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Maternal mood, anxiety and mental health functioning after combined myo-inositol, probiotics, micronutrient supplementation from preconception: Findings from the NiPPeR RCT

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ABSTRACT

Observational studies have reported associations between nutrition during pregnancy and mental wellbeing. As secondary outcomes, the NiPPeR double-blind randomized trial in women planning conception investigated whether a myo-inositol, probiotics and enriched micronutrients formulation (intervention) taken preconception and throughout pregnancy could improve mental wellbeing during pregnancy and post-delivery, compared with a standard micronutrient supplement (control). Mood and anxiety symptoms were ascertained (Edinburgh Postnatal Depression Scale (EPDS), State-Trait Anxiety Inventory (STAI-state)) at preconception (baseline), 7, 28 and 34 weeks gestation, 3-weeks and 6-months post-delivery. EPDS>=13 was categorised as low mood; STAI-state>=45 as high anxiety. Change in mental health functioning was assessed as difference between preconception baseline and 6-month post-delivery 12-item Short-Form Health Survey (SF-12v2) mental component scores. Adjusting for site, ethnicity and baseline scores, there were no robust differences in EPDS and STAI-state scores between intervention and control groups across pregnancy (n = 630) and post-delivery (n = 532). Compared to controls, intervention group women averaged a 1.21 (95 %CI 0.04,2.39) higher change in SF-12v2 mental component score from preconception to 6-months post-delivery. Taking a myo-inositol, micronutrient and probiotic supplement during preconception/pregnancy had no effect on mood and anxiety, but there was evidence of a modest improvement in mental health functioning from preconception to 6-months post-delivery.

1. Introduction

While maternal mental wellbeing is important for optimal pregnancy outcomes and child neuropsychological and physical development (Howard et al., 2014; Stein et al., 2014), the pregnancy and postpartum periods represent times of increased susceptibility to mental ill-health

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(O'Hara and Wisner, 2014). Depression and anxiety are the two most common mental health disorders affecting women during pregnancy, and the wide variations in such symptomatology are increasingly thought to have relevance for child development (Phua et al., 2020). Maternal symptoms of depression or anxiety, such as loss of appetite, poor sleep, tiredness, mood swings and forgetfulness, may be dismissed as part of pregnancy without women seeking help (Lee et al., 2007). Women who have experienced low mood during pregnancy are at higher risk of experiencing obstetric complications, such as pre-eclampsia (Kurki et al., 2000; Shay et al., 2020), preterm delivery (Ding et al., 2014), gestational diabetes (Damé et al., 2017) and caesarean section (Zochowski et al., 2021), as well as postpartum depression (Robertson et al., 2004). Newborns may suffer from poor growth and experience problems in behaviour, socio-emotional adjustment and emotion regulation, which can persist beyond childhood (Coussons-Read, 2013; Davis et al., 2011; Glover, 2014; Sohr-Preston and Scaramella, 2006). Maternal anxiety and depression quite frequently co-exist; they have been linked with similar adverse outcomes in the mother and child but it remains possible that they may work through differing biological pathways (Alder et al., 2007).

Among non-pregnant adults, social, psychological, environmental and genetic factors have been associated with mood disorders (Remes et al., 2021; Schneiderman et al., 2005), with increasing evidence for a role of nutrition (Muscaritoli, 2021). Deficiencies in B vitamins (notably vitamins B6, B12, and folate), vitamin C, zinc, iron, calcium, and polyunsaturated fatty acids (PUFAs) have been associated with poor mental health in the general adult population (Cornish and Mehl-Madrona, 2008; Kaplan et al., 2007; Simopoulos, 1999). Low levels of the carbocyclic sugar myo-inositol have also been linked with neuropsychiatric disorders (Vadnal et al., 1997) and optimising levels has shown some promise for treating anxiety disorders in adults (Mukai et al., 2014). Additionally, individuals who have depression demonstrate differences in their microbiome compared to those who do not (Benton et al., 2007), and probiotics have been reported to reduce psychological distress in healthy volunteers (Dinan and Quigley, 2011; Jiang et al., 2015; Messaoudi et al., 2011). Wider aspects of maternal mental health functioning have been less often studied in the perinatal period, but include emotional wellbeing and its impact on daily function, along with non-specific psychological distress (Yu et al., 2015; Kessler et al., 2002).

