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Original Article

The impact of maternal diet fortification with lipid-based nutrient supplements on postpartum depression in rural Malawi: a randomised-controlled trial

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Abstract

Perinatal depression is highly prevalent in low-and-middle-income countries and has been linked to poor child health. Suboptimal maternal nutrition may be a risk factor for perinatal depression. In this randomised-controlled trial conducted in rural Malawi, we set out to test the hypothesis that women taking a fatty acid-rich lipid-based nutrient supplement (LNS) would have fewer depressive symptoms postpartum than those taking iron-folate (IFA) or multiple-micronutrient (MMN) capsules. Women were recruited from antenatal clinics and randomised to receive LNS or MMN during pregnancy and for 6 months postpartum, or IFA during pregnancy only. Maternal depressive symptoms were measured using validated translations of the Self Reporting Questionnaire (SRQ) and Edinburgh Postnatal Depression Scale (EPDS), antenatally (SRQ only) and at 6 months postpartum (SRQ and EPDS). Analysis was by modified intention to treat. One thousand three hundred and ninety one women were randomised (LNS = 462, MMN = 466, IFA = 463). The groups were similar across a range of baseline variables. At 6 months postpartum, 1078 (77.5%) had SRQ completed; mean (SD) scores were LNS 1.76(2.73), MMN 1.92(2.75), IFA 1.71(2.66), $P = 0.541$. One thousand and fifty seven (76.0%) had EPDS completed; mean (SD) scores were LNS 5.77(5.53), MMN 5.43 (4.97), IFA 5.52(5.18), $P = 0.676$. There were no statistically significant differences between the groups on SRQ or EPDS scores (continuous or dichotomised) in unadjusted or adjusted models. In conclusion, fortification of maternal diet with LNS compared with MMN or IFA did not reduce postnatal depressive symptoms in this study.

Keywords: low income countries, maternal mental health, nutritional interventions, polyunsaturated fatty acids, pregnancy and nutrition, randomised, controlled trial.

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Introduction

Ten to twenty per cent of women in low-and-middle-income countries (LMIC) experience significant depression or anxiety during pregnancy or the postnatal period (Fisher *et al.* 2012). Perinatal depression is distressing, disabling and has a negative impact on child health and development (Stewart 2007; Murray & Cooper 1999). In LMIC, perinatal depression has been associated with low birth weight (Patel & Prince 2006; Rahman *et al.* 2004; Rondo *et al.* 2003; Nasreen *et al.* 2010; Niemi *et al.* 2013), preterm birth (Rondo *et al.* 2003; Niemi *et al.* 2013), breastfeeding difficulties (Hanlon *et al.* 2009; Patel & Prince 2006; Adewuya *et al.* 2008), increased infant diarrhoeal episodes (Ross *et al.* 2011; Rahman *et al.* 2007; Okronipa *et al.* 2012) and infant growth impairment (reviewed in Surkan *et al.* 2011). In Malawi, prevalence estimates for major depressive disorder were 10.7% antenatally (Stewart *et al.* 2014a) and 14% amongst mothers of children (mean age 10 months) brought to a child health clinic (Stewart *et al.* 2010).

Maternal nutritional deficiencies remain a major health problem in LMIC (Black *et al.* 2013). Poor nutrition has been identified as a potential risk factor for depression (Rechenberg & Humphries 2013; Leung & Kaplan 2009). There has been particular interest in nutrition and mood in the perinatal period because of the nutritional stresses associated with pregnancy and lactation, and the implications of perinatal depression for infant development. In observational studies, deficiencies in iron, zinc, B-vitamins and fatty acids have been associated with perinatal depression (Leung & Kaplan 2009). A number of randomised controlled trials (RCT) in LMIC have investigated the impact of nutritional supplementation upon maternal mental health during the perinatal period. A RCT in South Africa showed that iron supplementation for women with mild anaemia during the first postnatal year reduced depressive symptoms (Beard *et al.* 2005). Multivitamin supplementation (B-complex, C and E) demonstrated a protective effect on incidence of depressive symptoms in HIV-infected women recruited in the second trimester of pregnancy in Tanzania (Smith Fawzi *et al.* 2007). Multiple micronutrient (MMN) supplements led to fewer depressive symptoms compared with low dose iron and folic acid (IFA) supplementation amongst women in the perinatal period in Bangladesh (Frith *et al.* 2009). However, in a cluster RCT comparing perinatal MMN to IFA supplementation in Indonesia, there was no effect of MMN supplementation on maternal mood despite an improvement in cognitive function (Prado *et al.* 2012).

Fatty acids play a critical role in neuronal functioning (Bazinet & Layé 2014). In high-income settings, epidemiological studies have shown an inverse relationship between depressive symptoms and dietary consumption of omega-3 polyunsaturated fatty acids (n-3 PUFA) (Appleton *et al.* 2010). In addition, depression has been associated with low serum levels of n-3 PUFA (Lin *et al.* 2010). A number of intervention studies have investigated the effectiveness of fatty acid supplementation in prevention and treatment of depression, including in the perinatal period; the results of these have been mixed (Bloch & Hannestad 2012). To date there have been no trials of fatty acid supplementation conducted in a low-income setting.

