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Abstract

Aims: First, the study first assessed the impact of maternal exposure to drought *in utero* on newborn size. Second, the study assessed the effect of prenatal supplementation in offsetting the negative intergenerational effects of maternal exposure to drought *in utero* on newborn size. **Methods:** The present study took advantage of a natural experiment from three droughts (1981/82, 1987/88, and 1992/93) of varying severity in rural Malawi to derive maternal exposure to drought *in utero* based on maternal date of birth. Other data for outcomes and control variables were sourced from the iLiNS-DYAD-M randomized clinical trial. **Results:** Among infants of mothers exposed to drought in the first trimester, non-significant effects on infant length-for-age Z score (LAZ) were observed for prenatal supplementation with small-quantity, lipid-based nutrient supplements (SQ-LNS) on infant LAZ compared to the iron-folic acid (IFA), controlling for the study covariates. However, prenatal supplementation with multiple micronutrients (MMN) compared to IFA produced significant effects on infant LAZ [-0.853 SD, 95% CI (-1.446: -0.259)]. **Conclusions:** These findings suggest that prenatal supplementation with SQ-LNS vs IFA or significantly with MMN vs IFA may sometimes not be beneficial for birth outcomes due to intergenerational external shocks in resource-poor, drought-prone settings.

Keywords

Droughts, Intergenerational effects, Maternal prenatal exposure, MMN, Newborn size, SQ-LNS, Supplementing Maternal and Infant Diet With High-energy Micronutrient Fortified Lipid-based Nutrient Supplements

Disciplines

Demography, Population, and Ecology | Family, Life Course, and Society | Maternal and Child Health | Social and Behavioral Sciences | Sociology

Comments

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Intergenerational Effects of Maternal Exposure to Drought in Utero on Newborn Size: Evidence from a Retrospective Cohort Study in Malawi

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Abstract

Aims: First, the study first assessed the impact of maternal exposure to drought *in utero* on newborn size. Second, the study assessed the effect of prenatal supplementation in offsetting the negative intergenerational effects of maternal exposure to drought *in utero* on newborn size. **Methods:** The present study took advantage of a natural experiment from three droughts (1981/82, 1987/88, and 1992/93) of varying severity in rural Malawi to derive maternal exposure to drought *in utero* based on maternal date of birth. Other data for outcomes and control variables were sourced from the iLiNS-DYAD-M randomized clinical trial. **Results:** Among infants of mothers exposed to drought in the first trimester, non-significant effects on infant length-for-age Z score (LAZ) were observed for prenatal supplementation with small-quantity, lipid-based nutrient supplements (SQ-LNS) on infant LAZ compared to the iron-folic acid (IFA), controlling for the study covariates. However, prenatal supplementation with multiple micronutrients (MMN) compared to IFA produced significant effects on infant LAZ [-0.853 SD, 95% CI (-1.446: -0.259)]. **Conclusions:** These findings suggest that prenatal supplementation with SQ-LNS vs IFA or significantly with MMN vs IFA may sometimes not be beneficial for birth outcomes due to intergenerational external shocks in resource-poor, drought-prone settings.

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Introduction

Despite decades of interventions and programmes, maternal and child undernutrition is still a global problem, especially in developing countries [1]. For example, 30% of children aged 0-5 worldwide are moderately or severely stunted for their age in sub-Saharan Africa [stunted: defined as > 2 standard deviations (SD) below the median], which is a marker of chronic poor nutritional status [2]. In addition, there is evidence that when stunted growth from childhood is not addressed there are negative spillover effects into adulthood in terms of future earnings and the ability to contribute to society [3]. Further, not only do spillover effects persist intragenerationally but also intergenerationally, whereby a mother's early life nutritional status may affect their offspring's birth outcomes [1].

Prenatal supplementation with small-quantity (SQ), lipid-based nutrient supplements (LNS) or close substitutes may prevent undernutrition and promote growth in offspring. In a randomized-controlled trial (RCT) in Burkina Faso, clinically important treatment effects on birth length (+12.0 mm; p = 0.01) and on birthweight (+111 g; p = 0.13) were observed in offspring of women who received fortified food supplements (FFS) but were also underweight, an important finding in a country with a low birthweight (LBW) rate of 16 percent [4]. In an RCT in Ghana, better birth outcomes were reported for newborns of 1057 mothers supplemented with SQ-LNS vs. iron-folic acid (IFA), or multiple micronutrients (MMN) [mean birthweight (p = 0.04); weight-for-age Z score (WAZ; p = 0.05); and body mass index- for-age Z score (BMIZ; p = 0.04)], notably, in a country where 11% of all infants have LBW [5]. A greater effect was observed among primiparous women [mean birthweight (+85 g; p = 0.04), WAZ (+0.19; p = 0.05), and BMIZ (+0.21; p = 0.04)] [5].

