterm birth (RR: 0.55, 95 % CI: 0.46, 0.67); LBW (RR: 0.53, 95 % CI: 0.40, 0.71); fetal loss (RR: 0.53, 95% CI: 0.34,0.82), very preterm (RR: 0.33, 95% CI: 0.17, 0.64) and VLBW (RR: 0.49, 95% CI: 0.26, 0.92) comparing women in highest vs. lowest quintiles.

**Conclusions:** PDQS was inversely associated with preterm, very preterm, LBW, VLBW and fetal loss and MDD-W was inversely associated with SGA. These findings suggest that in

addition to diet diversity, diet quality should be considered as important in understanding dietary risk factors for poor birth outcomes.

## Introduction

Global progress in child survival cannot be achieved without addressing poor birth outcomes [2-4]. There were 5.4 million deaths in children under 5 years in 2016, many (40%) in the neonatal period [5]. Low birth weight (LBW), and its contributing factors - preterm birth and intrauterine growth restriction (IUGR) - are key determinants of neonatal mortality [6-10]. LBW affects approximately 14.6% of children and preterm birth affects 1 in 10 births yearly, the majority in developing regions [7, 10, 11]. Tanzania is not an exception as shown by high rates of preterm (15.3%), small for gestational age (SGA) (16.6%) and LBW (10.5%) births [11, 12]. Poor birth outcomes are risk factors for morbidity including pneumonia, diarrhea, sepsis and mortality in early life and predispose children to stunting, wasting, poor cognitive development, and obesity and non-communicable diseases in adulthood [6, 10, 13-18]. Understanding the factors that lead to poor birth outcomes is thus of great public health importance.

Pregnancy is associated with changes in nutrient metabolism and maternal physiology to support fetal growth, maintain maternal health, and prepare for lactation [19, 20]. If physiologic and maternal changes, including dietary changes, are inadequate to meet pregnancy demands, fetal growth and development may be impaired [19]. While nutrient requirements increase during pregnancy [20], in Africa, Asia and Latin America, both pregnant and non-pregnant women have poor intakes of micronutrients [21, 22]. Limited evidence has been published about optimal dietary patterns during pregnancy to promote healthy birth outcomes in low and middle income countries (LMICs) [23].

Dietary pattern analysis, which considers the effects of overall diets on disease rather than individual nutrients or foods has been under-utilized in LMICs, because it requires conduct of expensive food consumption studies and complex analysis [22, 24]. Diet quality indices, have

great potential for use in LMICs given their ease of collection and interpretation [22]. In previous studies in LMICs, maternal diet diversity (DD) in pregnancy has been inversely associated with LBW, preterm and SGA [16, 25, 26]. However, studies are few and limited by small sample sizes, and differences in measurement of DD, making firm conclusions difficult.

The Food and Agriculture Organization (FAO) has proposed the Minimum Dietary Diversity for Women (MDD-W), as a tool to measure nutrient adequacy [27, 28]. In multi-country analysis, the MDD-W was shown to be predictive of micronutrient adequacy for vitamin A, folate, iron, zinc and other micronutrients [22, 28]. However, the MDD-W has not been evaluated for its associations with birth outcomes. The Prime Diet Quality Score (PDQS) is also a food group-based dietary score that has been developed to measure diet quality. Simple and easy to compute, the PDQS has been evaluated for associations with chronic diseases such as coronary heart disease and pregnancy related morbidities (gestational diabetes and hypertensive diseases of pregnancy) in developed country settings [29, 30]. However, the association of the PDQS with birth outcomes has not been evaluated in LMICs.

We hypothesized that high quality maternal diets during pregnancy will protect against the occurrence of poor birth outcomes. The current study therefore examined the associations of maternal dietary diversity and dietary quality, respectively measured by the MDD-W and PDQS during pregnancy, with birth outcomes in a cohort of HIV-negative pregnant women in Tanzania.

## Methods

### Study population

The parent study was a double-blind, randomized placebo-controlled trial, conducted to evaluate the effect of multivitamin supplementation on birth outcomes in Dar es Salaam, Tanzania from August 2001 to July 2004. The study included 8,428 HIV-negative pregnant women who were randomized to receive multivitamin supplementation (vitamin B1, B2, B6, niacin, B12, C and E) or placebo from enrollment to 6 weeks post-partum [31]. Participants were women aged 18-45 years who were between 12 and 27 weeks gestation at enrollment and intended to stay in the city for 1 year after delivery. All women received standard of care including iron (60 mg of elemental iron) and folic acid (0.25 mg) supplementation and malaria prophylaxis (Fansidar) according to then current Tanzanian national guidelines [31]. The parent study and its main findings are described elsewhere [31].

*Study procedures and follow-up*

Study participants were recruited from 9 antenatal clinics in urban areas. Gestational age at enrollment was established based on menstrual history. Consenting, eligible pregnant women received pre-test counseling and were screened for HIV and syphilis. Trained research nurses administered a baseline questionnaire that included sociodemographic and obstetrical history for recruited women. Women attended monthly follow-up visits up to 6 months post-partum as per the trial protocol. In monthly follow-up visits, questionnaires were administered to evaluate interim medical problems. As standard of care, all women received routine antenatal care (ANC) visits. Research midwives attended to the women at delivery and measured birth weights of infants to the nearest 10 grams and birth length to the nearest 0.1cm [31].

**Dietary diversity and quality**

The primary exposures of interest, maternal dietary diversity (MDD-W) and maternal

dietary quality (PDQS) during pregnancy, were assessed using 24-hour dietary recall questionnaires administered to mothers at recruitment and at subsequent monthly follow-up visits during pregnancy. Women were asked to recall food consumed in the previous 24 hours, from when they woke up the previous day to the time they went to bed. Common household utensils were used to estimate portion sizes.

*MDD-W*

Diet diversity food groups were computed based on guidance provided by FAO for the MDD-W [27]. The MDD-W was proposed for adoption in low and middle income regions based on evidence that it was positively correlated with mean nutrient adequacy for 11 micronutrients (vitamin A, thiamin, riboflavin, niacin, vitamin B-6, folate, vitamin B-12, vitamin C, calcium, iron, and zinc) [22, 27]. As proposed by FAO, 10 food groups were computed: starchy staples; beans and peas; nuts and seeds; dairy; flesh foods (meat, fish); eggs; vitamin A rich dark green vegetables; other vitamin A rich fruits and vegetables; other vegetables; and, other fruits [27]. For mixed dishes, we categorized foods based on their main components based on the Tanzania food composition tables to minimize misclassification [32]. We included fruit juices under other fruits, and maize and kidney bean dishes under cereals and legumes groups. If a food was eaten at least once in the previous 24 hours, it was considered to contribute to the food group. No minimum weight restriction was considered for classifying foods into food groups. Scores for MDD-W were computed as the total number of food groups consumed in the previous 24 hours. All available measures of dietary intake during pregnancy were used, with mean dietary diversity computed as the arithmetic mean of all available measures of prenatal diet diversity scores for each woman.

*PDQS*

Foods consumed by women during pregnancy in each 24 hour recall were classified into 21 food groups for the PDQS. Foods were classified as healthy (dark green leafy vegetables, other vitamin A rich vegetables (including carrots), cruciferous vegetables, other vegetables, whole citrus fruits, other fruits, fish, poultry, legumes, nuts, low fat dairy, whole grains, eggs, liquid vegetable oils) or unhealthy (red meat, processed meats, refined grains and baked goods, sugar sweetened beverages, desserts and ice cream, fried foods obtained away from home and potatoes) based on criteria determined by previous studies [29, 30]. We modified the score with the creation of "other vitamin A rich fruits and vegetables" category which included red and orange fruits and vegetables compared to the inclusion of carrots only as a food group as in previous studies [29]. In our study location, while consumption of carrots may be low, there are other fruits and vegetables that are local sources of Vitamin A.

The number of servings of food groups were calculated for each day of dietary recall. We considered each occasion of consumption of a food group as a serving. We then computed the mean number of servings over the available recall days for each woman. The mean number of servings for each food group were then multiplied by 7 to standardize to the number of servings per week, from which points for each food group could be assigned based on whether the food was categorized as healthy and unhealthy [30]. Points were assigned for consumption of healthy food groups as: 0–1 serving/week (0 points), 2–3 servings/week (1 point) and ≥4 servings/week (2 points). Scoring for unhealthy food groups was assigned as: 0–1 serving/week (2 points), 2–3 servings/week (1 point) and ≥4 servings/week (0 points). Points for each food group were then summed to give an overall score. Consumption of low fat dairy and processed meats was not recorded in the parent study, but is believed to be low in Tanzania [33]. Refined grains were defined based on classification from previous studies [29, 30]. Millet- and sorghum-

based foods were categorized as whole grains and maize flour based were classified as refined grains in the analysis.

**Study outcomes**

The primary study outcomes were preterm birth (<37 weeks gestation), small for gestational age (determined using the INTERGROWTH standards of birth weight <10th percentile for gestational age and sex) [34], LBW (defined as birth weight <2,500 grams) and fetal loss defined as spontaneous abortion or stillbirth. The secondary outcomes of the study were very low birth weight (VLBW, birth weight < 2,000 grams), very preterm births (<32 weeks gestation), and severe SGA (defined as birth weight <3rd percentile for gestational age and sex based on INTERGROWTH standards) [35].

*Ethics*

Approval for the study was provided Muhimbili University College of Health Sciences (Dar es Salaam) and Harvard T. H. Chan School of Public Health (Boston) institutional review boards. Written informed consent was obtained from all enrolled women.

**Statistical analysis**

The analysis was restricted to women with singleton births. Extreme diet measures for women, defined as total daily caloric intake < 500 kcal or > 4,000 kcal or total daily protein intake < 7 grams or > 200 grams, were excluded from the analysis. MDD-W and PDQS quintiles were calculated based on all available dietary data. We computed Spearman correlations between continuous MDD-W and PDQS scores to evaluate their association. Socio-economic and demographic characteristics of the study population were evaluated comparing quintiles 1

and 5 of diet scores, using the chi-square (categorical variables) and the Wilcoxon rank-sum tests (continuous variables). Consumption of PDQS food groups by study women was similarly compared. Consumption of PDQS food groups by study women was also described. Log binomial regression [36] was used to evaluate the associations of MDD-W and PDQS with the primary and secondary outcomes.