We set out to investigate the impact of fortification of maternal diet with a fatty acid-rich nutritional supplement on maternal mood in a rural sub-Saharan African setting. The International Lipid-based Nutrient Supplement study group, enrolling mother-child dyads in Malawi (iLiNS-DYAD-M) trial was primarily designed to study the impact on child growth of providing a lipid-based nutrient supplement (LNS) to mothers during pregnancy and the first six months postpartum, and to the children from 6 to 18 months of age. In this study, our objective was to test the *a priori* hypothesis that women provided with a LNS would have fewer depressive symptoms postnatally than those provided with IFA or multiple micronutrient capsules.

Materials and methods

The ILINS-DYAD-M trial was conducted in Mangochi District, a predominantly rural area situated at the southern end of Lake Malawi. Key economic activities in the district are subsistence farming, fishing and small-scale business. The trial methodology is described in full elsewhere (Ashorn *et al.* 2015a). The trial is

Key messages

- Perinatal depression is highly prevalent in low-and-middle-income countries and has been linked to poor child health.
- Suboptimal maternal nutrition may be a risk factor for perinatal depression.
- In this randomised controlled trial conducted in rural Malawi, fortification of maternal diet with a lipid-based nutrient supplement, compared to iron-folate or multiple-micronutrient capsules, did not reduce postnatal depressive symptoms.

registered at the clinical trial registry at the National Institute of Health (USA) under identifier NCT01239693 (https://clinicaltrials.gov/ct2/show/NCT01239693).

Participants were recruited from the population of women attending antenatal clinics in the government-run Mangochi District Hospital, a part-private hospital (Malindi) and two government-run health centres (Lungwena and Namwera).

Inclusion criteria were: pregnancy of no more than 20 completed gestation weeks (confirmed by ultrasound), being resident in the defined catchment area and available during the study period, and giving informed consent (signed or thumb print). Exclusion criteria were: age less than 15 years, a chronic health condition requiring regular medical attention, asthma (formally diagnosed and on treatment), a severe illness requiring referral to hospital or emergency medical care, peanut allergy, history of any serious allergic reaction, significant pregnancy complications at enrollment visit, previous recruitment to the trial (during a previous pregnancy) or current enrollment in another clinical trial.

Intervention and comparator arms

The enrolled women were randomly allocated to one of three study arms; the intervention arm (LNS) or one of two comparator arms (IFA and multiple micronutrients (MMN)). Women in the IFA comparator group received supplementation from enrollment to delivery with one capsule per day containing 60-mg iron and 400-μg folic acid, as is recommended in standard antenatal care in Malawi. Participants in the MMN control group received one capsule per day that contained IFA plus 16 additional micronutrients. The LNS daily dose (20 g) was designed to contain the same micronutrients as the MMN capsules, plus 4 additional minerals, protein and fat, optimised to provide high amounts of essential fatty acids thought to be important in pregnancy (Coletta *et al.* 2010). The fatty acids contained in the supplement were 0.59-g alpha-linolenic acid (ALA) (42% of RDA in pregnancy and 45% RDA in lactation) and 4.59 g of linoleic acid (LA) (35% of RDA in pregnancy/lactation). The daily LNS dose also provided 118 kcal of energy. The iron dose for participants in the MMN and LNS groups (20 mg/day) was lower than for those in the IFA group (60 mg), because the MMN and LNS supplementation was continued during the first 6 months postpartum, when the recommended iron intake for lactating women is much lower than the recommended antenatal dose (Arimond *et al.* 2013). Data collectors delivered supplements fortnightly to each participant. At each visit, the data collectors counted and recovered any supplement doses that were unused.

During the trial period, new international guidance advised that LNS used in the management of acute childhood malnutrition be tested for the presence of Cronobacter sakazakii bacteria, with any untested or infected product being withdrawn. In response to this guidance, distribution of LNS to the iLiNS-DYAD trial participants was suspended until testing had been completed. During this time (1 to 21 August 2012), 160 pregnant women in the LNS arm missed supplement for a period ranging from 1 to 20 days. Of these women, 127 were provided with IFA capsules instead; the other 33 were not located during the IFA distribution.

The study participants attended antenatal and under-5 clinics according to the same schedule as all other Malawian pregnant women and infants and received all normal preventive services provided by the national health system. Participants were refunded for any medical costs incurred during the study period.

The IFA and MMN interventions were provided using double-masked procedures: the capsules appeared identical, and neither participants nor the research team members were aware of the nutrient contents of the capsules. For the group receiving LNS (which was easily distinguished from the capsules), we used single-masked procedures: the data collectors who administered the postnatal depressive symptom outcome measures were blind to group allocation and the participants were asked not to disclose information about which supplement they were taking. Researchers responsible for the data cleaning remained blind to the trial code until the database was fully cleaned.

Randomisation

Randomisation code lists were generated by an independent statistician. At enrolment participants were randomised to trial arm using allocation codes sealed in opaque envelopes. Full details of the randomisation procedure are described in Ashorn *et al.* (2015a).