Evidence examining the role of nutrition in maternal mental wellbeing during pregnancy and post-delivery remains inconsistent. Deficiencies in n-3 polyunsaturated fatty acids (PUFA), B vitamins, vitamin D, and trace minerals have been linked to postpartum depression (Ellsworth-Bowers and Corwin, 2012). Low plasma vitamin B6 concentrations are linked to symptoms of depression (Hvas et al., 2004), as are low levels of zinc (Ellsworth-Bowers and Corwin, 2012). One trial reported that women who received Lactobacillus rhamnosus HN001 during pregnancy and post-delivery had lower depression and anxiety scores in the postpartum period (Slykerman et al., 2017), but a number of other interventional studies have reported no marked benefits of probiotic use in pregnancy on maternal depression and anxiety symptoms (Dawe et al., 2020; Hulkkonen et al., 2021; Browne et al., 2021).

The aim of this study was to determine whether a supplement enriched with myo-inositol, vitamin D, riboflavin, vitamin B6, vitamin B12 and zinc with probiotics together with standard folic acid, iodine, calcium, β-carotene and iron (Godfrey et al., 2017) could improve maternal mood, anxiety and mental health functioning during pregnancy and postpartum.

2. Methods

The data for this study were collected as part of the Nutritional Intervention Preconception and during Pregnancy to maintain healthy glucosE metabolism and OffspRing health (NiPPeR) trial (Godfrey et al., 2017). NiPPeR is a double-blind randomized controlled trial that recruited from the community 1729 UK, Singapore, and New Zealand women aged 18–38 years planning conception. In brief, participants were randomized to receive a standard micronutrient supplement or an enhanced micronutrient, myoinositol and probiotics supplement starting in preconception (1–12 months prior to pregnancy) until delivery of the baby (Godfrey et al., 2017). Baseline data was collected preconception including sociodemographic data, obstetric history and history of mental illness. Longitudinal outcome measures on mood and anxiety symptoms were pre-specified secondary outcomes and obtained by the repeated administration of the Edinburgh Postnatal Depression Scale (EPDS) and the State-Trait Anxiety Inventory (STAI) at preconception (baseline), 7, 28 and 34 weeks gestation and postpartum at 3 weeks ($n = 531$) and 6 months ($n = 533$) post-delivery. Numbers of participants at each visit are given in Supplementary Figure 1.

The EPDS is a self-administered questionnaire that has proven to be reliable and sensitive in assessing mood and detecting antenatal and postnatal depression (Gibson et al., 2009). The EPDS comprises ten four-point Likert scale items, with scoring calculated by adding the scores for each of the items (scored 0 to 3, with some items reverse scored). Possible total scores range from 0 to 30. Higher total EPDS scores indicate more severe depressive symptoms. In this study, a score of 13 points or greater was categorised as low mood (Gibson et al., 2009; Broekman et al., 2014).

The STAI has 40 items, each with a four-point scale, with 20 items allocated to each of the subscales – the STAI-state and STAI-trait. The STAI-state is used to evaluate the current state of anxiety, while the STAI-trait assesses more general and long-standing anxiety traits and is thought to be stable over time. As we aimed to evaluate the effects of the intervention on contemporaneous anxiety, the predefined subset of 6 items constituting the validated 6 item short-form STAI-state subscale (Marteau and Bekker, 1992) was used. A short-form STAI-state score of 45 points and above was categorised as high anxiety, based on published normative values (Austin et al., 2007). To examine comparability between the control and intervention groups in having an anxious personality trait, we compared the 20-item STAI-trait subscale between groups at baseline, as presented in Table 1.