Potential confounders for each outcome were selected based on associations with the outcome in univariate regression models at levels of $p < 0.20$. Confounders considered included maternal characteristics (age, marital status, education, history of fetal loss, parity, maternal height or maternal shortness (height<145cm)), household income and wealth characteristics (food expenditure less than 500 Tanzanian shillings/person/day, wealth index developed using the Filmer-Pritchett wealth methodology [37] (households above/below the median)), season (dry (December to March), long rains (April to May), harvest (June to September) and short rain (October to November)) [38]. All models adjusted for multivitamin group assignment (placebo/multivitamin) and child sex (male/female). Final models adjusted for energy intake using restricted cubic splines, maternal body mass index (underweight (BMI<18.5), normal weight (BMI 18.5 - 24.99), overweight (BMI 25 - 29.99), obese (BMI $\geq$ 30 kg/m$^2$)), and anemia ((severe, haemoglobin <8.5 g/dL), (moderate, haemoglobin 8.5 -10.9 g/dL), (none, haemoglobin $\geq$11 g/dL)) at baseline. The missing indicator method was used to deal with missingness in the confounder data [39]. Complete case analysis was conducted as a sensitivity test.

Tests for trend were conducted for multivariate models using median scores for MDD-W and PDQS quintiles. Exploratory analyses were conducted with a binary indicator for MDD-W, defined as the consumption of 5 or more food groups out of 10 in the previous 24 hours [27]. At this predetermined cut-off, women are most likely to meet their micronutrient intake based on

validation studies [22, 27].

Finally, effect modification by treatment regimen was tested in fully adjusted models. The likelihood ratio test (LRT) based on a significance level of p less than 0.05 was used to evaluate effect modification. Statistical analysis was conducted using SAS version 9.4.

**Results**

A total of 7,553 pregnant women with singleton births and at least one 24hr dietary recall during pregnancy were included in the analysis. The analysis excluded 133 women with extreme dietary intake (total daily caloric (<500 kcal or > 4,000 kcal) or protein (< 7 grams or > 200 grams) intake). Missing observations for covariates ranged from 0-16%.

Diet was assessed in women up to 7 times during pregnancy. In 6,293 women, diet was measured a second time, 3,883 women had diet measured on 3 occasions, and 1,499 women had 4 diet measurements. Mean gestational age of the baseline/first measure for women was 28.8 (SD ±3.8) weeks. Diet diversity was very low for study women. The median MDD-W score during pregnancy was 3.0 (IQR: 2.5-3.5). Only 213 (2.8%) of the women assessed had a mean score of MDD-W of at least 5, the FAO definition of minimum dietary diversity. PQDS scores for women ranged from 10 to 28, with a median score of 19 (IQR:17-20). The Spearman correlation between the MDD-W and the PDQS was 0.36 ($p<0.001$)

Table 2.1 describes the baseline characteristics of the study population. The distribution of baseline characteristics was similar for MDD-W and PDQS, comparing women in quintile 1 to those in quintile 5. Women in quintile 5 of both indices were older and more educated, consumed more calories, and had lower prevalence of anemia, compared to women in the lowest quintile of intake. For MDD-W, women with most diverse diets had greater food expenditure per day and higher prevalence of BMI between 25 and 30 kg/m$^2$, and BMI of 30 kg/m$^2$ or greater.

There were no significant differences in assignment to multi-vitamins or placebo within the main trial in either score.

**Table 2.1: Baseline socio-demographic characteristics by mean diet diversity score quintiles**

| | **Mean diet diversity score[2] (MDD-W)** | | **Prime diet quality score (PDQS)** | |
|---|---|---|---|---|
| **Characteristics** | **Quintile 1** | **Quintile 5** | **Quintile 1** | **Quintile 5** |
| | **N=1550** | **N=1448** | **N=1732** | **N=1390** |
| **Study characteristics[1]** | | | | |
| *Multivitamin regimen* | | | | |
| Placebo | 781 (50.4) | 698(48.2) | 852(49.3) | 664(47.8) |
| Multivitamin | 769 (49.6) | 750(51.8) | 878(50.7) | 726(52.2) |
| *Gestational age at recruitment (wks)* | 21.5±3.4 | 21.4±3.4 | 22.0±3.3 | 20.6±3.4** |
| **Maternal demographic characteristics** | | | | |
| *Maternal age (years)* | | | | |
| Mean (±SD) | 24.7±4.9 | 25.9±5.1** | 25.0±5.0 | 25.8±5.1** |
| 15-<25 | 924(59.9) | 721(48.2)** | 998(57.9) | 690(50.0)* |
| 25 -<35 | 558(36.2) | 667(46.4)** | 640(37.1) | 616(44.6)* |
| ≥35 | 61(4.0) | 79(5.5)** | 87(5.0) | 74(5.4)* |
| *Education achievement* | | | | |
| Primary school or none | 1329(86.0) | 942(65.4)** | 1391(80.6) | 959(69.4)** |
| Secondary school | 183(11.8) | 332(23.1)** | 267(15.5) | 307(22.3)** |
| Tertiary education | 34(2.2) | 166(11.5)** | 67(3.9) | 115(8.3)** |

***Table 2.1 (Continued)***

| | **Mean diet diversity score[2] (MDD-W)** | | **Prime diet quality score (PDQS)** | |
|---|---|---|---|---|
| **Characteristics** | **Quintile 1** | **Quintile 5** | **Quintile 1** | **Quintile 5** |
| Overweight | 380(27.9) | 398(31.0)* | 3431(28.9) | 360(29.8) |
| Obese (BMI≥30) | 124(9.1) | 143(11.1)* | 137(9.2) | 126(10.4) |
| *Haemoglobin at baseline* | | | | |
| Mean (±SD) *(g/dL)* | 10.2±1.6 | 10.3±1.5* | 10.2±1.5 | 10.4±1.5* |
| Severe anaemia (<8.5 g/dL) | 174(13.1) | 124(10.1)* | 186(12.3) | 110(9.3)* |
| Moderate anaemia (8.5-10.9 g/dL) | 726(54.8) | 673(54.7)* | 849(56.3) | 639(53.8)* |
| Normal (≥11 g/dL) | 424(32.0) | 34(35.3)* | 472(31.3)) | 439(37.0)* |
| **Other Characteristics** | | | | |
| *Energy intake* | | | | |
| Median (±IQR) *kcal* | 2,095(±1,286) | 2,390(±1,267)** | 2,158(±1,352) | 2,270(±1,222)* |
| *Season of maternal dietary* | | | | |
| Dry (Dec to Mar) | 630(40.7) | 577(39.9) | 647(27.4) | 619(44.5)** |
| Long rains (April-May) | 133(8.6) | 120(8.3) | 153(8.8) | 88(6.3)** |
| Harvest (June-Sept) | 546(35.2) | 507(35.0) | 682(39.4) | 435(31.3)** |
| Short rain (Oct-Nov) | 241(15.6) | 244(16.9) | 250(14.4) | 248(17.8)** |
| *Sex of child* | | | | |
| Female | 766 (49.4) | 712(49.2) | 848(49.0) | 691(49.7) |

Abbreviations: *p<0.05, ** p<0.001. MDD-W: Minimum dietary diversity for women. PDQS: Prime diet quality score.

[1] Frequencies (%) are shown for categorical variables, mean ±SD for continuous variables. Chi square p values reported for categorical/binary variables and the Wilcoxon test for continuous variables.

[2] Diet diversity scores for women based on mean of repeated 24-hour dietary recalls. Quintiles were calculated.

[3] TShs, Tanzanian shillings (US dollar is estimated at ~1250 shillings) at the time of the study.

Table 2.2 shows food groups consumed by pregnant women in the previous 24 hours at all prenatal measurements. In the previous 24 hours, 99.9% of women reported consuming grains, roots and tubers, 57.9% meats, 4.7% eggs and 0.5% nuts and seeds. Consumption of meats ranged from 43.8% in the lowest quintile of MDD-W to 70.4% in the highest quintile, while consumption of other fruit ranged from 4.6% to 54.9% in the same groups. Table 2.3 shows PDQS classification for women in the study. All women consumed 4 or more servings of dark green leafy green vegetables and 64.7% other vegetables per week. However, other healthy foods, including nuts, whole grains, citrus fruits and eggs were consumed infrequently by women (Table 2.3). Refined grains (99.6%) were the most commonly consumed unhealthy food group. Consumption of 4 or more servings of red meats was higher in women in the lowest quintile compared to the highest quintile (36.7% vs. 12.7%) of the PDQS, while consumption of legumes was highest in quintile 5 compared to the lowest quintile (75.5% vs. 8.3%).

*Preterm birth and very preterm birth*

There were 1152 cases (15.3%) of preterm and 112 cases (1.5%) of very preterm births in the study. In multivariate analysis (Table 2.4), there were no significant associations between the MDD-W and risk of preterm (RR: 0.97, 95% CI: 0.82, 1.16) and very preterm births (RR: 0.97, 95% CI: 0.55, 1.73), comparing women in quintile 5 to those in quintile 1 of the MDD-W. Models for the PDQS showed an inverse association with preterm birth. In adjusted models,

women in the highest quintile of PDQS had 45% lower risk of preterm (RR:0.55, 95% CI: 0.46, 0.67, P<0.001), and 67% lower risk of very preterm births (RR: 0.33, 95% CI: 0.17, 0.64, P<0.01) compared to women in the first quintile.

*Small for gestational age and severe SGA*

There were 1,120 cases (16.4%) of SGA and 460 (6.7%) cases of severe SGA in the study. There was a significant association between MDD-W and SGA. In multivariate analysis (Table 2.4), women with highly diversified diets (quintile 5 of MDD-W) during pregnancy had a 26% reduction in risk of SGA (RR=0.74, 95% CI=0.62, 0.89, P<0.01), compared to women with least diversified diets (quintile 1). There was no association between PDQS and SGA (RR=0.91, 95% CI=0.76, 1.08) and severe SGA (RR=0.85, 95% CI=0.64, 1.13) comparing women in the quintile 5 of the PDQS to women in the quintile 1 (lowest quality diets).

*Low birth weight and very low birth weight*

There were 448 cases (6.3%) of LBW and 96 cases (1.4%) of VLBW in the study. In multivariate analysis (Table 2.4), the MDD-W showed no association with risk of LBW (RR: 0.80, 95% CI 0.61, 1.04), and VLBW (RR: 1.18, 95% CI 0.64, 2.19) comparing women in the fifth quintile to women in the first quintile. The PDQS was significantly associated with LBW in multivariate models. Women with the highest diet quality (quintile 5, PDQS) had a 47% lower risk of having LBW births (RR =0.53, 95% CI: 0.40, 0.71, P<0.001), compared to women with lowest quality diets. Similarly, women in the highest quintile of PDQS had a lower risk of VLBW (RR:0.49, 95% CI: 0.26, 0.92, P=0.03) compared with women in the lowest quintile.