Outcome measures

Maternal depressive symptoms were measured using the Self Reporting Questionnaire (SRQ) and the Edinburgh Postnatal Depression Scale (EPDS). The SRQ was designed by the World Health Organisation as a screen for common mental disorders that could be used internationally and particularly in developing countries (WHO 1994). It consists of 20 questions with yes/no answers exploring symptoms of depression, anxiety and somatic manifestations of distress experienced over the previous 4 weeks. Scores are obtained by totaling the number of yes answers, with higher scores indicating higher number of depressive symptoms (possible score range 0–20). Unlike the SRQ, the EPDS was specifically designed for the postnatal period and excludes somatic items (sleep, appetite, energy or other bodily complaints) that might overlap with physical symptoms typical of the perinatal period (Cox *et al.* 1987). The EPDS consists of 10 questions asking about frequency of symptoms over the last 7 days, each answered from a choice of 4 options, scored 0–3. Scores are obtained by totaling the individual scores on the 10 items, with higher scores indicating higher number and frequency of depressive symptoms (possible score range 0–30). Both measures were validated in the local population (Stewart *et al.* 2013).

In this study, we used SRQ and EPDS mean scores as primary outcome measures at 6 months postpartum (SRQ and EPDS). The SRQ and EPDS are best analysed as continuous variables to reduce loss of information (Altman & Royston 2006). We also analysed the proportion of women scoring above SRQ ≥ 8 and SRQ ≥ 5, and EPDS ≥13 and EPDS ≥9 cut-offs. In the earlier validation study, at a cut-off score of SRQ ≥8 (a cut-off commonly chosen in previous studies (Harpham *et al.* 2003)), the SRQ Chichewa version had sensitivity 50.4%, specificity 88.4% and positive predictive value (PPV) of 41.2% for detection of Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV) major depressive episode (Stewart *et al.* 2013). In the same study, at a cut-off score of EPDS ≥ 13 (the most commonly chosen cut-off in previous studies (Cox *et al.* 2014)), the EPDS Chichewa version had sensitivity 33.7%, specificity 94.9% and PPV 50.0%. The test characteristics of the Chiyao translation of the SRQ and EPDS were similar (unpublished data).

Data collectors were trained in the administration of the SRQ and EPDS by a trilingual clinical psychologist (EU) and given written instructions for later reference. At interview, any participant answering yes to the item about suicidal thoughts was asked further questions regarding suicidal ideation. Any participant reporting active or persistent suicidal ideas was referred to local mental health care services (nurse-led outpatient clinics). During the study, no participants fulfilled this criterion.

Other variables

We measured the following baseline variables: maternal age, number of years of education completed, number of previous pregnancies, household ownership of a set of assets (combined into an index (with a mean of zero and standard deviation of one) using principal components analysis (Vyas & Kumaranayake 2006)), Household Food Insecurity Access (HFIA, a measure of food insecurity), mid-upper arm circumference (MUAC), weight, height and BMI at recruitment, HIV status, malarial infection and haemoglobin at recruitment, season of enrolment (divided into quarters: Jan–Mar, Apr–Jun, Jul–Sept, Oct–Dec), gestational age at enrolment, antenatal SRQ score (done within 21 days of enrollment) and Multidimensional Scale of Perceived Social Support (MSPSS) score (a measure of the perception of the adequacy of support from others that was translated and locally validated (Stewart *et al.* 2014b)).

Ethics statement

The trial was conducted according to Good Clinical Practice guidelines and Helsinki Declaration standards. The study was approved by the College of Medicine Research and Ethics Committee, University of Malawi and the Ethics Committee of Pirkanmaa Hospital District, Finland. An independent data safety and monitoring board monitored the study for suspected serious adverse events and performed 2 interim analyses for safety.

Statistical analysis

All presented analyses were pre-specified either in the trial protocol or in the statistical analysis plan (http://www.ilins.org/ilins-project-research/data-analysis/iLiNS-DYAD-M%20Statistical%20Analysis%20Plan-%20version%2016.0%20with%20appendices%201-19-%202014-12-20.pdf/at_download/file). Analysis was conducted on the principle of modified intention to treat. All randomly allocated participants were included in the analyses, but participants with missing data on an outcome variable were excluded from the analysis of that outcome and two participants whose group allocation was incorrectly transcribed and assigned during enrollment were included in the group corresponding to the actual intervention they received.

The outcome measures (SRQ and EPDS) were administered by data collectors during participant study clinic visits at 6 months postpartum. Data collectors made tracing home visits if a participant did not come for the scheduled visit within 14 days of the appointment. We used outcome data if measured between 22 and 34 weeks following delivery. Data collected outside of these limits were regarded as missing. Occasional missing item values on the SRQ (8 participants) and EPDS (11 participants) were imputed using mean substitution for the same scale and participant. Mean substitution was done if there were <50% missing data points.

Sample size

The sample size was calculated based on the primary study outcomes of birth size and growth at 18 months. Allowing for 20% missing values, with a sample size of 1400 participants the study had 80% power to detect an effect size of 0.24 (difference between groups, divided by the pooled SD) for each continuous outcome. For SRQ and EPDS, this is equivalent to 0.65 and 1.27 points, respectively.