Participant mental health functioning was measured using the 6-item Mental Health Component Score (MCS) of the Short-Form Health Survey (SF-12v2) (Ware et al., 2002) as a continuous variable at baseline and at 6 months postpartum. This scale reflects how mental health affects ability to function in everyday life; six questions, whose combined score was calculated to give the MCS, asked if over the last 4 weeks: a) have you accomplished less than you would like?, b) did work or other activities less carefully than usual?, c) have you felt calm and peaceful?, d) did you have a lot of energy?, e) have you felt downhearted and blue?, f) How much of the time have your physical health or emotional problems interfered with your social activities? Change in SF-12 MCS was calculated using the formula (6 months postpartum SF-12 MCS – baseline SF-12 MCS). A positive value indicates improved mental health functioning at 6 months postpartum compared to preconception (Gill et al., 2007). As a confirmatory analysis, we compared SF-12 MCS scores between the control and intervention groups at 6 months postpartum (Mann Whitney test).

As this study focused on pregnant and post-delivery women in the NiPPeR Trial, descriptive statistics split by intervention group were calculated for characteristics collected at baseline for all 630 women who reached 7 weeks gestation; further analyses adjusted for any characteristics that were unbalanced between groups and of prognostic importance. Mixed effect models were run with continuous EPDS or STAI-state as outcomes, including intervention group, site, White/non-White ethnicity and visit (timepoint) as fixed effects, and participant trial-identification number as a random effect. Logistic regression models were run using the categorised EPDS or STAI-state at each visit as outcomes, with intervention group, site, White ethnicity and corresponding baseline EPDS or STAI-state as predictors. A Bonferroni correction was applied to account for multiple testing these two measures over five visits. Intervention group was therefore considered to be

Table 1
Baseline preconception characteristics of women providing data at 7 weeks gestation, by control/intervention group allocation.

Characteristic		Control (n = 306)	Intervention (n = 324)
Study site	UK	100 (32.7 %)	107 (33.0 %)
	Singapore	86 (28.1 %)	90 (27.8 %)
	New Zealand	120 (39.2 %)	127 (39.2 %)
Age, years	Mean (SD)	30.13 (3.32)	30.52 (3.45)
Ethnicity	Non-White	128 (41.8 %)	129 (39.8 %)
	White	178 (58.2 %)	195 (60.2 %)
Household income[#]	Low income	14 (4.7 %)	15 (4.8 %)
	Middle income	118 (40.0 %)	123 (39.7 %)
	High income	163 (55.3 %)	172 (55.5 %)
Parity	Nulliparous	214 (69.9 %)	194 (59.9 %)
	Parous	92 (30.1 %)	130 (40.1 %)
BMI, kg/m^2	Median (IQR)	23.75 (21.46, 27.62)	23.71 (21.17, 26.7)
Alcohol intake (per week)	None	64 (20.9 %)	72 (22.2 %)
	>0 and ≤2.5 units	122 (39.9 %)	115 (35.5 %)
	>2.5 units	120 (39.2 %)	137 (42.3 %)
Smoking status	Never	241 (79.0 %)	253 (78.1 %)
	Previous	50 (16.4 %)	57 (17.6 %)
	Active	14 (4.6 %)	14 (4.3 %)
Instances of moderate/vigorous physical activity in past 7 days	Number of instances	4 (2, 6)	3 (2, 5)
Psychological Stress and Pressure[&]	None	81 (26.5 %)	83 (25.6 %)
	Slight	151 (49.3 %)	172 (53.1 %)
	Moderate/ Extreme	74 (24.2 %)	69 (21.3 %)
EPDS score	Median (IQR)	4 (2, 7)	5 (2, 8)
EPDS (<13)	Normal mood	294 (96.1 %)	307 (95.3 %)
(>=13)	Low mood	12 (3.9 %)	15 (4.7 %)
STAI-trait score	Median (IQR)	34 (29, 39)	34 (29, 40)
STAI-state score	Median (IQR)	26.7 (20, 33.3)	26.7 (20, 33.3)
Short form STAI-state (<45)	Not Anxious	294 (96.1 %)	307 (95.0 %)
(>=45)	Anxious	12 (3.9 %)	16 (5.0 %)
History of depression, anxiety or bipolar disorder, or taking mood-modifying medication#	No	290 (94.8 %)	308 (95.1 %)
	Yes	16 (5.2 %)	16 (4.9 %)
SF12 Mental health functioning component $	Median (IQR)	52.4 (47.0, 57.28)	52.3 (46.7, 56.9)
Infant sex	Male	129 (45.6 %)	140 (48.4 %)
	Female	154 (54.4 %)	149 (51.6 %)