**Table 2.2: Food groups consumed at all times by pregnant women in Tanzania by MDD-W quintiles**

| Food Group[2] | Food list | Overall N (%) | Q1 N=3937 N (%) | Q2 N=4250 N (%) | Q3 N=4244 N (%) | Q4 N=4162 N (%) | Q5 N=3673 N (%) |
|---|---|---|---|---|---|---|---|
| Starchy staples[2] | *Traditional doughnut(mandazi), maize, bread, cassava, chapati, irish potato, pilau, plantain, sweet potato, taro, ugali* | 20232(99.9) | 3911(99.6) | 4250(100) | 4244(100) | 4157(99.9) | 3670 (99.9)** |
| Beans and peas[2] | *Bambara nuts, beans, mung bean (choroko), chickpea (dengu), cowpea (kunde), pigeon peas (mbaazi), peas* | 8224(40.6) | 1176(30.0) | 1663(39.1) | 1747(41.2) | 1851(44.5) | 1787(48.6)** |
| Nuts and seeds | *Groundnuts* | 103(0.5) | 3(0.1) | 7(0.2) | 11(0.3) | 26(0.6) | 56(1.5)** |
| Dairy | *Cow's milk* | 1240(6.1) | 40(1.0) | 118(2.8) | 183(4.3) | 324(7.7) | 575(15.7)** |
| Flesh foods (meats) [2] | *Beef, chicken, fish, goat, liver, pork* | 11734(57.9) | 1721(43.8) | 2231(52.5) | 2450(57.7) | 27147(66.0) | 2585(70.4) ** |

*Table 2.2 (Continued)*

| Food Group[2] | Food list | Overall N (%) | Q1 N=3937 N (%) | Q2 N=4250 N (%) | Q3 N=4244 N (%) | Q4 N=4162 N (%) | Q5 N=3673 N (%) |
|---|---|---|---|---|---|---|---|
| Eggs | *Eggs* | 943(4.7) | 49(1.3) | 91(2.1) | 169(4.0) | 213(5.1) | 421(11.5)** |
| Vitamin A rich dark green vegetables | *Cassava leaves (kisamvu), cowpea leaves (kunde leaves), pumpkin leaves, spinach, sweet potato leaves* | 8800(43.4) | 996(25.4) | 1541(36.3) | 2033(47.9) | 2035(48.9) | 2195(59.8) ** |
| Other vitamin A rich fruits & vegetables[2] | *Peppers (fresh hoho), mango, papaya, pumpkin, passion fruit, passion fruit juice* | 2806(13.9) | 83(2.1) | 216(5.1) | 451(10.6) | 777(18.7) | 1279(34.8) ** |
| Other vegetables | *Bitter tomato, chinese cabbage, cabbage, eggplant, hare lettuce (mchunga), okra, tomato, green maize* | 1672(8.3) | 100(2.6) | 235(5.5) | 344(8.1) | 388(9.3) | 605(16.5) ** |

| *Table 2.2 (Continued)* | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Food Group**[2] | **Food list** | | **Q1** | **Q2** | **Q3** | **Q4** | **Q5** |
| | | **Overall** | **N=3937** | **N=4250** | **N=4244** | **N=4162** | **N=3673** |
| | | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** | **N (%)** |
| Other fruits | *Avocado, baobab, cucumber, guava, jackfruit, lemon, lime, orange, peach, pineapple, plum, banana, tangerine, watermelon, other fruit juices* | 5040(24.9) | 182(4.6) | 581(13.7) | 916(21.6) | 1343(32.3) | 2018 (54.9) ** |
| MDD-W Score[3] | *Median (± IQR)* [1] | 3.0(±1.0) | 2.0(±0.3) | 2.7(±0.3) | 3.0(±0.2) | 3.5(±0.2) | 4.0(±0.5)** |

[1] IQR – Interquartile range, Significance based on Fishers exact test and Wald t statistics for continuous variables. Abbreviations: MDD-W: Minimum dietary diversity for women. *p<0.05, ** p<0.001. N=total number of times that consumption of food group is reported by study women in all study visits.

[2] We categorized african doughnuts under starchy staples, maize and kidney bean dish under starchy staples and beans and peas, banana with meat and coconut milk, as well as rice and meat pillau were categorized as starchy staples and meats groups. Passion fruit was categorized under other vitamin A rich fruits & vegetables.

[3] Diet diversity for women based on baseline (single) 24-hour dietary recall.

**Table 2.3: Servings of PDQS food groups consumed by pregnant women in Tanzania in a week and point allocation**

| **Healthy foods** | | | |
|---|---|---|---|
| **Servings and points** | **0–1 serving/wk (0 point)** | **2–3 servings/wk (1 point)** | **≥4 servings/wk (2 points)** |
| cruciferous vegetables | 6592 (86.4) | 761 (10.1) | 265 (3.5) |
| dark leafy green vegetables | 2 (0.0) | 2 (0.0) | 7549 (100) |
| eggs | 6661 (88.2) | 707 (9.4) | 185 (2.5) |
| fish | 5237 (69.3) | 1511 (20.0) | 805 (10.7) |
| legumes | 2687 (35.6) | 1754 (23.2) | 3112 (41.2) |
| liquid vegetable oils | 7519 (99.6) | 32 (0.42) | 2 (0.03) |
| low fat dairy | 7553 (100) | 0 (0) | 0 (0) |
| nuts | 7453 (98.7) | 87 (1.1) | 13 (0.2) |
| other vegetables | 1397 (18.5) | 1272 (16.8) | 4885 (64.7) |
| other vitamin A rich vegetables (incl. carrots) | 2625 (34.8) | 1746 (23.1) | 2625 (34.8) |
| other whole fruits | 2368 (31.4) | 2043 (27.1) | 3142 (41.6) |
| poultry | 5997 (79.4) | 1109 (14.7) | 447 (5.9) |
| whole citrus fruits | 6661 (88.2) | 707 (9.4) | 185 (2.5) |
| whole grains | 6888 (91.2) | 515 (6.8) | 150 (2.0) |

| *Table 2.3 (Continued)* | | | |
|---|---|---|---|
| **Unhealthy foods** | | | |
| **Servings and points** | **0–1 serving/wk (2 points)** | **2–3 servings/wk (1 point)** | **≥4 servings/wk (0 point)** |
| desserts and ice cream | 4588 (60.7) | 1992 (26.4) | 973 (12.9) |
| fried foods obtained away from home | 7338 (97.2) | 189 (2.5) | 26 (0.3) |
| potatoes | 7453 (98.7) | 87 (1.1) | 13 (0.2) |
| processed meat | 7553 (100) | 0 (0) | 0 (0) |
| red meats | 4149 (54.9) | 1744 (23.1) | 1660 (22.0) |
| refined grains and baked goods | 15 (0.2) | 13 (0.2) | 7525 (99.6) |
| sugar sweetened beverages | 5920 (78.4) | 1132 (15.0) | 501 (6.6) |

Abbreviations: PDQS: Prime diet quality score.

**Table 2.4: Association of Minimum Dietary Diversity for Women score and Prime Diet Quality Score with birth outcomes in HIV negative women in Tanzania**

| Clinical Outcome | Quintile 1<br>RR[1] (95% CI) | Quintile 2<br>RR[1] (95% CI) | Quintile 3<br>RR[1] (95% CI) | Quintile 4<br>RR[1] (95% CI) | Quintile 5<br>RR[1] (95% CI) | P value for trend |
|---|---|---|---|---|---|---|
| **Preterm**[2] (<37 weeks gestation) | | | | | | |
| ***MDD-W*** | 252/1550 | 201/1428 | 344/1765 | 149/1362 | 206/1448 | |
| Univariate | ref | 0.87 (0.73,1.03) | 1.20 (1.03,1.39)* | 0.67 (0.56,0.81)* | 0.88 (0.74,1.04) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.87 (0.74,1.04) | 1.24 (1.06,1.44)* | 0.72 (0.60,0.88)* | 0.97 (0.82,1.16) | 0.24 |
| ***PDQS*** | 338/1732 | 347/2194 | 133/1022 | 192/1215 | 142/1390 | |
| Univariate | ref | 0.81 (0.71,0.93)* | 0.67 (0.55,0.80)* | 0.81 (0.69,0.95)* | 0.52 (0.44,0.63)* | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.82 (0.71,0.93)* | 0.66 (0.55,0.80)* | 0.82 (0.70,0.96)* | 0.55 (0.46,0.67)* | <0.001** |
| **Small for gestational age**[3] (<10th percentile for gest age/sex ) | | | | | | |
| **MDD-W** | 245/1400 | 231/1284 | 266/1601 | 207/1221 | 171/1318 | |
| Univariate | | 1.03 (0.87,1.21) | 0.95 (0.81,1.11) | 0.97 (0.82,1.15) | 0.74 (0.61,0.89)* | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 1.01 (0.87,1.19) | 0.95 (0.81,1.11) | 0.97 (0.82, 1.15) | 0.74 (0.62,0.89)* | <0.01* |

*Table 2.4 (Continued)*

| | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P value for trend |
|---|---|---|---|---|---|---|
| **Clinical Outcome** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | |
| **PDQS** | 1264/1605 | 338/1971 | 149/906 | 187/1110 | 182/1232 | |
| Univariate | | 1.04 (0.90,1.21) | 1.00 (0.83,1.20) | 1.02 (0.86,1.21) | 0.90 (0.76,1.09) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 1.04 (0.90,1.21) | 0.97 (0.81,1.17) | 1.01 (0.85,1.19) | 0.91 (0.76,1.08) | 0.26 |
| **Low birth weight[4]** (<2,500 grams) | | | | | | |
| **MDD-W** | 114/1458 | 71/1359 | 107/1641 | 71/1287 | 85/1373 | |
| Univariate | | 0.67 (0.50,0.89)* | 0.83 (0.65,1.08) | 0.71 (0.52,0.94)* | 0.79 (0.60,1.04) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.66 (0.50,0.88)* | 0.84 (0.65,1.08) | 0.70 (0.53,0.94)* | 0.80 (0.61,1.04) | 0.11 |
| **PDQS** | 145/1606 | 124/2067 | 56/962 | 58/1149 | 65/1334 | |
| Univariate | | 0.66 (0.53,0.84)* | 0.64 (0.48,0.87)* | 0.56 (0.42,0.75)* | 0.54 (0.41,0.77)* | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.67 (0.53,0.84)* | 0.63 (0.47,0.84)* | 0.55 (0.41,0.74)* | 0.53 (0.40,0.71)* | <0.001** |

*Table 2.4 (Continued)*

| | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P value for trend |
|---|---|---|---|---|---|---|
| **Clinical Outcome** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | |
| **Fetal loss**[5] (Spontaneous abortion, stillbirth) | | | | | | |
| **MDD-W** | 46/1550 | 34/1428 | 72/1765 | 41/1362 | 45/1448 | |
| Univariate | | 0.80 (0.51,1.24) | 1.37 (0.96,1.98) | 1.01 (0.67,1.53) | 1.05 (0.70,1.57) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.73 (0.46,1.15) | 1.37 (0.95,1.98) | 0.90 (0.58,1.40) | 0.95 (0.62,1.45) | 0.98 |
| **PDQS** | 68/1732 | 71/2194 | 38/1022 | 30/1215 | 31/1390 | |
| Univariate | | 0.82 (0.59,1.14) | 0.95 (0.59,1.40) | 0.63 (0.41,0.96)* | 0.57 (0.37,0.86)* | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.78 (0.56,1.08) | 0.86 (0.57,1.30) | 0.62 (0.40,0.95)* | 0.53 (0.34,0.82)* | <0.01* |

Abbreviations: *p<0.05, ** p<0.001. Test for trend conducted using median MDD-W scores for diet quintiles or median PDQS scores for PDQS quintiles. MDD-W: Minimum dietary diversity for women, PDQS: Prime diet quality score.