Comparison of continuous SRQ and EPDS scores between the three intervention groups

The group means and standard deviations for SRQ total and EPDS total at 6 month postpartum were tabulated by intervention group. The difference between the three groups was tested with ANOVA and null-hypothesis of no difference between groups was rejected if $P < 0.05$.

Comparison of dichotomised SRQ and EPDS scores between the three intervention groups

The proportions of women scoring SRQ ≥5 and ≥8 and EPDS ≥ 9 and ≥13 at 6 month postpartum were tabulated by intervention group. The difference between the three groups was tested with chi-squared test, and null hypothesis of no differences between groups was tested with global null-hypothesis rejected if $P < 0.05$.

Covariate adjustment

In order to adjust for covariates, for the primary continuous outcomes (SRQ total and EPDS total at 6 month postpartum) we constructed linear regression models including antenatal SRQ score, assets score, social support, height, BMI at enrolment, gestational age at enrollment, haemoglobin at enrollment, age, maternal education, number of previous pregnancies, season at enrollment, child sex and twin pregnancy. Categorical variables (study arm and season) were included as dummy variables. Study arm was analysed as two dummy variables, LNS vs. IFA and MMN vs. IFA; season was analysed as three dummy variables, Jan–March, April–June and July–September, with Oct–Dec as reference category. Each regression analysis used multiple imputation with 20 imputations per missing item of data on each covariate using the multivariate normal model based on the relevant dependent variable and all the covariates. We present the mean difference and 95% confidence intervals for the two group comparisons as described above. For the dichotomized outcome measures we adjusted for the same covariates and using multiple imputation for missing data on covariates as described above for the continuous outcome measures. We present odds ratio and 95% confidence intervals for the two group comparisons.

We conducted the main analyses including women who had either singleton or twin deliveries. We repeated the analysis restricting to women who had singleton deliveries. We also conducted a sensitivity analysis that restricted the analysis to the most adherent participants (participants who received and did

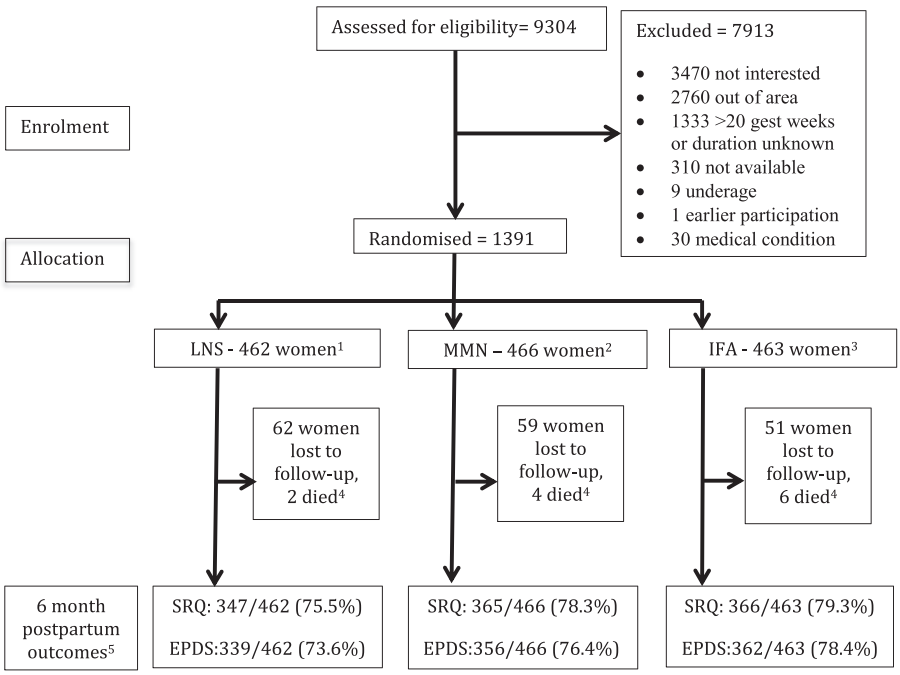
not return supplements for more than 80% of the antenatal follow-up days).

Interaction and effect modification

We tested for interaction between the intervention group and variables that could modify the effect of the nutritional intervention on depression outcomes, as per the analysis plan; these were antenatal SRQ score, assets score, social support, height, BMI at enrolment, gestational age at enrollment, haemoglobin at enrollment, age, maternal education, number of previous pregnancies, season at enrollment and child sex. If a statistically significant interaction ($P < 0.1$) was found, the adjusted analysis was completed as stratified by the respective predictor. All analyses were carried out using SPSS version 22, and Stata version 14.

Results

Between February 2011 and August 2012, 9304 women were approached at the antenatal clinics of the four study sites. Of these, 4449 were excluded and 3470 were not interested in participating (see Fig. 1). 1391 (15.0%) were enrolled to the trial. The flow of participants is shown in Fig. 1. The enrolled participants and those who refused or were not eligible were similar in



1. In the LNS group there were 436 deliveries of 444 live infants (428 singletons, 8 sets twins).
2. In the MMN group there were 434 deliveries of 435 live infants (433 singletons, 1 set twins).
3. In the IFA group there were 437 deliveries of 440 live infants (434 singletons and 3 sets twins).
4. Dropouts/deaths without SRQ/EPDS having been done prior to 34 weeks postpartum.
5. Outcome measures conducted between 22-34 weeks postpartum.