Data presented as number (%) unless otherwise stated. Sample sizes do not always equal 306 for control group and 324 for intervention group due to missing values. [#] Measured according to within-country deciles, grouped as "Low income" 1st-3rd decile, "Middle income" 4th-7thdecile, "High income" 8th-10th deciles.
[&]Responses to the question "In general, how much stress or pressure have you experienced in your daily living in the last 4 weeks?".
Abbreviations: BMI, body mass index; IQR, interquartile range; SD, standard deviation.
#Citalopram/Escitalopram, Venlafaxine, Sertraline, Fluoxetine/Paroxetine, Antidepressant, unspecified, Quetiapine, Amitriptyline/nortriptyline.
$ SF-12 Mental component questions relating to the last 4 weeks: Have you accomplished less than you would like? Did work or other activities less carefully than usual? Have you felt calm and peaceful? Did you have a lot of energy? Have you felt downhearted and blue? How much of the time have your physical health or emotional problems interfered with your social activities?.

significantly associated with EPDS or STAI if the p value was less than or equal to 0.005 [0.05/(2 × 5)]. The sample size was based on the trial primary outcome of gestational glycemia, as described previously (Godfrey et al., 2021); a post-hoc power calculation for this study indicated that a total of 532 participants has 44 % power to detect an odds ratio of 0.38 for a lowering in incidence of a EPDS score >=13, along with 72 % power to detect a similar lowering of a STAI-state>=45. Linear regression was used to analyse change in SF-12 MCS with intervention group, baseline SF-12 MCS, site and white ethnicity as covariates. Randomisation was stratified by site and ethnicity and so these were included as covariates.

In confirmatory analyses, further adjustment was made using baseline parity as this variable was slightly unbalanced between intervention and control groups. Multiple imputation was not performed as missing values were <1 % in the 630 women who provided data at the clinic visit at 7 weeks gestation.

The trial was approved by the UK, Singapore, and New Zealand research ethics services (Southampton: Health Research Authority NRES Committee South Central Research Ethics Committee, reference 15/SC/0142l; Singapore: the National Healthcare Group Domain Specific Review Board, reference 2015/00205; New Zealand: the Health and Disability Ethics Committee, reference 15/NTA/21). The relevant regulatory authorities confirmed that the formulation was not an investigational medicinal product. All participants gave written informed consent. Trial oversight and monitoring were provided by an independent data and safety monitoring committee. This trial was prospectively registered at ClinicalTrials.gov NCT02509988, UTN U1111-1171-8056.

3. Results

Table 1 shows descriptive statistics of the baseline preconception characteristics of women providing data for this present study, split by intervention and control groups. Most characteristics were well balanced between the groups except for parity (those in the control group were more likely to be nulliparous at baseline). The proportions of women with preconception EPDS >=13 and short-form STAI-state>=45 and median EPDS, STAI-trait, STAI-state and SF-12 MCS scores were also balanced between intervention and control groups at baseline, as were history of mental illhealth/mental health medication.