[1]Relative risk (RR) and confidence intervals were estimated from binomial regression models. RR below 1 indicates that the risk of the outcome is lower in women with more diversified diets. Diet diversity assessed as quintiles of mean dietary diversity throughout pregnancy. We also report p values for trend test.

[2] Multivariate models for preterm adjusts for multivitamin group assignment (placebo/multivitamin), child sex (male/female) low food expenditure(yes/no), married(yes/no), wealth index above median(yes/no), maternal age (<30, 30-39, >40years) and maternal education (no/primary, secondary, tertiary).

[3] Multivariate models for small for gestational age (SGA) adjust for multivitamin group assignment (placebo/multivitamin), low food expenditure (yes/no), wealth index above median (yes/no), maternal age (<30, 30-39, >40years), parity (0, 1-2, 3+children), child sex (male/female) and maternal shortness (height <145cm).

[4] Multivariate models for low birth weight adjust for multivitamin group assignment (placebo/multivitamin), history of fetal loss (yes/no), married (yes/no), parity (0, 1-2, 3+children), child sex (male/female), wealth index above median(yes/no), maternal age (<30, 30-39, >40years), and maternal shortness (height <145cm).

[5] Multivariate models for fetal loss adjusts for multivitamin group assignment (placebo/multivitamin), low food expenditure (yes/no), parity (0, 1-2, 3+children), and history of fetal loss at first pregnancy (yes /no), married (yes/no) and maternal height.

[6] Energy, BMI and anemia adjusted models adjusts for BMI (<18.5, 18.5-24.99, 25.0-29.9, >30), anemia status(none, moderate, severe) status at randomization and energy using restricted cubic splines in addition to covariates controlled for in multivariate models.

**Table 2.5: Association of Minimum Dietary Diversity for Women score and Prime Diet Quality Score with additional birth outcomes in HIV negative women in Tanzania**

| Clinical Outcome | Quintile 1<br>RR[1] (95% CI) | Quintile 2<br>RR[1] (95% CI) | Quintile 3<br>RR[1] (95% CI) | Quintile 4<br>RR[1] (95% CI) | Quintile 5<br>RR[1] (95% CI) | P value for trend |
|---|---|---|---|---|---|---|
| **Very Preterm** [2] (<32 weeks) | | | | | | |
| **MDD-W** | 29/1499 | 12/1392 | 40/1691 | 10/1318 | 21/1401 | |
| Univariate | | 0.45 (0.23,0.87)* | 1.22 (0.76,1.96) | 0.39 (0.19,0.80)* | 0.77 (0.44,1.35) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.45 (0.23,0.88)* | 1.29 (0.80,2.09) | 0.44 (0.21,0.92)* | 0.97 (0.55,1.73) | 0.69 |
| **PDQS** | 45/1658 | 27/2117 | 14/983 | 15/1185 | 11/1358 | |
| Univariate | | 0.47 (0.29,0.75)* | 0.52 (0.29,0.95)* | 0.47 (0.26,0.83)* | 0.30 (0.16,0.57)* | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.48 (0.30,0.77)* | 0.51 (0.28,0.93)* | 0.48 (0.27,0.85)* | 0.33 (0.17,0.64)* | <0.001** |

*Table 2.5 (Continued)*

| | Quintile 1 | Quintile 2 | Quintile 3 | Quintile 4 | Quintile 5 | P value for trend |
|---|---|---|---|---|---|---|
| **Clinical Outcome** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | **RR[1] (95% CI)** | |
| **Severe SGA** (<3rd percentile for gestational age/sex) | | | | | | |
| **MDD-W** | 104/1400 | 98/1284 | 100/1601 | 83/1221 | 75/1318 | |
| Univariate | | 1.03 (0.79,1.34) | 0.84 (0.64,1.10) | 0.92 (0.69,1.21) | 0.77 (0.57,1.02) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 1.01 (0.77,1.31) | 0.83 (0.64,1.08) | 0.90 (0.68,1.19) | 0.76 (0.57,1.02) | 0.06 |
| **PDQS** | 114/1606 | 136/1971 | 64/906 | 673/1110 | 73/1232 | |
| Univariate | | 0.97 (0.76,1.24) | 0.99 (0.74,1.34) | 0.93 (0.70,1.23) | 0.83 (0.63,1.11) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.98 (0.77,1.24) | 0.97 (0.72,1.30) | 0.91 (0.69,1.21) | 0.85 (0.64,1.13) | 0.24 |

*Table 2.5 (Continued)*

| Clinical Outcome | Quintile 1 RR[1] (95% CI) | Quintile 2 RR[1] (95% CI) | Quintile 3 RR[1] (95% CI) | Quintile 4 RR[1] (95% CI) | Quintile 5 RR[1] (95% CI) | P value for trend |
|---|---|---|---|---|---|---|
| **Very low birth weight [3]** (< 2,000 grams) | | | | | | |
| **MDD-W** | 22/1458 | 15/1359 | 26/1641 | 13/1287 | 20/1373 | |
| Univariate | | 0.73 (0.38,1.40) | 1.05 (0.60,1.84) | 0.67 (0.34,1.32) | 0.97 (0.53,1.76) | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.76 (0.39,1.46) | 1.16 (0.66,2.04) | 0.75 (0.37,2.19) | 1.18 (0.64,2.19) | 0.66 |
| **PDQS** | 33/1606 | 29/2067 | 8/962 | 13/1149 | 13/1334 | |
| Univariate | | 0.68 (0.42,1.12) | 0.40 (0.19,0.87)* | 0.55 (0.29,1.04) | 0.47 (0.25,0.90)* | |
| Multivariate, energy, BMI and anemia adjusted[6] | | 0.67 (0.41,1.10) | 0.39 (0.18, 0.83)* | 0.55 (0.29,1.06) | 0.49 (0.26,0.92)* | 0.01* |

Abbreviations: *p<0.05, ** p<0.001. Test for trend conducted using median MDD-W scores for diet quintiles or median PDQS scores for PDQS quintiles. MDD-W: Minimum dietary diversity for women, PDQS: Prime diet quality score.

[1]Relative risk (RR) and confidence intervals were estimated from binomial regression models. RR below 1 indicates that the risk of the outcome is lower in women with more diversified diets. Diet diversity assessed as quintiles of mean dietary diversity throughout pregnancy. We also report p values for trend test.

[2]Multivariate model for very preterm controls for multivitamin group assignment (placebo/multivitamin), male sex (yes/no), low food expenditure (yes/no), married (yes/no), wealth index above median (yes/no), child sex and maternal height and maternal education.

[3]Multivariate model for severe SGA controls for multivitamin group assignment (placebo/multivitamin), male sex (yes/no), low food expenditure (yes/no), married (yes/no), wealth index above median (yes/no), child sex and maternal height and maternal education.

[4]Multivariate model for very low birth weight adjusts for multivitamin group assignment (placebo/multivitamin), history of fetal loss (yes/no), married (yes/no), parity (0, 1-2, 3+children) and child sex and maternal shortness (height <145cm).

[5] Energy, BMI and anemia adjusted models adjusts for BMI (<18.5, 18.5-24.99, 25.0-29.9, >30), anemia status(none, moderate, severe) status at randomization and energy using restricted cubic splines in addition to covariates controlled for in multivariate models.

*Fetal loss*

There were 238 cases (3.2%) of fetal loss occurred in the study. MDD-W was not significantly associated with fetal loss (RR 0.95, 95% CI:0.62, 1.45) comparing women in quintile 5 to those in quintile 1 of the MDD-W. We found an inverse association between PDQS and fetal loss comparing women in the fifth (RR 0.53, 95% CI:0.34, 0.82, $P < 0.01$) quintile to those in the first quintile.

We considered the possibility that the associations observed in our analysis may be due to multivitamin intake in the parent trial. However, we did not find evidence of effect modification of the associations of the MDD-W and PDQS with multivitamin treatment on any outcome. When we restricted the analysis to the placebo group, our findings were unchanged (results not shown). Finally, findings from the sensitivity analysis were similar to the missing indicator method.

**Discussion**

This study prospectively evaluated the relationship between maternal dietary diversity and dietary quality in pregnancy with adverse birth outcomes in urban Tanzania. Women with higher quality diets, defined using the PDQS, had significantly lower risk of preterm, very preterm, LBW, VLBW and fetal loss, independent of energy intake and other maternal characteristics. Comparatively, women with relatively more diversified diets defined by MDD-W were less likely to deliver infants with intra-uterine growth retardation (SGA), independent of energy intake and other maternal characteristics.

Previous studies have shown associations between dietary diversity and birth outcomes. Zerfu et al (2016) found that Ethiopian women with poor dietary diversity (consuming less than 4 food groups out of 9) based on the women's dietary diversity score (WDDS) index, had 4.6

times the risk of preterm births and 2.1 times the risk of LBW compared to women with adequate diets [26]. Saaka et al (2012) using an 11 food group index (e.g. individual dietary diversity score (IDDS) including flesh meats, fish, eggs, milk and milk products, organ meat, legumes, cereals, roots and tubers, dark green leafy vegetables, vitamin A rich fruits and fats and oils) found that higher maternal IDDS in the third trimester was associated with 57% lower risk of LBW, but found no association with preterm birth in Ghana [25]. The studies we reviewed did not find associations between maternal DD and still birth [25, 26]. Associations of maternal diet quality with SGA have been shown in studies in developed countries, with high-quality dietary patterns composed of fruits, vegetables and dairy (New Zealand); rice, fish and vegetables (Japan); and, a 'varied' diet composed of bread, vegetables, poultry, fish and dairy (China) [40-43].