IFA, Iron-folate; MMN, multiple micronutrients; LNS, lipid-based nutrient supplements; SRQ, Self Reporting Questionnaire; EPDS, Edinburgh Postnatal Depression Scale.

Fig. 1. Participant flow.

demographic and socio-economic characteristics, obstetric history and maternal nutritional status.

Participants randomised to each of the three intervention arms (LNS = 462 (33.2%), MMN = 466 (33.5%) and IFA = 463 (33.3%)) were similar across a range of baseline variables (Table 1). Antenatal SRQ was done within 21 days of enrollment for 742/1391 (53.3%) of the participants (LNS = 244/462 (52.8%), MMN = 246/466 (52.8%) and IFA = 252/463 (52.3%)). Statistical testing showed no differences between the groups on any variables. Of the participants, 1078/1391 (77.5%) had data on depressive symptoms for at least one depression outcome. A comparison of those with and without data on depressive symptoms is shown in Table 2. Those without such data were younger, had more years of education and higher assets scores, were later in gestation at enrolment, had had fewer previous pregnancies, were more likely to be primiparous, and had higher BMI and antenatal SRQ scores. There was a trend for more missing data in the LNS arm compared to the other 2 arms but this was not a significant difference (p=0.311).

Table 3 shows 6 months postpartum mean SRQ and EPDS scores for the three groups, and associated *P*-values. Table 4 shows the proportions of 6 months postpartum SRQ scores ≥5 and ≥8 and EPDS scores ≥9 and ≥13 for the three groups, and associated *P*-values.

There were no statistically significant differences between the groups for either continuous or dichotomised depressive symptom scores in the unadjusted models. Adjustment for covariates did not alter this finding, either on a complete cases analysis or using multiple imputation for missing values on the covariates.

Neither exclusion of women who gave birth to twins or restricting the analysis to only those mothers who had consumed supplements on >80% of days altered the findings.

Of the variables analysed, only number of previous pregnancies was shown to moderate the relationship between study arm and SRQ score at 6 months in an unadjusted model ($P = 0.033$). Amongst women with 0–2 previous pregnancies, the mean (SD) SRQ scores at 6 months were LNS: 1.48 (2.29), MMN: 2.02 (2.86) and IFA: 1.44 (2.22), ($P = 0.026$). Amongst women with

Table 1. Baseline/antenatal[a] characteristics of the participating women at enrolment, by study group

Characteristic	LNS	MMN	IFA
No. of participants	462	466	463
Maternal age (years) (Mean (SD))	25 (6)	25 (6)	25 (6)
Maternal education (completed years) (Mean (SD))	4.0 (3.5)	4.1 (3.4)	3.9 (3.4)
Household asset score (Mean (SD))	0.04 (1.85)	0.02 (1.78)	−0.03 (1.78)
Proportion with severely food insecure households%	36	38	35
Gestational age at enrollment (weeks) (Mean (SD))	16.9 (2.2)	16.8 (2.1)	16.8 (2.1)
Number of previous pregnancies (Mean (SD))	2.2 (1.7)	2.1 (1.8)	2.1 (1.8)
Proportion of nulliparous women, %	22	23	20
Height, cm (Mean (SD))	156.2 (5.7)	156.0 (5.6)	156.1 (5.7)
Weight, kg (Mean (SD))	54.3 (8.4)	54.0 (8.1)	53.9 (7.4)
MUAC, cm (Mean (SD))	26.5 (2.7)	26.3 (2.8)	26.4 (2.4)
BMI, kg/m^2 (Mean (SD))	22.3 (3.0)	22.2 (2.9)	22.1 (2.6)
Proportion of women with a BMI $<18.5\ kg/m^2$, %	6	5	6
Blood haemoglobin concentration, g/L (Mean (SD))	112 (16)	111 (16)	111 (17)
Proportion of anaemic women (haemoglobin 100 g/L) %	21	20	21
Proportion of women with a positive HIV test, %	14	11	16
Proportion of women with positive malaria test (RDT) %	23	24	23
Antenatal SRQ score (Mean (SD))	3.97 (3.30)	4.20 (3.27)	4.04 (3.39)
Proportion of women scoring SRQ ≥ 8 antenatally[2,] %	16	16	15
MSPSS score antenatally (Mean (SD))	37.6 (8.4)	37.2 (8.0)	36.5 (8.9)

IFA, iron-folate; MMN, multiple micronutrients; LNS, lipid-based nutrient supplements; SRQ, Self Reporting Questionnaire; MSPSS, Multi-dimensional Scale of Perceived Social Support.

[a]Most variables were collected pre-intervention; household characteristics were done within 1-week of enrolment; SRQ scores were included if done within 21 days of enrolment ($n = 742$).

Table 2. Characteristics of participants with at least one outcome point (SRQ or EPDS score) vs. those missing all outcome data.