Mixed effect models with continuous EPDS scores as outcome adjusting for site, ethnicity and visit, showed that intervention group had no effect on mood (beta=0.29 (95 %CI −0.18, 0.76) p = 0.224). Mixed effect models with continuous STAI-state scores as outcome, adjusting for site, ethnicity and visit, showed that intervention had no effect on anxiety (beta=−0.19 (95 %CI-0.88, 1.26 p = 0.722). The box plots in Supplementary Figures 2 and 3 confirm the results from the mixed models.

Table 2 shows the odds ratios of women experiencing EPDS>=13 or STAI-state>=45 at each visit during pregnancy and post-delivery. Results are presented adjusting for site, ethnicity and corresponding baseline EPDS or STAI-state score (first column), and then additionally adjusting for parity (second column). Table 2 shows there were generally no associations between randomisation group and either EPDS>=13 or STAI-state>=45 during early pregnancy and post-delivery. Although those in the intervention group were more likely to experience low mood at 3 weeks postpartum, this trend was not significant following Bonferroni correction for the multiple time points assessed. Supplementary Figure 4 shows a histogram of EPDS scores at 3

Table 2
Maternal Mood (EPDS/STAI) at 5 timepoints covering 7 weeks gestation to 6 months postpartum, Intervention vs control group.

Outcome	n/N	[a]Odds Ratio (95 %CI)	P value	[b]Odds Ratio (95 %CI)	P value
7 weeks gestation EPDS>=13	30/628	0.68 (0.30, 1.52)	0.351	0.67 (0.29, 1.51)	0.329
7 weeks gestation STAI>=45	75/629	0.92 (0.55, 1.55)	0.763	0.89 (0.53, 1.50)	0.657
28 weeks gestation EPDS>=13	29/584	1.19 (0.52, 2.72)	0.681	1.18 (0.51, 2.72)	0.699
28 weeks gestation STAI>=45	48/585	1.01 (0.55, 1.88)	0.963	1.02 (0.55, 1.90)	0.949
34 weeks gestation EPDS>=13	24/568	1.27 (0.54, 2.99)	0.588	1.19 (0.50, 2.84)	0.701
34 weeks gestation STAI>=45	57/570	1.24 (0.71, 2.18)	0.452	1.19 (0.67, 2.09)	0.555
3 weeks postpartum EPDS>=13	31/528	2.62 (1.17, 5.87)	0.019	2.98 (1.31, 6.77)	0.009
3 weeks postpartum STAI>=45	71/529	1.34 (0.80, 2.25)	0.269	1.54 (0.90, 2.62)	0.115
6 months postpartum EPDS>=13	21/531	1.02 (0.41, 2.49)	0.971	1.08 (0.43, 2.70)	0.871
6 months postpartum STAI>=45	39/532	0.81 (0.41, 1.58)	0.533	0.76 (0.39, 1.51)	0.436

[a]Logistic regressions adjusting for site, white ethnicity, and corresponding baseline EPDS or STAI score.
[b]Logistic regressions adjusting for site, white ethnicity, parity and corresponding baseline EPDS or STAI score.
Higher scores EPDS>13 and STAI-state>45 indicate lower mood or greater anxiety, respectively.
Sample sizes for further adjusted [b] logistic regressions do not always equal numbers in the n/N column due to missing values. $P < 0.005$ taken as statistically significant with Bonferroni correction.

weeks postpartum split by intervention/control group; the similar overall distributions for the intervention and control groups is consistent with the association at a single time point being a type-1 statistical error (false positive).