The observed differences in strength of associations comparing our study to others may be partially explained by the fact that we report on an urban cohort in Tanzania, while Zerfu et al for example, reports on a rural cohort in Ethiopia [26]. In the urban sample in Tanzania, women may have had relatively greater access to food, including animal source foods, as well as fruits and vegetables throughout the year. However, in rural areas of Ethiopia women may have had more limited dietary intake and increased risk of micronutrient deficiencies due to limited income, poor availability of nutritious foods, such as animal source foods in markets, as well as, seasonality and its effects on availability of food and household income Therefore women in Ethiopia may benefit more from diversified dietary intake. Finally, the studies in Ethiopia and Ghana had smaller sample sizes and they had higher incidence of LBW. These factors may have influenced observed associations.

MDD-W and PDQS associations with birth outcomes differ and this may be explained by the fact that two scores measure different aspects of diet. The MDD-W index has been validated for micronutrient adequacy and does not address aspects of diet quality, such as moderation and balance (including consumption of saturated fats, energy intake, sodium, refined grains or sugars) [22]. The PDQS, however, negatively scores the consumption of refined grains, saturated and trans fatty acids, and red and processed meats (unhealthy foods), and positively scores the consumption of fruits and vegetables [29, 30]. The consumption of unhealthy foods such as red meats, sugar sweetened beverages and refined grains has been associated with overweight and obesity, triglyceride levels, insulin resistance and other markers of inflammation [44]. The PDQS may therefore be more suited to determine effects of consumption of unhealthy foods and dietary patterns on birth outcomes in our study population. Additionally, the computation of PDQS takes into account serving frequency, with lower scores assigned to high consumption (4 or more servings/week) of unhealthy foods, and accordingly higher scores for more frequent consumption of healthy foods.

The MDD-W may have some utility in low income settings where micronutrient deficiencies are still prevalent and birth outcomes may be determined in part by micronutrient deficiencies prior to and during pregnancy [21]. Poor quality "usual" diets and pregnancy dietary intake can result in chronic undernutrition, and multiple rather than single nutrient deficiencies [16]. Therefore, it is important to consider the effects of these deficiencies on birth outcomes.

Diet quality warrants greater consideration in Tanzania where a nutrition transition in underway [45]. For example, studies indicate trends of increasing purchase of foods, including processed foods, consumption of bread and cakes (usually fried in oil) and sugar, increasing body mass index and childhood obesity in urban areas as well as nutrition transition even in the

rural areas in Tanzania [46, 47]. Diet quality assessment is important in this setting because although the pace of transition of diets has been rapid, there have been insufficient research to characterize the changes in dietary patterns and their effects on women's nutrition status and birth outcomes. PDQS could be a possible measure of diet quality used in the future in this and other contexts.

There are different mechanisms through which maternal nutrition may influence birth outcomes. Maternal nutritional status prior to and during pregnancy affects availability of nutrients for transfer to the fetus, thus it is important for *in utero* and early child growth [10, 19, 48]. Studies also suggest that protein-energy supplements during pregnancy may decrease SGA, implying a role for energy and protein intake in preventing SGA and subsequently LBW [49]. We controlled for energy intake in this analysis, however observed associations between maternal diets and poor birth outcomes persisted.

Diversified maternal diets are associated with greater micronutrient adequacy and may be important for maternal weight gain, birth weight and protection against poor birth outcomes [31, 50]. They may also act by enhancing nutrition status and decreasing infections and morbidity during pregnancy [31], which may be important for reducing the risk of preterm birth [51]. Other non-nutritional factors that may influence preterm and poor birth outcomes include fetal inflammation due to infection and oxidative stress, maternal stress and epigenetic programming [52-55]. However, these factors are not easily modified, while diet diversity and quality during pregnancy are modifiable factors that can influence birth outcomes.

There are several strengths of this study. First, we had a large population sample and we measured diet at multiple times during the pregnancy using the 24-hour dietary recall. We used the mean of multiple measures to reflect overall diet during pregnancy (reducing error compared

to the case if only one measurement was used). Secondly, while the PDQS has been shown to predict poor health outcomes in other contexts, it is the first time it has been associated with birth outcomes. It is a simple tool to incorporate analysis of diet quality in the analysis of diets in LMICs, and can be easily incorporated into programs.

There were several limitations of the study. We were unable to measure diet quality prior to or early in pregnancy (mean gestational age at first diet measurement = 28.8 (SD ±3.8) weeks). It is possible that early pregnancy diets may also be important for fetal development given rapid cell growth and development of immune cells and organs in the first trimester [54]. However, we still observed significant associations based on our measures, suggesting that second and third trimester diets may still have consequences for growth in utero The second limitation is that PDQS data was obtained from 24 hour recalls, and there was no precedent for the conversion of 24 hour recall derived PDQS scores to an equivalent score for the food frequency questionnaire (FFQ).

Finally, our study findings may not be generalizable to other populations where dietary intake patterns and determinants of poor birth outcomes may differ from the urban Tanzanian population evaluated in this study. Associations may be stronger in populations where micronutrient and other deficiencies may be more prevalent in pregnant women for example rural populations as compared to the urban population in Tanzania, or where there is greater variability and wider distribution of diet scores.

**Conclusion**

Low maternal dietary diversity and quality may be modifiable risk factors for adverse birth outcomes in Tanzanian mothers. PDQS, a measure of maternal diet quality, was shown to

be associated inversely with preterm, very preterm, LBW, VLBW and fetal loss in this analysis. MDD-W, a measure of diet diversity was inversely associated SGA. These findings suggest that in addition to diet diversity, diet quality should be considered as important in understanding risk factors for poor birth outcomes. Intervention trials should evaluate whether increasing diet diversity and quality can improve maternal and infant health outcomes.

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**Authors' contributions**

I.M. conceived the study, conducted the data analysis, and drafted the article. W.F. was the principal investigator for the parent study, conceived the study, contributed to study design, interpreted the data, and guided revisions of the manuscript. C.D., S.I and M.W. contributed to study design, interpreted the data, and guided revisions of the draft manuscript. E.H. contributed to study design and interpreted the data. G.M. and W.U. where co-principal investigators for the parent study, participated in the study implementation and field supervision, interpreted the data, and guided revisions of the manuscript. All authors read and approved the final manuscript.

**Conflict of interest**

All authors have nothing to disclose.

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**Paper III**

# Diet diversity during pregnancy and infant growth outcomes in Uganda: a longitudinal birth cohort study

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**Abstract**

*Introduction:* Growth faltering in early childhood is prevalent in many low resource countries. Maternal diet diversity during pregnancy may have a role in fetal and perhaps infant growth.

*Objective:* To evaluate the role of dietary diversity during pregnancy on infant growth in a rural Ugandan birth cohort.

*Methods:* Data from 3291 women and infant pairs enrolled in a birth cohort from 2014-2016 were analyzed. Maternal diets were assessed using 24 hour dietary recall in the second and third trimester of pregnancy. Maternal diet diversity was calculated using the Food and Agriculture Organization's 10 food group minimum diet diversity score for women (MDD-W) index. Cox hazard regression models were used to evaluate associations of MDD-W with the incidence of underweight, stunting and wasting in infants from 3 to 12 months, adjusting for multiple confounding factors.

*Results:* In the previous 24 hours of the survey, 99% of women reported consuming grains, roots and tubers, 71% beans and peas, 44% other vegetables, 13% orange and yellow fruits and vegetables, 12% dairy and 2% eggs. The median MDD-W score for women was low at 3.0 (IQR ±1.0). Infants of women in quartile 4 (adjusted HR:0.70, 95% CI: 0.62, 0.80) of MDD-W were less likely to be underweight compared to infants of women in quartile 1 (p for trend <0.001). There was no significant association between the MDD-W and infant stunting or wasting.

*Conclusion:* Infants whose mothers were in the higher quartiles of dietary diversity were at 30-35% lower risk of developing underweight through age 12 months. These findings, if confirmed through research in other contexts, may have significant implications for policy and programs to provide nutrition counselling for women during pregnancy in LMIC in an effort to decrease child undernutrition globally.

## Introduction

Childhood growth faltering, defined as a deficit in a child's length or weight compared to their age and gender, is prevalent in many low resource countries [56, 57]. Underweight, a form of growth faltering, affects 13.5 percent of the world's children under 5 years, while stunting affects 21.9 percent, and wasting affects 7.3 percent [58, 59]. Growth faltering is a significant problem in Uganda, where recent estimates show that 11 percent of the children under 5 years are underweight, 28.9 percent stunted, and 4 percent wasted [60]. Consequences of poor child growth are severe. Approximately 45% of all child deaths under 5 years are attributed to undernutrition [17]. Children with malnutrition have increased risk of infections, and underweight, stunting and wasting have all been associated with greater risk of mortality in children [17, 61]. In addition, poor child growth in the first 1000 days and poor linear growth in childhood increases the risk of obesity and non-communicable diseases in adulthood and have been associated with poor education achievement and wage income losses in later life [17, 62].

Studies of early child growth in sub-Saharan Africa indicate that on average, infants begin life with generally normal weight for height (WHZ) and weight for age (WAZ) Z- scores [57], and lower than average height for age (HAZ)[56]. There is then a progressive decline in growth, starting from early infancy and continuing into the first 2 years of life [56, 63]. The period of infancy therefore offers an important window for the prevention of poor growth. Importantly, adequately addressing poor infant growth may also require addressing maternal factors during pregnancy that may impact fetal and infant growth. Maternal diet quality during pregnancy is one such modifiable factor, however its role in early child growth has not been well described.

Nutrient requirements for women are higher during pregnancy due to increased requirements for fetal growth and other pregnancy mediated physiological changes. On average, energy requirements increase by 13%, protein requirements are 54% higher, and demand for micronutrients, including iron and folate also increase during pregnancy [64, 65]. Consumption of diversified diets during pregnancy increases the likelihood that a woman meets increased micronutrient needs for the pregnancy, including for fetal growth and for her own nutritional status [22, 27, 28]. Poor dietary diversity and quality during pregnancy has been shown to increase the risk that women have low birth weight (LBW), small for gestational age (SGA), and preterm births [17, 25, 26, 66-71]. Poor birth outcomes predispose children to poor growth outcomes, including underweight, stunting and wasting [72-74]. Given these associations, it is feasible that maternal diets could also influence infant growth outcomes.

In developing country settings, there is limited evidence on the influence of prenatal maternal diets on early child growth and their role in preventing poor infant growth. We therefore evaluated the role of maternal diet diversity during pregnancy on growth outcomes in infants of women enrolled in a birth cohort in Uganda.

## Materials and methods

### Study Context and location

The parent study, the Uganda Community Connector Program (UCCP), was a five-year cluster randomized integrated agriculture-nutrition program, designed with a goal of reducing malnutrition among the most vulnerable populations in Uganda. Study participants received interventions on intra-household gender dynamics, nutrition and health behaviors, farming as a

business, water, sanitation and hygiene (WASH), as well as savings and a range of agricultural-based enterprises to improve disposable income (we still need to reference this study somehow).