Characteristic	Included	Missing	*P*-value [a]
Number and proportion of participants (%)	1078 (77.5%)	313 (22.5%)	
Maternal age (years) (Mean (SD))	25 (6)	24 (6)	<0.005
Maternal education (completed years) (Mean (SD))	3.8 (3.3)	4.9(3.8)	<0.005
Household asset score (Mean (SD))	0.17(1.65)	0.73 (2.22)	<0.005
Proportion with severely food insecure households %	35	36	0.800
Gestational age at enrollment (weeks) (Mean (SD))	16.7 (2.1)	17.1 (2.1)	0.005
Number of previous pregnancies (Mean (SD))	2.3(1.7)	1.7(1.8)	<0.005
Proportion of nulliparous women, %	19	33	<0.005
Height, cm (Mean (SD))	156.1 (5.6)	156.0 (5.7)	0.388
Weight, kg (Mean (SD))	53.9 (7.9)	54.7 (8.2)	0.136
MUAC, cm (Mean (SD))	26.4 (2.6)	26.4 (2.9)	0.781
BMI, kg/m^2 (Mean (SD))	22.1 (2.7)	22.5 (3.1)	0.029
Proportion of women with a BMI <18.5 kg/m^2, %	5	6	0.330
Blood haemoglobin concentration, g/L (Mean (SD))	111.9 (16.1)	110.1(17.1)	0.085
Proportion of anaemic women (haemoglobin 100 g/L) %	20	24	0.094
Proportion of women with a positive HIV test, %	14	12	0.255
Proportion of women with positive malaria test (RDT) %	23	25	0.331
Antenatal SRQ score (Mean (SD)) [b]	3.9 (3.4)	4.8 (3.1)	0.003
Proportion of women scoring SRQ ≥ 8 antenatally[b], %	15	18	0.289
MSPSS score antenatally (Mean (SD))	37.2 (8.3)	36.6 (9.1)	0.269
Proportion of women in trial arm (IFA), arm included vs missing %	79	21	0.311
Proportion of women in trial arm 2 (MMN), arm included vs missing %	78	22	
Proportion of women in trial arm 3 (LNS), arm included vs missing %	75	25	

IFA, iron-folate; MMN, multiple micronutrients; LNS, lipid-based nutrient supplements; SRQ, Self Reporting Questionnaire; MSPSS, Multi-dimensional Scale of Perceived Social Support.
[a]Comparison used the *t*-test for scored and continuous data, and Chi squared or Fishers exact test for categorical data.
[b]Antenatal SRQ score done within 21 days of enrolment ($n = 742$).

Table 3. SRQ and EPDS total scores (continuous outcomes) by intervention group (model with covariates and using multiple imputation for missing data on the covariates)

	Result by study group				Comparison between LNS and IFA group	Comparison between MMN and IFA group
Variable	LNS	MMN	IFA	*P*-value[a]	Difference in means (95 % CI) [b]	Difference in means (95 % CI) [b]
6 months postpartum SRQ score, mean (SD), *n*	1.76 (2.73) $n = 347$	1.92 (2.75) $n = 365$	1.71 (2.67) $n = 364$	0.560	0.07 (−0.33 to 0.47)	0.20 (−0.19 to 0.59)
6 months postpartum EPDS score, mean (SD), *n*	5.78 (5.53) $n = 339$	5.43 (4.97) $n = 356$	5.54 (5.18) $n = 362$	0.654	0.38 (−0.38 to 1.13)	0.04 (−0.71 to 0.79)

IFA, iron-folate; MMN, multiple micronutrients; LNS, lipid-based nutrient supplements; SRQ, Self Reporting Questionnaire; EPDS, Edinburgh Postnatal Depression Scale; 95% CI = 95% confidence interval.
[a]ANOVA.
[b]ANCOVAR adjusting for antenatal SRQ score, assets score, social support, height, BMI at enrolment, gestational age at enrollment, haemoglobin at enrollment, age, maternal education, number of previous pregnancies, season at enrollment and twin pregnancy.

Table 4. SRQ ≥5, SRQ ≥8 and EPDS ≥9 and ≥13 (dichotomous outcomes) by intervention group. Odds ratio for LNS vs. IFA and MMN vs. IFA are presented with 95% confidence intervals.

	Result by study group (unadjusted analyses)				Analyses adjusted for covariates	
					Comparison between LNS and IFA group	Comparison between MMN and IFA group
Variable	LNS	MMN	IFA	*P*-value[a]	Odds ratio (95 % CI)	Odds ratio (95 % CI)
6 months postpartum prevalence of SRQ ≥ 5	49/347 (14.1 %)	55/365 (15.1 %)	49/366 (13.4 %)	0.808	1.08 (0.70 to 1.68)	1.15 (0.75 to 1.77)
6 months postpartum prevalence of SRQ ≥ 8	24/347 (6.9 %)	21/365 (5.8 %)	17/366 (4.6 %)	0.435	1.63 (0.85 to 3.15)	1.32 (0.68 to 2.58)
6 months postpartum prevalence of EPDS ≥ 9	94/339 (27.7 %)	92/356 (25.8 %)	113/362 (31.2 %)	0.281	0.87 (0.62 to 1.21)	0.80 (0.57 to 1.12)
6 months postpartum prevalence of EPDS ≥ 13	41/339 (12.1 %)	37/356 (10.4 %)	43/362 (11.9 %)	0.747	1.12 (0.70 to 1.80)	0.93 (0.58 to 1.51)

IFA, iron-folate; MMN, multiple micronutrients; LNS, lipid-based nutrient supplements; SRQ, Self Reporting Questionnaire; EPDS, Edinburgh Postnatal Depression Scale; 95% CI = 95% confidence interval
[a]Chi squared test.