In view of the highlighted literature, the aims of the present study were, (1) to examine the associations between maternal exposure to drought *in utero* - an environmental exposure – and offspring’s nutritional status length-for-age Z score (LAZ), WAZ and imputed birthweight and (2) to examine the associations between maternal exposure to drought *in utero* and offspring’s LAZ, infant WAZ, and imputed birthweight, after prenatal supplementation SQ-LNS vs. iron-folic acid (IFA).

Methods

Data and Study population

This natural experiment reports on mothers who were enrolled in the iLiNS-DYAD-M trial (a registered clinical trial, #NCT01239693 at clinicaltrials.gov) from 2011-2013 but with a smaller sample size (N = 1262). In the main trial, women were recruited from four health centres rural areas (Lungwena: n = 508; Malindi: n = 232; Namwera: n = 210) and more urban areas (Mangochi *Boma*: n = 312) of Mangochi District, in Southern Malawi. The adjusted trial groups comprised the SQ-LNS (20g, daily dose: n = 419), MMN (1 tablet/day: n = 421), and the IFA (1 tablet/day: n = 422) groups. In this study, only women with known date of birth (DoB) were assessed to ensure the derivation of maternal exposure to drought *in utero* was more precise. The variable “date of birth known” (0, 1) was used for inclusion into the study if the corresponding value was 1.

Measures

Three droughts were found in the literature which corresponded with the range of ages of the study mothers (14-48 yr): the 1981/82 [8], 1987/88 [9], and 1992/93 [8] droughts, which all began after the lean season ended with failed rains in 1981, 1987, and 1992, respectively.
The present study defined the start of the drought period from May YYYY, (where YYYY refers to the relevant year), regardless of the preceding lean season in Dec XXXX – Apr YYYY, (where XXXX is the preceding year), and ending just before the next harvest (May YYYY*) the following year. The first trimester exposure to drought *in utero* was for mothers born from November YYYY-April YYYY* while the second-third trimester exposure to drought *in utero* was for mothers born from May YYYY-October YYYY (where YYYY denotes the drought year itself, i.e., the year of the initial failed/poor harvest and YYYY* is the year immediately following a drought). No severe droughts reported for the study area - only after the RCT (10).

Independent Variables

The study’s exposure variables and covariates included the sex of the child, maternal education, maternal BMI, marital status, maternal height, mother as head of household (HH), household food insecurity access score (HFIAS), household asset index Z score (HAIZ), primiparity, and “normal vs. at risk” pregnancy by age. There was also a locality dummy variable called peri-urban (vs. rural). The main clinical trial arms for mothers were the treatment groups of SQ-LNS, MMN, and the control group, IFA. The covariates were added to the ordinary least regressions (OLS) to minimize confounding.

Outcome Measures

The study outcomes were infant LAZ, infant WAZ, and imputed birthweight. In brief, imputed birthweight was ascribed if the weight measurement occurred within 3-5 days of birth [11] and was more common for those infants born at home rather than at a health facility. Otherwise, the variable for imputed birthweight included actual measured birthweight and imputed birthweights for children with missing actual measured birthweight (n = 123). Thereafter, birth length and weight were measured based on neonatal age within 42 days from birth using calculations for LAZ and WAZ in the WHO's 2006 child growth standards [12].

Statistical Analyses

Descriptive statistics were obtained for the outcomes, exposure variables, and covariates used in the models, including for interacted variables (exposures and trial supplements).
Restricted models for LAZ, WAZ, and imputed birthweight contained the drought exposure variables adjusted for covariates. Interaction terms between maternal exposure to drought in utero and the trial supplements were added to the expanded models. Using OLS and the statistical software Stata 14 and 14.2, equations were regressed for the birth outcomes. In statistics, OLS is a method that estimates or predicts the values of unknown parameters (outcomes) in multiple linear regression (MLR) models.

In the present study, alpha was set at 0.05, which meant that a regression coefficient with a probability of $p < 0.05$ was deemed statistically significant. The study was, however, underpowered to detect effect sizes at power = 80% due to the nature of the study.

