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Statistical Analysis Plan: Effect of LNS during pregnancy and lactation on maternal cognition and mental and physical health at 4-6 years postpartum (iLiNS-DYAD-G2)

Background and Objectives

Small-quantity lipid-based nutrient supplements (SQ-LNS) were designed to prevent undernutrition during the critical "first 1,000 days." In the iLiNS DYAD-G randomized controlled trial in Ghana, the provision of SQ-LNS to mothers during pregnancy increased mean birth size, particularly among first-time mothers (Adu-Afarwuah et al., 2015) and maternal plus child supplementation with SQ-LNS increased mean attained size at 18 months of age (Adu-Afarwuah et al., 2016). In a follow-up study when children were 4-6 years of age, we collected data on maternal cognition, depression, blood pressure, hemoglobin, and body mass index (BMI).

The primary objectives of this analysis are as follows:

1. Determine the effect of SQ-LNS on maternal depressive symptoms at 4-6 years postpartum
2. Determine the effect of SQ-LNS on maternal systolic and diastolic blood pressure at 4-6 years postpartum
3. Determine the effect of SQ-LNS on maternal hemoglobin at 4-6 years postpartum
4. Determine the effect of SQ-LNS on maternal BMI at 4-6 years postpartum
5. Determine the effect of SQ-LNS on maternal cognition at 4-6 years postpartum

Description of the Intervention

The iLiNS DYAD-G randomized controlled trial and the effects of the provisions of SQ-LNS on birth outcomes, growth, and development have been described elsewhere in detail (Adu-Afarwuah et al., 2015; Adu-Afarwuah et al., 2016; Prado et al., 2016).

The main DYAD-G trial was conducted between December, 2009 and March, 2014. The 'DYAD-G2' follow-up study collected data from the mother, her child (the index child), and other members of the index child's family between January, 2016 and December, 2016 when the index children were between 4 and 6 years of age. As a component of the follow-up data collection activities, we collected data on maternal cognition and mental and physical health from all enrolled women, which included maternal depressive symptoms, blood pressure, hemoglobin, and BMI.

Description of Variables

Outcome Variables

There are six primary outcomes for this analysis which are specified in the table below (Table 1).

Table 1. Primary outcomes.

Outcome Variable	**Definition**	**Type of Variable**
Maternal depressive symptoms	Edinburgh Postpartum Depression Scale (EPDS), a 10-item structured questionnaire. Score ranges from 0-30.	Continuous

Maternal systolic blood pressure	mmHg, measured from the mother during clinic visit	Continuous
Maternal diastolic blood pressure	mmHg, measured from the mother during clinic visit	Continuous
Maternal BMI	Kg/m^2, constructed from maternal weight and height measured during clinic visit	Continuous
Maternal hemoglobin	g/dl, measured from the mother during the clinic visit	Continuous
Maternal cognition	Mean of the z-scores on the mental rotation, digit span forward, and digit span backward tests	

Secondarily, we will analyze the outcomes according to the categories listed in the table below (Table 2).

Table 2. Secondary outcomes.

Outcome Variable	**Definition**	**Type of Variable**
At risk for maternal depression	EPDS score ≥ 12	Dichotomous
High maternal systolic blood pressure	≥ 130 mmHg	Dichotomous
High maternal diastolic blood pressure	≥ 80 mmHg	Dichotomous
Overweight or Obese	BMI <25, ≥ 25-30, ≥ 30 kg/m^2	Ordinal
Anemia	Hb < 10 g/dl	Dichotomous
Maternal cognition	Lowest decile	Dichotomous

Covariates and Effect Modifiers

The following variables will be examined as potential covariates:

- infant sex
- maternal years of formal education
- maternal height
- maternal age at enrollment
- pre-pregnancy BMI
- marital status at enrollment
- anemia at enrollment
- gestational age at enrollment
- nulliparity at enrollment
- household asset index at enrollment
- household food insecurity index at enrollment
- season when depression data were collected (for analysis of depression outcomes only)
- maternal systolic blood pressure at enrollment (for analysis of systolic blood pressure outcomes only)
- maternal diastolic blood pressure at enrollment (for analysis of diastolic blood pressure outcomes only)
- maternal cognition data collector (for analysis of maternal cognition only)

The following variables will be examined as potential effect modifiers:

- infant sex
- household asset index at enrollment
- pre-pregnancy BMI
- maternal age
- nulliparity
- season when depression data were collected (for analysis of depression outcome only)
- maternal systolic blood pressure at enrollment (for analysis of systolic blood pressure outcome only)