>2 previous pregnancies, the mean (SD) SRQ scores at 6 months were LNS: 2.07 (3.14), MMN: 1.78 (2.58) and IFA: 2.13 (3.22) ($P = 0.558$). This moderating effect was not found in an adjusted model.

Discussion

This study tested the hypothesis that women provided with a LNS would have fewer depressive symptoms postnatally than those provided with IFA or multiple micronutrient capsules in rural Malawi. There was no difference between the groups in mean SRQ and EPDS scores at 6 months postpartum. We did not find that antenatal depressive symptoms or antenatal BMI moderated the effect of the intervention upon postnatal depressive symptoms. The study findings do not support the hypothesis that this formulation of LNS reduces postnatal depressive symptoms in the study area. The adjusted effect sizes for LNS vs. IFA are −0.02 for postpartum SRQ and −0.07 for postpartum EPDS, where a positive effect size means that LNS is better than IFA, and a negative effect size means that LNS is worse than IFA. For LNS vs. MMN the adjusted effect sizes are 0.05 and −0.06, respectively. All these effect sizes are regarded as small.

Mean baseline antenatal SRQ score was similar to that in our earlier study conducted in Mangochi district hospital antenatal clinic (Stewart *et al.* 2014a). In that study, the weighted prevalence of DSM IV major depressive episode was 10.7%, which is consistent with the prevalence estimate of antenatal depression (11.3%) from a meta-analysis of studies in sub-Saharan Africa (Sawyer *et al.* 2010), and indicates that antenatal depression is a common health problem in the study population. In this study, mean SRQ scores postnatally were lower than those antenatally. This is consistent with prospective cohort studies from Ethiopia (Medhin *et al.* 2010) and Cote d'Ivoire (Guo *et al.* 2013) in both of which the prevalence of depressive symptoms dropped between pregnancy and the postnatal period.

Strengths of the study included our use of measures of depressive symptoms that had been validated in the study population (Stewart *et al.* 2013). Confidence in our finding was increased by our use of two outcome measures, the SRQ and EPDS, and our analysis of scores as both continuous and dichotomised variables. The study sample was large, the trial randomisation procedure was robust, and efforts were made to ensure that the outcome data collectors were masked to allocation. We conducted analysis by modified intention to treat, according to a plan that had been published prior to analysis.

A limitation of the study was the high proportion of missing outcome data. Those with no outcome data differed significantly from those included, and there was a

trend for more missing data in the LNS arm compared to the other 2 arms although this was not a significant difference. One reason for the high proportion of missing data was a misunderstanding of study protocol by some data-collectors who, if they found that the participant was not available when they visited to administer the SRQ/EPDS, did not attempt a repeat visit. Multiple imputation for missing data on covariates did not alter the finding of no significant differences between the 3 groups.

This was the first RCT investigating the effect of fatty acid supplementation on maternal postnatal depressive symptoms in a low income country. Fatty acids play an important role in brain function, in particular the n-3 PUFAs, docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) (Grosso *et al.* 2014a; Bazinet & Layé 2014). These are obtained in the diet mainly from oily fish. ALA is the precursor of DHA and EPA and is obtained from plant sources. Less than 10% of ALA is converted into DHA/EPA in adults (Burdge & Calder 2005; Gibson *et al.* 2011) conversion of ALA to DHA/EPA is competitively inhibited by the n-6 PUFA, LA. In this study, the fatty acids contained in the supplement were 0.59-g ALA (42% of RDA in pregnancy and 45% RDA in lactation) and 4.59 g of LA (35% of RDA in pregnancy/lactation). For use as a dietary supplement in LMIC, plant-based fatty acids have advantages of low cost and local acceptability (Arimond *et al.* 2013). An earlier trial in Ghana suggested that plant-based fatty acids, and in particular ALA, played an important role in promoting linear growth in children (Adu-Afarwuah *et al.* 2007)

Observational and ecological studies have demonstrated an inverse association between depression and both n-3 PUFA consumption and plasma levels, including in the perinatal period (Appleton *et al.* 2010; Lin *et al.* 2010). Most observational studies investigating fatty acids and depression have focused on DHA/EPA, and there have been few studies of ALA. In a 10-year cohort study of US women, ALA intake was inversely associated with risk of experiencing a depressive episode with an adjusted risk ratio for 0.5 g per day increment of 0.82 (95% CI 0.71–0.94) (Lucas *et al.* 2011). This association was stronger in women with low LA intake.