Results

Descriptive Statistics

Table 1 summarises the descriptive statistics of the data among the three trial groups. Notably, of the 1262 out of the 1391 women from the main trial with known DoB, 195 women were exposed to drought *in utero*. In terms of maternal exposure to the pooled droughts during the first trimester, 18 women received SQ-LNS; 21 women received MMN; and, 20 women received IFA. In terms of maternal exposure to the pooled droughts during the second and third trimesters of pregnancy, 46 women received SQ-LNS; 41 women received MMN; and 49 women received IFA.

Regression Results

The results in Table 2 show a list of the variables, the predictor coefficients with the confidence intervals (CIs) in parentheses set at the 95% level of confidence for the three outcomes (LAZ, WAZ, and imputed birthweight) for MLR models. The strength of the associations between predictors and study outcomes were represented by asterisks ("*") with "**" as $p < 0.05$, and "***" as $p < 0.01$. Robust standard errors were used for all the MLR models.

There were no statistically significant first trimester effects on birth outcomes from maternal exposure to drought *in utero*, controlling for maternal effects variables and socioeconomic variables in the restricted models. All the associations between the maternal exposure to drought *in utero* variables and the birth outcomes variables were positive although all were insignificant except for one result in the imputed birthweight model. Thus, maternal second-third trimester exposure compared to non-drought exposure *in utero* was positively associated with imputed birthweight ($p < 0.05$).

In terms of statistical significance, the results changed when the models were additionally controlled for trial supplements (expanded models, Table 2). Among infants of mothers who received IFA, there was a larger effect on LAZ [+0.540 SD, 95% CI (0.136: 0.943)] if mothers were exposed to drought during the first trimester compared to mothers not exposed to drought *in utero*. Among infants of mothers not exposed to drought *in utero*, there was a slight improvement in infant LAZ [+0.198 SD, 95% CI (0.014: 0.383)], if their mothers received MMN (compared to IFA). Finally, among infants of mothers exposed to drought in the first trimester *in utero*, there was a larger but negative effect of maternal prenatal supplementation with MMN on infant LAZ, [-0.853 SD, 95% CI (-1.446: -0.259)] compared to prenatal supplementation with IFA. The study's sensitivity analyses, which removed the effect of maternal exposure to drought at age 0-5 yr in the models generally did not alter the results of the restricted models and the expanded models. However, the interaction between maternal non-drought exposure *in utero* and MMN was no longer statistically significant. Finally, the joint-tests of significance for the drought exposure variables in the sensitivity analyses were all significant.

Discussion and Conclusion

First, the study investigated the effects of maternal exposure to drought on offspring's birth outcomes. Second, the study investigated whether prenatal supplementation could offset any intergenerational effects of maternal exposure to drought *in utero*. Overall, any intergenerational effects and prenatal supplementations effects in the present study centred on infant LAZ and not the other birth outcomes.

Surprisingly there was a positive association observed between maternal exposure to drought during the second-third trimester *in utero* and infant LAZ, controlled for covariates. The sensitivity analyses, which removed the effect of maternal exposure to drought at age 0-5 yr in the control group, did not significantly alter the results. The little evidence there is in the literature has shown, for example, that in a study on neonatal adiposity and later adult health, mothers with gestational exposure to the Dutch Famine were more likely to report that their offspring had decreased birth length but not decreased birthweight compared to unexposed controls [13]. Similarly, in terms of birth length, Fung and Ha reported more theoretically-aligned results for the Great Chinese Famine [14]. Maternal *in utero* exposure to the Great Chinese Famine was not only negatively and significantly associated with infant LAZ but also for infant WAZ [14]. However, the anthropometry measurements were taken between age 0-18 yr, a range that extends beyond the scope of the present study [14]. In comparison, the present study's *in utero* effects outcomes, specifically for maternal second-third trimester exposure, produced a larger and positive effect size on birthweight than reported in a Dutch cohort study (which controlled for maternal birthweight but not maternal adult height) [15]. Therefore, there was a marked difference in the direction of the intergenerational effects of maternal exposure to drought *in utero* on infant birth length in the present study akin to the unexpected result reported a Huang and colleagues study [16]. Intergenerational associations, surprisingly, increased offspring birthweight (+72g) and, less remarkably, birth length (+0.3cm), even after controlling for maternal height, maternal education, and maternal age at delivery, in a Great Chinese Famine cohort [16].