- maternal diastolic blood pressure at enrollment (for analysis of diastolic blood pressure outcome only)
- Maternal cognition only:
    - Maternal Hb at enrollment
    - Maternal iron status at enrollment (ZPP/sTfR)
    - Maternal RDT positive at enrollment

Primary Research Questions

Using a 3-group comparison model, we propose to examine the following questions at 4-6 years postpartum:

1. Do women assigned to SQ-LNS supplementation differ in their EDPS depression score compared with women assigned to IFA or MMN?
2. Do women assigned to SQ-LNS supplementation differ in their systolic and diastolic blood pressure compared with women assigned to IFA or MMN?
3. Do women assigned to SQ-LNS supplementation differ in their BMI compared with women assigned to IFA or MMN?
4. Do women assigned to SQ-LNS supplementation differ in their maternal hemoglobin concentration compared with women assigned to IFA or MMN?
5. Do women assigned to SQ-LNS supplementation differ in their maternal cognition compared with women assigned to IFA or MMN?

Analysis Principles

Data Cleaning

To the extent possible, data cleaning happened concurrently with follow-up data collection. Queries were identified using SAS syntax and were relayed to the local home visit and clinic visit team managers for queries as needed. Queries were then resolved by seeking clarification from the field worker who completed the form and/or by re-contacting the respondent.

Outliers

Outliers will be identified by visually inspecting histograms and/or densities of continuous variables and scatterplots of related variables. Outliers that are clearly impossible or implausible values will be corrected if possible and otherwise recoded as missing. Outliers which are plausible or possible will be retained. In cases where extreme outliers are retained, sensitivity analysis truncating the top and bottom 2.5% of the distribution to the 97.5^{th} and 2.5^{th} percentiles, respectively, will be performed to determine whether the extreme outliers have undue influence on the results.

Data Transformation

We will inspect the distribution of outcome variables for normality and transform as necessary. If no suitable transformation is found, normalized ranks will be calculated, or categories will be created.

Model Assumptions

Models will be checked to ensure that the residuals are normally distributed and the heteroscedasticity assumption is met through the residual versus fit plot.

Software

All analyses will be performed using SAS 9.4 statistical package.

Attrition and Balance

Baseline covariates will be summarized by sample (follow-up analytic sample and lost-to-follow-up sample) using mean ± SD or median (Q1, Q3) for continuous and count variables and percentages for dichotomous variables. P-values for tests of differences in sample means between the follow-up and lost-to-follow-up groups will be reported. To assess balance, p-values for tests of difference in group means will be reported.

Analysis of the Effect of the Intervention

The analysis will be by intent-to-treat. That is, by-group analysis will be according to group assignment regardless of any protocol violations. Missing data will not be imputed. All tests will be two-sided and determined significant at $p < 0.05$. Secondarily, two per protocol analyses will be performed based on self-reported adherence to supplementation during the main trial. The first per protocol analysis will include women with ≥ 80% adherence to supplement during pregnancy. The second per protocol analysis will include women with ≥80% adherence during the entire period of pregnancy up to 6 months postpartum. To address the issue of the supplement switch that occurred during the main trial between IFA and MMN, data will be analyzed both according to: 1) supplement received at enrollment and 2) intended supplement at enrollment. All analyses will be performed in a 3-group comparison model and we will perform post-hoc pairwise comparisons when $p <0.05$ for the 3-group comparison of each outcome. If there is no difference between the IFA and MMN groups, these groups may be combined for a 2-group comparison model (LNS vs. non-LNS). The 2-group comparison model may be used for all outcomes listed in this SAP except for hemoglobin concentration, since IFA and MMN differed in iron content.

The effect of intervention group will be assessed as follows according to the type of the outcome variable:

- Continuous outcome variables will be analyzed using ordinary least squares regression models.
- Dichotomous outcome variables will be analyzed using logit or probit regression models.

All models will include age of index child. For adjusted analyses, we will additionally control for baseline covariates that are significantly associated with a particular outcome ($p <0.10$) in a bivariate analysis. If the null hypothesis of no difference between groups is rejected, post-hoc pairwise comparisons of group means will then be performed.

Effect modification will be assessed using interaction terms, and statistically significant interactions ($p<.10$) will be further examined. For dichotomous effect modifiers, the treatment effect by effect modifier will be estimated. For continuous effect modifiers, the treatment effect at values along the range of the effect modifier will be estimated with the possibility of stratifying the effect modifier to examine differences within subgroups.

References

Adu-Afarwuah, S., Lartey, A., Okronipa, H., Ashorn, P., Zeilani, M., Peerson, J. M., Arimond, M., Vosti, S., Dewey, K. G., 2015. Lipid-based nutrient supplement increases the birth size of infants of primiparous women in Ghana. Am. J. Clin Nutr. 101(4): 835-846.

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