The study population was the Nutrition Innovation Laboratory birth cohort study implemented in 12 districts in northern and south-western Uganda from 2014-2016. In the cohort study, mother-infant pairs were prospectively followed from the time of enrollment in the second and third trimesters of pregnancy, until infants reached 12 months of age. Study participants were women aged 15-49 years, who were pregnant and consented to the study and intended to stay in the study area throughout the study period.

*Study procedures and follow-up:*

A pregnancy surveillance system was established in study areas to screen and enroll women who met the eligibility criteria. Village Health Technicians (VHTs) visited women of reproductive age in study areas and enrolled eligible, consenting women. Pregnancy was confirmed by a urine pregnancy test at the enrolment visits conducted every 3 months. Study research assistants then visited women at home, every 3 months, from the time of recruitment until their offspring were 12 months old. A 24-hour dietary recall was administered to pregnant women in the first (or first 2) prenatal visits.

Anthropometric measurements for infants were made at birth (+ 3 weeks), 3, 6, 9 and 12 month postpartum scheduled visits, by trained project staff. Length measurements were made to the nearest 0.1 cm using length boards, and weight measures were made to the nearest 0.1 kg using digital Seca weighing scales. Length and weight measures for infants were made in triplicate, and mean measures were used in this analysis.

**Dietary diversity**

The primary exposure of interest, maternal diet diversity during pregnancy, was assessed using 24-hour recall of foods administered to study women by project staff. Women were asked to recall foods eaten in the previous 24 hours, from the time they woke up to the time they slept. The 24-hour recall form was composed of a prelist of locally available foods and food groups. Recalled foods were categorized into 10 food groups based on FAO's minimum diet diversity for women (MDD-W) index [27]. Food groups included were grains, white roots and tubers, and plantains; legumes (beans, peas and lentils); nuts and seeds; dairy; meats, poultry and fish; eggs; vitamin A rich dark green vegetables; other vitamin A rich fruits and vegetables; other vegetables; and, other fruits. If a food was eaten at least once in the previous 24-hour recall, it was included in the food group. Diet diversity scores were computed as the sum of food groups consumed in the previous 24 hours based on the baseline prenatal dietary recall for women. The MDD-W scores were categorized into quartiles for analysis. In addition, a binary indicator for minimum dietary diversity was defined as consumption of 5 of more food groups in the previous 24 hours as recommended by FAO [27]. A binary indicator for MDD-W greater than median was also defined for the secondary analysis.

**Study Outcomes**

Infants included in this analysis were aged 0-12 months and with weight and length measures at 3 months. Growth outcomes of LAZ, WLZ and WAZ were computed using the WHO growth reference standards (2006) [75]. Extreme outliers were determined based on WHO growth standards and infant measurements of WAZ<-6 or WAZ>5; LAZ<-6 or LAZ>6; or WLZ<-5 or WLZ>5 were excluded from the analysis [76]. Outliers for infant length changes over time were defined as standardized residuals <= -3 or >= +3 and were replaced with predicted height

obtained from linear regression adjusting for weight and age to prevent undue influence of extreme values [77, 78]. Given the greater likelihood of measurement error for anthropometric measures in early infancy, and concerns about accuracy and reliability of measures obtained at birth, we restricted our analyses to anthropometric measurements obtained from 3 months onwards.

The primary outcomes were underweight, stunting and wasting. Stunting was defined as LAZ below 2 standard deviations, wasting as WLZ below 2 standard deviations and underweight as WAZ below 2 standard deviations from the median based on WHO growth standards [76].

**Statistical analysis**

Analysis was restricted to women who met study eligibility criteria, had at least 1 prenatal dietary assessment and anthropometry measures for their infants at the 3 month visit. We excluded twin births and all infants in the analysis were singleton births. We excluded women that were HIV positive. Descriptive statistics were used to summarize baseline characteristics of the study population, and differences between quartiles of dietary diversity were compared using chi-square test for categorical variables and Wilcoxon rank-sum test for continuous variables. We assessed differences in underweight, stunting and wasting by the categorical child age using chi-square tests. Hazard ratios (HR) with respect to incident stunting, wasting and underweight were calculated using Cox regression models with the exact method for ties [79] treating child age as the time scale. The follow up time was from the 3 month visit until infants had the outcome event, which were lost to follow-up, died or reached the end of follow-up at the 12 month visit, whichever occurred first. The assumption of proportional hazards in the study was assessed by addition of an interaction term for MDD-W and infant age, and the

significance of the interaction term was evaluated using the likelihood ratio test (LRT). If there was evidence of non-proportional hazards, we included the interaction term with infant age in the final model. All models adjust for clustering by sub-county. Tests for trend were conducted for multivariate models using median scores for MDD-W quartile.

We also conducted secondary analyses to determine if a dichotomous indicator of MDD-W for minimum diet diversity (consuming 5 food groups or more: yes/no), or median maternal diet diversity (yes/no) was associated with stunting, wasting and underweight in infants.

*Confounders*

We considered the following as potential confounders: maternal age (<20 years, 20-29 years, ≥ 30 years), marital status (married/single), maternal nutrition knowledge score (tertiles), maternal education and paternal education (none and primary (0-6 years), secondary and higher (7+ years)), maternal height, infant gender (male/female), household wealth index (tertiles), and breastfeeding (yes/no). Confounding variables were selected for inclusion in adjusted models based on univariate association with the outcome, using a significance criteria of $p<0.20$ [80]. All models adjusted for maternal height, child gender, region (North (Apac, Kole, Lamwo, Lira, Nebbi, Pader, Zombo) /Southwest (Kabale, Kabarole, Kamwenge, Kanungu, Rukungiri)) in Uganda, grouping by sub-county, and assignment to the USAID community connector program. The missing indicator method was used to adjust for missing confounder data [39]. Statistical analysis was conducted using SAS version 9.4.

**Ethics**

Written informed consent was obtained from study women prior to participation in the study. Ethical approval was obtained from the Makerere University School of Public Health, the

Uganda Science and Technology Council, Tufts University, and the Harvard T.H. Chan School of Public Health.

**Results**

The study recruited 5,044 women who met eligibility criteria in the Nutrition Innovation Laboratory birth cohort study from November, 2014 to June, 2016. Information on maternal diets and pregnancy outcomes was collected for 4,574 women. Analysis excluded women who did not have live births (N=120), were HIV positive (N=227), whose infants did not have anthropometric measures at the 3 month visit (N=873) (Figure 3.1). The analysis was on 3,291 women and infant pairs (Table 3.1).

Women in the study population were on average 25.6 (SD ± 6.2) years old and the majority had primary school education or lower (66.7%). There were sociodemographic differences in baseline characteristics by quartiles of maternal diet diversity. Women in the highest quartile of diet diversity were more likely to have secondary or higher education, as did their partners, compared to women in the lowest quartile of diversity. Women with highest diet diversity were more likely to be in the highest tertile of wealth index, have electricity and running water in the household compared to women with the least diets. Women in the lowest quartile of diet diversity were more likely to participate in the community connector intervention (61.1% vs. 46.0%). There was no difference in maternal age or marital status by diet diversity quartiles.