Subsequently, the present study showed some notable prenatal supplementation effects on maternal first trimester exposure *in utero* on infant LAZ. For example, among mothers who received IFA, there was an increased likelihood of improved infant LAZ if mothers experienced first-trimester exposure *in utero* compared to non-drought exposure *in utero*, controlling for the study covariates. Conversely, among mothers exposed to drought during the first trimester *in utero*, a large but negative effect of prenatal supplementation with MMN was observed on infant LAZ compared to prenatal supplementation with IFA. Finally, among mothers not exposed to drought i*n utero*, there was an increased likelihood of improved infant LAZ if mothers where supplemented with MMN compared to mothers supplemented with IFA.

It is noteworthy that there were problems with the statistical integrity and validity of the present study. For example, the estimation of maternal *in utero* drought exposure and subsequent analyses were limited by the lack of data on the residence of the women in early life, by some of the women in the main trial being unaware of their DoB, and by a dependence on self-reported DoB without supporting documents [6]. Further, this study was underpowered to detect effects within different drought exposure sub-groups because their numbers were very small (notably, n < 18 for SQ-LNS and IFA among women exposed to drought during the first trimester and n < 46 for SQ-LNS and IFA among women exposed to drought during the second-third trimester. However, sensitivity analyses which featured joint-significant tests of the drought exposure variables showed significant results which appears to confirm that intergenerational effects of maternal exposure to drought *in utero* and the modifying effects of prenatal supplementation with MMN (compared to IFA) on infant LAZ were important in this study.

Overall, non-significant effects on infant LAZ were observed for prenatal supplementation with SQ-LNS compared IFA, controlling for covariates. Finally, prenatal supplementation with MMN significantly showed no beneficial effects from compared to the standard ante-natal care (IFA) on infant LAZ, controlling for covariates, among mothers exposed to drought during the first trimester *in utero*.

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Conflicts of Interest

None.

Ethical Standards

The author asserts that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation in Malawi and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the institutional committees (University of Waterloo Research Ethics Committee, University of Malawi, College of Medicine

Research and Ethics Committee (COMREC), and the ethics committee of Pirkanmaa Hospital District, in Finland).

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Table 1: Summary Statistics of the Study Outcome and Independent Variables

Variables	LNS Mean (SD, range, n) %, n	MMN Mean (SD, range, n) %, n	IFA Mean (SD, range, n) %, n	Total n n/N
Mean Length-for-Age Z Score (SD)	-0.97 (1.08, -4.64 : 2.13, 331)	-0.98 (1.10, -6.52 : 1.92, 352)	-1.09 (1.19, -5.32 : 1.52, 328)	1011
Mean Weight-for-Age Z Score (SD)	-0.54 (1.08, -4.02 : 2.42, 338)	-0.57 (1.04, -6.00 : 1.97, 354)	-0.64 (1.05, -451 : 1.95, 330)	1022
Mean Imputed Birthweight (g)	2970.66 (468.64, 1308.08 : 4315, 372)	2964.32 (464.12, 1100 : 4260, 368)	2937.09 (446.38, 1212.12 : 4300, 372)	1112
First Trimester Effects	4.30%, 18	4.99%, 21	4.74%, 20	59/1262
Second-Third Trimester Effects	10.98%, 46	9.74%, 41	11.61%, 49	136/1262
Child Sex (Male)	49.8%, 404	46.8%, 406	50.3%, 404	1214
Maternal Education (yr)	4.0 (3.6, 1 - 12, 413)	4.0 (3.43, 1 - 12, 413)	3.9 (3.3, 1 - 12, 417)	1243
Maternal BMI (kg^2/cm)	22.2 (22.20, 16.26 : 36.85, 418)	22.1 (22.09, 16.63 : 37.81, 417)	22.0 (22.08, 16.10 : 34.49, 419)	1254
Marital Status	88.78% (419)	87.41% (421)	88.86% (422)	1262
Maternal Height (cm)	156.2 (156.21, 132.8 : 172.6, 419)	156.0 (156.00, 140.9 : 175.7, 418)	156.1 (156.20, 139.1 : 171.8, 421)	1258
Mother Household Head	5.97%, 25	7.60%, 32	6.40%, 27	84/1262
Food Insecurity Access Scale	4.5 (4.1, 0 : 23, 412)	5.3 (4.7, 0 : 24, 410)	5.0 (4.5, 0 : 27, 415)	1237