There have been a number of intervention studies investigating DHA/EPA supplements for the prevention and treatment of depression. The results of these studies have been mixed, and there is evidence of publication bias toward positive trials (Bloch & Hannestad 2012). Of six trials that have been conducted in the perinatal period, only one open trial found a beneficial effect of n-3 PUFA supplementation on maternal mood (Grosso *et al.* 2014b). In the only intervention trial of ALA supplementation and depression, 2 g/day of ALA had no impact on depression post-myocardial infarction despite increasing EPA blood concentrations (Giltay *et al.* 2011). Thus, our negative finding was consistent with the majority of previous studies.

A possible explanation for the negative finding is that, as the LNS in this study was not specifically designed to optimise impact on depression, it may have contained a suboptimal formulation of fatty acids to have a beneficial effect on mood. Previous positive studies have used supplements containing fish-derived DHA/EPA rather than plant based fatty acids (Grosso *et al.* 2014b). There is some evidence that supplements that have a high proportion of EPA may be most effective; in a meta-analysis of depression treatment studies, EPA/DHA supplements containing $\geq$ 60% EPA, in a dose range of 0.2 to 2.2 g/day of EPA in excess of DHA, were more likely to be effective (Sublette *et al.* 2011). Thus reformulating the supplement with EPA/DHA (with high EPA:DHA ratio) rather than ALA would be an option.

ALA, however, has advantages in terms of acceptability and cost (Arimond *et al.* 2013) but, in this study, the ALA dose may have been too low. Only a small proportion of ALA is converted to EPA/DHA, although most of the conversion is to EPA, and the process is more efficient in women than men, particularly in those of reproductive age (Burdge & Calder, 2005). We estimate that, to achieve a dose of 0.2 g/day of EPA, at least 2 g/day ALA would be needed. It is also possible that the ratio of LA:ALA (7.8:1) was too high. Observational studies indicate that diets with a high ratio of n-6 to n-3 PUFAs are associated with greater risk of depression (Grosso *et al.* 2014b), possibly as a result of competitive inhibition of ALA metabolism by LA, and the pro-inflammatory actions of n-6 metabolites (cf: the anti-inflammatory effects of n-3 metabolites) (Marventano *et al.* 2015). The LNS used in this study was soy oil-based; reformulation with canola oil would give an LA:ALA ratio of approximately 2

(Gibson *et al.* 2011). However, Canola is not widely available in many low-income countries, and this would have implications for cost and sustainability (Arimond *et al.* 2013).

Alternatively, the negative result may be explained by the inclusion of all women whether they were depressed or not antenatally. Trials of FA supplementation have tended to show positive results in participants with major depression rather than sub-syndromal depressive symptoms or in those who are well (where the focus is on prevention of incident depression) (Grosso *et al.* 2014b). We found no interaction between intervention and antenatal SRQ score ≥ 8, suggesting that this explanation is unlikely. However, SRQ score is only a screening measure for depression; use of a diagnostic interview for depression would have improved our confidence in this analysis but was beyond the resources of the study. Loss to follow-up is also a limitation as mean antenatal SRQ score was higher for those without outcome data than for those included.

Another possible explanation for the negative result is the relatively high dietary intake of fish in the study population. Keenan *et al.* (2012) showed that baseline FA status is inversely associated with change in FA status following supplementation. It has been suggested that FA supplements may have a beneficial effect on mood only in individuals with poor fatty acid status (Marangell *et al.* 2003). There is evidence that n-3 PUFA intake amongst mothers in Mangochi District is adequate because of the inclusion in the diet of small fishes ('Usipa') from Lake Malawi (Jimenez *et al.* 2015).

A nutritional intervention might reduce symptoms of perinatal depression through (1) a direct effect upon brain physiological processes including neurotransmitter synthesis, membrane function and inflammatory processes; (2) an effect on general nutritional status leading to increased energy, fewer infections, reduced obstetric complications, etc.; or (3) by reducing maternal stress through improving infant health. Caring for a sick infant may be a risk factor for common mental disorder (CMD); in particular, there is an association between infant diarrhoeal episodes and CMD symptoms that may be bidirectional (Rahman *et al.* 2007). It is of note that, in this study, the intervention had no effect on birth outcome (Ashorn *et al.* 2015a) or infant growth by 6 months (Ashorn *et al.* 2015b), so a reduction in carer stress would not be expected, although we did not attempt to directly measure this.

Conclusion

In summary, this study did not provide support for LNS fortification of maternal diet as a strategy for reducing depression postnatally in Malawi. As the LNS used was not specifically formulated to have an impact on maternal mood and had no effect on maternal BMI or child growth, a role for an alternative nutritional intervention for perinatal depression cannot be ruled out and further studies are required.

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Contributions

The authors' responsibilities were as follows: KM, PA, KD, UA, BP, EU, RS, FC and AR designed the research; KM, PA, KD, UA, RS and EU conducted the research; RS and BT analysed data; RS wrote the manuscript, with critical input and comments from all other authors; and RS, PA and KM had primary responsibility for final content. All authors read and approved the final manuscript. The findings and conclusions contained within the article are those of the authors and do not necessarily reflect positions or policies of the Bill & Melinda Gates Foundation, USAID, the US government or the other funders.

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