**Figure 3.1: Study profile for pregnant women in Uganda Nutrition Innovation Laboratory birth cohort**

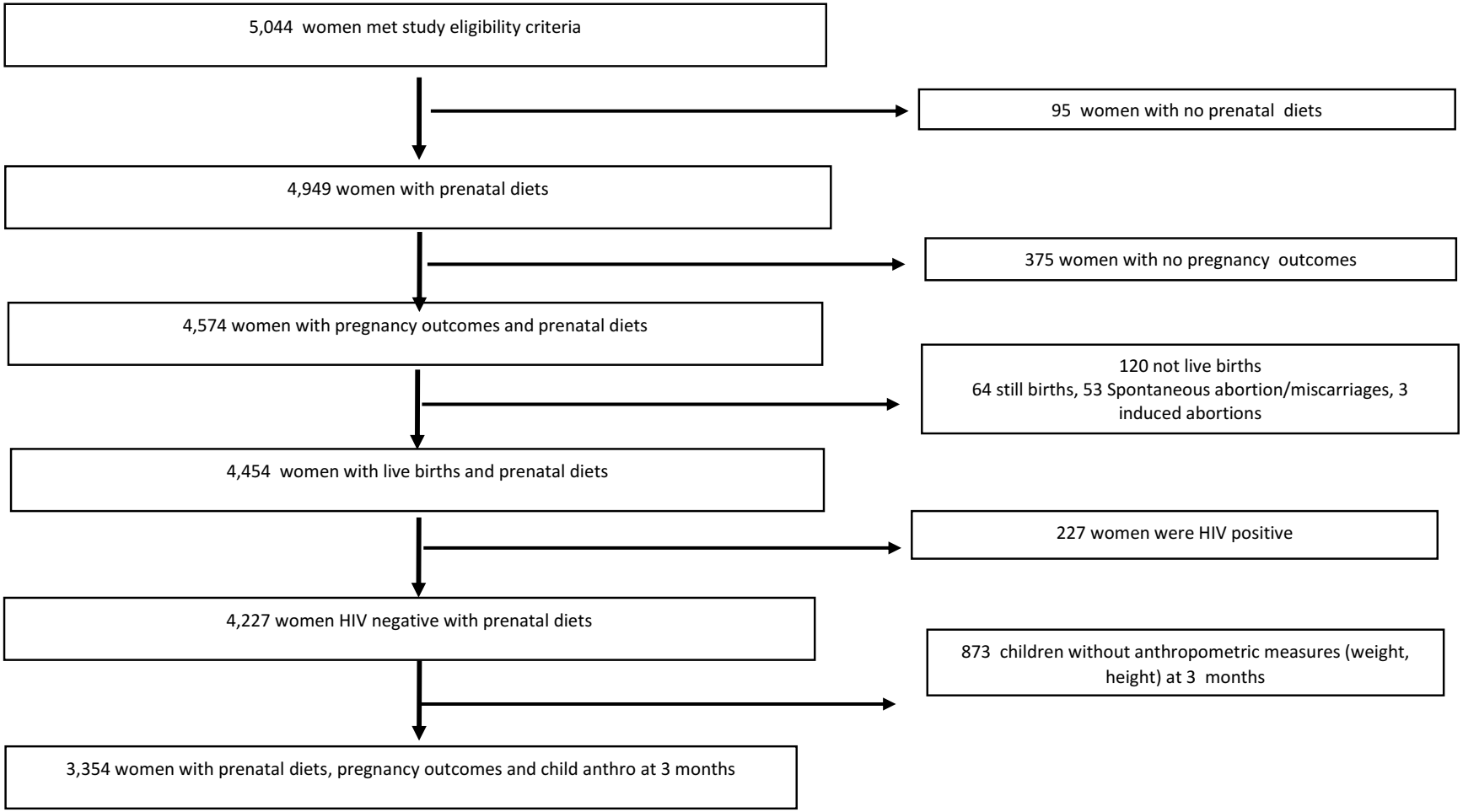


**Table 3.1: Baseline socio-demographic characteristics of pregnant women in rural Uganda birth cohort**

| | **Maternal diet diversity (MDD-W) score** | | | |
|---|---|---|---|---|
| **Characteristics** | **Q1 N=725 (0-2)** | **Q2 N=1130 (3)** | **Q3 N=843 (4)** | **Q4 N=593 (5-9)** |
| | **N(%)** | **N(%)** | **N(%)** | **N(%)** |
| *Maternal characteristics* | | | | |
| Woman is head of household | 72 (9.9) | 71 (6.3) | 47 (5.6) | 26 (4.4)** |
| Married | 688(94.9) | 10496 (92.8) | 785 (93.1) | 549 (92.6) |
| Age, years ( mean, SD) | 25.4±6.3 | 25.6±6.2 | 25.6±6.2 | 25.4±5.9 |
| <20 years | 126 (17.5) | 187 (16.6) | 148 (17.6) | 99 (16.7) |
| 20-29 years | 416 (57.8) | 645 (57.3) | 468 (55.7) | 357 (6.2) |
| 30 years or more | 178 (24.7) | 294 (26.1) | 224 (26.7) | 137 (23.1) |
| Maternal education | | | | |
| None or primary | 509 (70.2) | 779 (68.9) | 582 (69.0) | 324 (54.6)** |
| Secondary school or higher | 216 (29.8) | 351 (31.1) | 261 (31.0) | 269(45.4)** |
| Paternal education | | | | |
| None or primary | 363 (50.0) | 574 (50.4) | 401 (47.6) | 279 (40.5)* |
| Secondary school or higher | 362 (50.0) | 556 (49.2) | 442 (52.4) | 353 (59.5)* |
| *Household characteristics* | | | | |
| Community connector participation | 443 (61.1) | 563 (49.8) | 376 (44.6) | 273 (46.0)** |

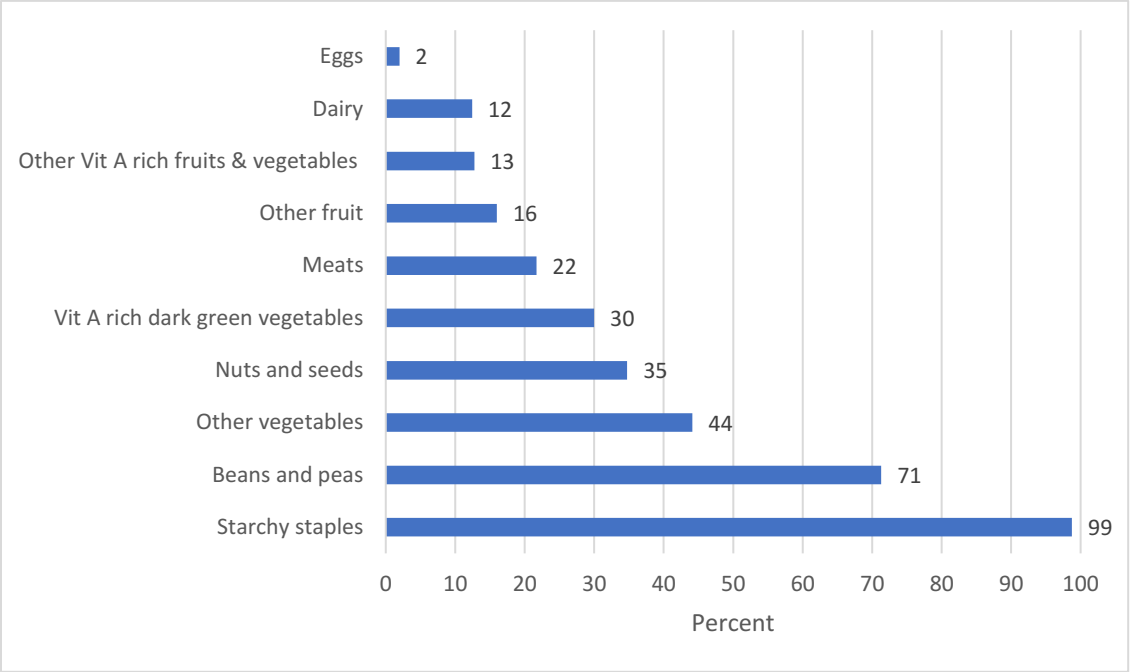
| *Table 3.1 (Continued)* | | | | |
|---|---|---|---|---|
| | **Maternal diet diversity (MDD-W) score** | | | |
| **Characteristics** | **Q1 N=725 (0-2)** | **Q2 N=1130 (3)** | **Q3 N=843 (4)** | **Q4 N=593 (5-9)** |
| | **N(%)** | **N(%)** | **N(%)** | **N(%)** |
| Wealth index | | | | |
| Tertile 1 | 315 (43.5) | 479 (42.4) | 381 (45.2) | 183 (30.9)** |
| Tertile 2 | 246 (33.9) | 377 (33.4) | 250 (29.7) | 187 (31.5)** |
| Tertile 3 | 164 (22.6) | 274 (24.3) | 212 (25.2) | 223 (37.6)** |
| Household fuel | | | | |
| Wood | 692 (95.5) | 1062 (94.0) | 790 (93.7) | 523 (88.2)** |
| Charcoal or other | 33 (4.6) | 66 (5.8) | 52 (6.2) | 68 (11.5)** |
| Household has electricity | 7(1.0) | 10(0.9) | 15 (1.8) | 21 (3.5)** |
| Household has running water | 17 (2.3) | 22 (2.0) | 34 (4.0) | 56 (9.4)** |
| Improved pit latrine or flush toilet | 14 (1.9) | 36 (3.2) | 36 (4.3) | 43 (7.3)** |

Abbreviations: *p<0.05, ** p<0.001. Chi square p values reported for categorical/binary variables and the Wilcoxon test for continuous variables.

[a] Northern region= Apac, Kole, Lamwo, Lira, Nebbi, Pader and Zombo districts

[b] South western region= Kabale, Kabarole, Kamwenge, Kanungu and Rukungiri district

**Figure 3.2: Prevalence of ever consumption of food groups in the previous 24 hours by pregnant women in Uganda birth cohort**




In the previous 24 hours , 99% of women reported consuming grains, roots and tubers, 71% beans and peas, 44% other vegetables, 13% orange and yellow fruits and vegetables, 12% dairy and 2% eggs (Figure 3.2). Dietary diversity in the study population was low, with a median dietary diversity score of 3.0 (IQR±1.0).

*Underweight*

The prevalence of underweight in infants was 6.4% at the 3 month visit and increased to 8.5%, 10.1% and 12.1% at 6, 9 and 12 month visits. The assumption of proportional hazards for the association of maternal diets and underweight in infants was not violated. We therefore present an estimate of HR of underweight for all infant age groups. Infants of women in quartile

4 of the MDD-W were less likely to be underweight (adjusted HR 0.70, 95% CI: 0.62, 0.80, p<0.001) compared to infants of women in quartile 1 (Table 3.2). Models for median diet diversity also showed an association between maternal diet diversity and underweight, with infants of women meeting median diet diversity or better likely to be underweight (p=0.02). No associations were found with minimum diet diversity (results not shown).

*Stunting*

Stunting was 27.1% at the 3 month visit and increased to 29.7%, 35.6% and 39.4% at 6, 9 and 12 month visits respectively. There was evidence that the association of MDD-W with stunting in infants changed over time, therefore an interaction term for MDD-W and infant age was included in the models (Table 3.2). Comparing infants of women in quartile 4 of the MDD-W to offspring of women in quartile 1, there was no significant association between MDD-W and stunting at 3, 6, 9 and 12 months in infants. There were no significant associations found between median diet diversity and minimum diet diversity with stunting (results not shown).

*Wasting*

The prevalence of wasting did not significantly increase from the 3 month visit (4.2%) to the 12 month visit (5.3%). There was evidence that that the association of MDD-W with wasting in infants changed over time (Table 3.2). An interaction term for maternal diets and infant age was included in the models. Comparing infants of women in quartile 4 of the MDD-W to offspring of women in quartile 1, there was no significant association between MDD-W and wasting at 3 (adjusted HR: 0.91, 95% CI : 0.69, 1.19), 6 (adjusted HR: 0.97, 95% CI : 0.80, 1.17), 9 (adjusted HR: 1.04, 95% CI : 0.83, 1.29) and 12 (adjusted HR 1.11, 95% CI : 0.80,

1.54) months. The test for trend in associations of MDD-W with wasting was not significant (p=0.68). There were no significant associations found between median diet diversity and minimum diet diversity with wasting in infants (results not shown).

**Table 3.2: Cox hazards models for incidence of underweight, stunting and wasting for children aged 3-12 months by prenatal MDD-W in Uganda birth cohort**

| Outcomes | Maternal diet diversity score (MDD-W )[a] | | | | P for trend |
|---|---|---|---|---|---|
| | Q1 (0-2) | Q2 (3) | Q3 (4) | Q4 (5-9) | |
| **Underweight[b]** | | | | | |
| **Univariate HR (95% CI)** | | | | | |
| n/N | 66/720 | 61/1128 | 50/842 | 34/589 | |
| HR | 1 | 0.63 (0.56,0.70)** | 0.64 (0.57,0.73)** | 0.65 (0.56, 0.74)** | |
| **Multivariate Model HR (95% CI) [d]** | | | | | <0.001** |
| HR | 1 | 0.65 (0.58,0.72)** | 0.67 (0.59,0.75)** | 0.70 (0.62, 0.80)** | |
| **Stunting [c]** | | | | | |
| n/N | 188/707 | 301/1106 | 240/824 | 144/583 | |
| **Univariate HR (95% CI)** | | | | | |
| 3 months | 1 | 0.95 (0.87,1.04) | 1.02 (0.93,1.12) | 0.99 (0.89,1.10) | |
| 6 months | 1 | 0.90 (0.85,0.97)* | 0.93 (0.86,1.00) | 0.95 (0.88,1.04) | |
| 9 months | 1 | 0.86 (0.79,0.95)* | 0.84 (0.76,0.94)* | 0.92 (0.82,1.03) | |
| 12 months | 1 | 0.82 (0.71,0.95)* | 0.77 (0.66,0.91)* | 0.89 (0.75,1.06) | |