Household Asset Index Z Score	0.02 (0.99, -0.73 : 3.29, 412)	-0.08 (0.99, -0.73 : 3.29, 412)	-0.06 (0.96, 0.73 : 3.29, 415)	1240
Primiparous	22.20%, 93	21.67%, 91	19.48%, 82	266/1262
Normal (vs. “At Risk”) Pregnancy by Age	20.05%, 84	16.39%, 69	18.48%, 78	231/1262
Peri-urban (vs. Rural)	24.11%, 101	25.18%, 106	24.88%, 105	312/1262

Table 2: Multiple Linear Regression Models of Infant LAZ, Infant WAZ, Imputed BWT (Expanded)

Variables	(1) Expanded Model: LAZ (N = 980)	(2) Expanded Model: WAZ (N = 991)	(3) Expanded Model: Imputed BWT (N = 1074)
First trimester # IFA	0.540***	0.234	24.605
	(0.136 , 0.943)	(-0.220 , 0.688)	(-143.246 , 192.456)
Second-third trimester #IFA	0.297	-0.025	110.030
	(-0.102 , 0.697)	(-0.420 , 0.371)	(-25.770 , 245.829)
Non exposure # MMN	0.198**	0.097	55.322
	(0.014 , 0.383)	(-0.073 , 0.267)	(-15.964 , 126.608)
Non exposure # LNS	0.127	0.082	25.426
	(-0.054 , 0.308)	(-0.092 , 0.256)	(-46.539 , 97.391)
First trimester # MMN	-0.853***	-0.436	-117.519
	(-1.446 , -0.259)	(-1.053 , 0.181)	(-382.257 , 147.218)
First trimester # LNS	-0.662*	-0.107	115.521
	(-1.385 , 0.060)	(-0.855,0.642)	(-163.765 , 394.806)
Second-third trimester # MMN	-0.460*	-0.122	-129.559
	(-0.975 , 0.055)	(-0.636 , 0.392)	(-314.264 , 55.146)
Second-third trimester # LNS	0.002	0.195	47.540
	(-0.524 , 0.529)	(-0.269 , 0.660)	(-135.650 , 230.730)
Child sex (girl)	0.108	0.036	-84.443***
	(-0.028 , 0.243)	(-0.093 , 0.165)	(-137.691 , -31.196)
Maternal education	0.008	0.011	-0.932
	(-0.016 , 0.032)	(-0.011 , 0.033)	(-10.025 , 8.162)
Maternal BMI	0.021	0.030**	14.883***
	(-0.006 , 0.049)	(0.004 , 0.057)	(4.248 , 25.518)
Marital status (married)	-0.081	0.047	-21.808
	(-0.319 , 0.157)	(-0.176 , 0.269)	(-106.184 , 62.568)
Maternal height	0.053***	0.043***	18.636***
	(0.040 , 0.066)	(0.030 , 0.055)	(13.768 , 23.505)
Head of household (mother)	-0.319*	-0.446**	-112.054
	(-0.695 , 0.056)	(-0.792 , -0.099)	(-249.209 , 25.101)
HH food insecurity access scale	0.007	0.013*	4.006

	(-0.009 , 0.024)	(-0.002 , 0.029)	(-2.186 , 10.197)
HH asset index Z score	0.071	0.064	24.454
	(-0.023 , 0.165)	(-0.026 , 0.154)	(-12.709 , 61.618)
Primiparous	-0.315***	-0.376***	-122.488***
	(-0.491 , -0.139)	(-0.543 , -0.209)	(-192.859 , -52.117)
Normal (vs. “at risk”) pregnancy by age	0.204**	0.080	49.629
	(0.020 , 0.388)	(-0.094 , 0.253)	(-21.930 , 121.187)
Periurban (vs. rural)	-0.287***	-0.079	-93.357**
	(-0.484 , -0.091)	(-0.260 , 0.102)	(-165.202 , -21.512)
Constant	-10.073***	-8.150***	-177.658
	(-12.310 , -7.836)	(-10.192 , -6.107)	(-951.830 , 596.515)

Notes:

Outcomes: LAZ - length-for-age Z score, WAZ - weight-for-age Z score, BWT - birthweight

Trial supplements: LNS - lipid-based nutrient supplement, MMN - multiple micronutrient supplement, IFA - iron-folic acid

HH - household

Confidence intervals (CI): 95% CI in parentheses

Statistical significance (p-values): *** $p < 0.01$, ** $p < 0.05$, * $p < 0.1$