*Table 3.2 (Continued)*

| | Maternal diet diversity score (MDD-W )[a] | | | | |
|---|---|---|---|---|---|
| | **Q1 (0-2)** | **Q2 (3)** | **Q3 (4)** | **Q4 (5-9)** | **P for trend** |
| **Stunting [c]** | | | | | |
| **Multivariate Model HR (95% CI)[d]** | | | | | 0.14 |
| 3 months | 1 | 0.94 (0.86,1.03) | 1.00 (0.91,1.11) | 0.98 (0.88,1.09) | |
| 6 months | 1 | 0.91 (0.85,0.98)* | 0.94 (0.87,1.01) | 0.97 (0.89,1.05) | |
| 9 months | 1 | 0.89 (0.81,0.98)* | 0.88 (0.79,0.98)* | 0.95 (0.85,1.07) | |
| 12 months | 1 | 0.86 (0.74,1.00)* | 0.82 (0.70,0.96)* | 0.94 (0.79,1.11) | |
| **Wasting [c]** | | | | | |
| **Univariate HR (95% CI)** | | | | | |
| n/N | 39/676 | 43/1061 | 30/805 | 18/556 | |
| 3 months | 1 | 0.63 (0.50,0.80)* | 0.60 (0.46,0.77)* | 0.86(0.66, 1.12) | |
| 6 months | 1 | 0.70 (0.60,0.81)* | 0.77 (0.70,0.88)* | 0.35 (0.77,1.12) | |
| 9 months | 1 | 0.76 (0.63,0.92)* | 0.91 (0.74, 1.12) | 1.00 (0.80, 1.25) | |
| 12 months | 1 | 0.83 (0.61,1.12) | 1.12 (0.83,1.53) | 1.08 (0.78,1.50) | |

*Table 3.2 (Continued)*

| | Maternal diet diversity score (MDD-W )[a] | | | | |
|---|---|---|---|---|---|
| | **Q1 (0-2)** | **Q2 (3)** | **Q3 (4)** | **Q4 (5-9)** | **P for trend** |
| **Wasting [c]** | | | | | |
| **Multivariate Model HR (95% CI)[d]** | | | | | 0.68 |
| 3 months | 1 | 0.62 (0.50, 0.78)* | 0.61 (0.47, 079)* | 0.91 (0.69,1.19) | |
| 6 months | 1 | 0.69 (0.59,0.81)* | 0.74 (0.63,0.89)* | 0.97 (0.80,1.17) | |
| 9 months | 1 | 0.76 (0.63, 0.92)* | 0.91 (0.74,1.12) | 1.04 (0.83,1.29) | |
| 12 months | 1 | 0.84 (0.63,1.13) | 1.12 (0.82,1.52) | 1.11 (0.80,1.54) | |

Abbreviations: *p<0.05, ** p<0.001. Test for trend conducted using median MDD-W scores for diet quartiles. MDD-W: minimum diet diversity score for women.

a/We estimated the Hazard ratios (HR) of stunting and wasting using Cox hazards regression. HR below 1 implies that the incidence of the outcome was less among infant of women with more diverse diets.

b/ For underweight models, the interaction of maternal diet diversity with child age was not significant, therefore the proportional hazards assumption is not violated. Models for underweight do not include an interaction term and we do not present HR by child age.

c/ We evaluated for proportional Hazards using interactions with child age. For stunting and wasting models, the interaction of maternal diet diversity with child age was significant, thus models include an interaction term. We present HR by child age.

d/ Multivariate models for child stunting adjust for community connector, child age, region ( north/south west), child gender(male/female), maternal height, breastfeeding status( yes/no), paternal education status ( 0-6 years/7 or more years), maternal nutrition knowledge (tertiles), and household wealth index (tertiles).

Models for wasting do not adjust for breastfeeding status to allow for convergence, and also exclude maternal nutrition knowledge. Multivariate model for underweight also adjusts marital status (married/not married). All models (except univariate models) adjust for region and participation in the community connector program. Models adjust for clustering by sub-county.

**Discussion**

In this prospective study we evaluated the association of prenatal maternal dietary diversity with the incidence of underweight, stunting and wasting among infants in rural Uganda. We found that diversified maternal diets during pregnancy, measured using the MDD-W index, were associated with a significantly lower hazard ratio of underweight in infants. We did not, however, find significant associations between maternal diet diversity and stunting or wasting in infants.

There are limited studies that have prospectively evaluated the association of maternal diets with infant growth outcomes. One study evaluated associations between the consumption of the alternative Mediterranean diet and the Alternative Healthy Eating Index (AHEI) during pregnancy with growth (WFL Z-scores) in infants aged 3 to 6 months and found no association [81]. Another study evaluated maternal consumption of unhealthy diets, composed of red and processed meats and fried foods and found associations with increased BMI-for-age in infants at 6 and 12 months of age, indicating increased risk for overweight [82]. Both of these studies were in a high income country, the United States, where maternal overnutrition is a key factor affecting infant growth. Though our study is in a different context, our findings are similar to the latter study in that they show that poor maternal diets in pregnancy can adversely affect infant growth. Finally, our findings are similar to the only study that we reviewed that was conducted in LMICs, a cross-sectional study that was conducted in Tanzania. The study found that the MDD-W was positively associated with WHZ and WAZ and lower risk of wasting in children under 24 months of age [83]. However, this study did not evaluate maternal diets during pregnancy.

In this study we found an association between maternal diets and underweight in infants but not with other growth outcomes, and this may be due to differences in causal factors. While

an interrelationship exists between all three outcomes and they share causal factors such including poor breastfeeding and complementary feeding practices and infectious diseases, stunting reflects long term exposures and their cumulative influence on child growth, wasting reflects an acute response to poor nutrition and underweight is a composite indicator that reflects both long term and acute deprivation [84-86]. Underweight represents children that are stunted, wasted, have both outcomes or none [87]. Underweight is therefore a complex indicator and its relationship with maternal diets required further evaluation.

The fact that we did not find a significant association with stunting may be explained in part by the possibility that there may be other factors besides maternal diets that may be important for stunting in infancy. It is likely that while there is an association between maternal diets and stunting, its importance is smaller compared to that of maternal height. Maternal height is a known determinant of infant growth [88], and has a strong influence on stunting, and may be less influential for underweight and wasting [89]. The effect of maternal height on stunting may be strongest in early infancy and may diminish over time, in comparison to the effects of maternal diets. In the study we adjusted for maternal height. We also did not find an association between maternal diets and wasting in infants. This may be explained in part by that there is little variation in wasting prevalence over time infancy in our study to be explained by maternal diets. Alternatively maternal prenatal diets may not be a key determinant of wasting in infants.

We considered that the relationship between maternal diets and underweight in infants could be due to the correlation with other factors that contribute to growth failure in infants. In this respect, we controlled for the infants' breastfeeding status. The observed associations persisted after this adjustment. We also considered that maternal diets in the study reflect the

importance of infant diets, given that mothers and infants in the same household share the same family resources and will most likely eat from the same family pot. Studies indicate that maternal diets are associated with child diets [90, 91]. In addition, we considered that birth weight may be an important factor for infant growth [89]. However, due to concerns over quality of birth anthropometric measures we were not able to control for birth weight or birth length.

We also considered that prenatal maternal diets could be associated with infant growth through their effect on breastmilk quality. Maternal diets during pregnancy are likely to be correlated with postnatal diets, and postnatal diets may influence breastmilk quality. For example, postnatal maternal diets that are high in selenium, omega 3 and omega 6 fatty acids, and vitamins A, B-6, and B-12 have been associated with higher content of these nutrients in breastmilk [92-94]. Associations have been shown between vitamin A and child growth and short chain fatty acids from breastmilk have been associated with weight gain in infants [95, 96]. In addition, maternal nutrient deficiencies during pregnancy may predispose infants to nutrient deficiencies that can affect their growth [97]. For example, maternal vitamin D status in pregnancy may influence infant vitamin D levels, given that prenatal vitamin D supplementation has been shown to influence vitamin D status of infants, and vitamin D may be important for infant growth [98, 99]. We also anticipated that maternal diet diversity could also be a reflection of family wealth and social status. In multivariate models we account for these factors and observed associations persist. However, residual confounding could still be a factor as is in all cohort studies.

The limitations of our study include that maternal diet quality was assessed with the MDD-W, an index that has been evaluated for associations with micronutrient adequacy, but not other aspects of diet quality [22]. Secondly, dietary intake was measured only once for women,

with most measurements in the second and third trimester thus, our study may have missed the effects of early pregnancy diets. Further, our study also experienced loss to follow up among infants, with the sample size decreasing at the 12-month follow up period. However, this is not likely to be a cause of bias, as censoring is likely to be non-informative and independent of the outcome. Additionally, there were other confounding variables that were not measured in the study, such as pregnancy weight gain and we did not have access to the gold standard for assessing pregnancy gestational age, the ultrasound. This study's generalizability is limited to the rural areas of sub-Saharan Africa that are similar to the study areas of Northern and South-west Uganda.

Finally, in this study, we exclude birth measures of weight and length from the analysis and include children with pre-existing underweight, wasting or stunting at 3 months (baseline). Since we include children with pre-existing growth failure, and do not report birth data, we are unable to determine if our findings are related to birth outcomes or post 3 month outcomes.

The strengths of our study include its large sample size and detailed anthropometric data at several time points during infancy. Our findings have implications in that we know that poor child growth in infancy lays the foundation for poor growth in childhood, however it is likely that maternal dietary intake during pregnancy could also have an important role in determining growth in childhood and therefore warrant attention. Further, while underweight has received limited attention compared to the other growth indices in nutrition programs globally, it may still be an important indicator of poor child growth. This is first time maternal prenatal dietary diversity has been linked with infant growth in LMIC.

**Conclusion**

This study suggests a relationship between maternal diet diversity and the development of underweight in infancy. Infants whose mothers were in the higher quartiles of dietary diversity were at 30-35% lower risk of developing underweight through age 12 months. Research is required to further evaluate this association and the role of maternal diets during pregnancy on other infant growth outcomes in diverse locations. These findings, if confirmed will have significant implications for policy and program approaches to provide nutrition counselling for women during pregnancy, to decrease child undernutrition in LMIC.

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**Authors' contributions**

I.M. conceived the study, conducted the data analysis, and drafted the article. C.D. S.G. and P.W. were the principal investigators for the parent study, conceived the study, contributed to study design, interpreted the data, and guided revisions of the manuscript, S.G. and P.W. were co-principal investigators for the parent study, interpreted the data, and guided revisions of the draft manuscript. B.B, E.A. and F.T. where co-principal investigators for the parent study, participated in the study implementation and field supervision, interpreted the data, and guided revisions of the manuscript. M.W. W.F., S.I. E.H and G.N. contributed to study design, interpreted the data, and guided revisions of the draft manuscript. All authors contributed to the editing of the final version of the manuscript.

**Conflict of interest**

All of the co-authors have nothing to disclose

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