Linear regression analysis of change in SF-12 MCS from preconception to 6 months postpartum showed that, compared to women in the control group, those in the intervention group averaged a 1.21 (95 %CI 0.04, 2.39, $p = 0.043$) higher change in SF-12 MCS from preconception to 6 months postpartum, equivalent to standardised effect size of 0.14. This indicates that, at 6 months postpartum, women in the intervention group had modestly improved mental health functioning compared to the control group. With further adjustment for parity, this difference attenuated marginally to 1.18 points (95 % CI −0.005, 2.37, $p = 0.051$). Fig. 1 shows that the distribution of difference in SF-12 MCS for the intervention group is centred slightly to the right of the control group, corroborating the linear regression results and suggesting a modest difference between groups. This was also confirmed by analysing the cross-sectional difference between the control and intervention groups at 6 months postpartum which similarly showed better mental health functioning in the intervention group (Mann Whitney test, $p = 0.044$).

4. Discussion

In this randomised trial of a nutritional supplement containing myo-inositol, probiotics and enriched micronutrients preconception and during pregnancy we demonstrated no differences in mean EPDS and STAI-state scores between intervention and control groups during pregnancy and up to 6 months post-delivery. Similar proportions had high EPDS and STAI-state scores in the intervention and control groups for all but one of the timepoints assessed. While mothers in the intervention group had a higher odds ratio of an EPDS score of ≥13 at 3 weeks post-delivery, this was not significant after correction for the multiple time points assessed and the distribution of scores suggested this is likely due to a Type 1-statistical error. We found a modest increase in the MCS component of the SF12 from preconception to 6 months post-delivery in the intervention compared with control group, providing some evidence an improvement in how mental wellbeing affects ability to function in everyday life in women in the intervention group.

Our EPDS and STAI-state findings suggest that the nutritional intervention preconception and during pregnancy did not have a substantive effect on maternal mood and anxiety during pregnancy and the 6 months post-delivery. In the setting of this double-blind trial including women from various ethnic backgrounds from three different continents we did, however, find a modest 1.21 point improvement of mental health functioning from preconception to 6-months post-delivery associated with the intervention. Confirmatory adjustment for a slight unbalance in parity between the control and intervention groups only marginally attenuated the effect size, suggesting that parity was not a true confounder in the association. A 1-point improvement in mean

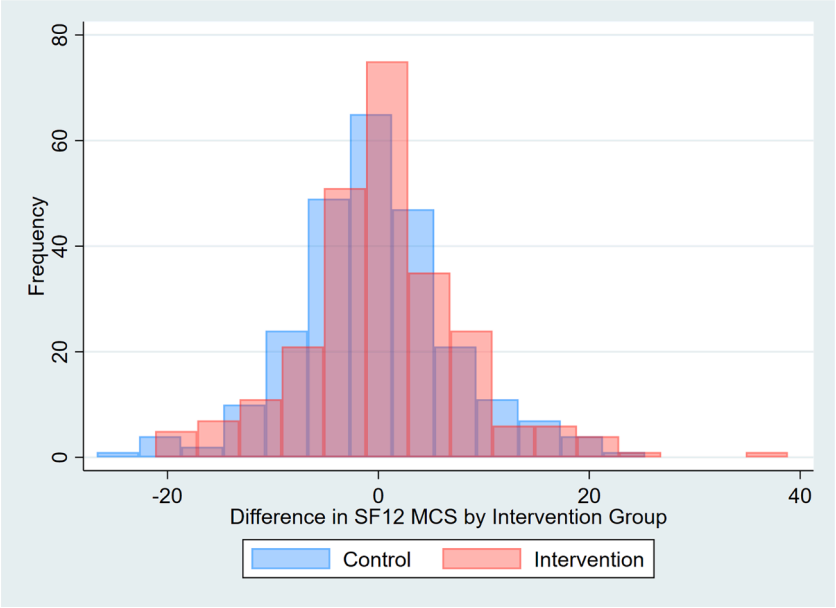

Fig. 1. Difference in SF-12 MCS from Baseline to 6 months Postpartum by Intervention Group.

mental health functioning score equates to a change from "most of the time" to "some of the time" for one of the six component items, such as "How much of the time have your physical health or emotional problems interfered with your social activities". The effect size found is similar to the reported "minimal clinically important difference" in MCS of 1.1 adjusting for pre-operative confounding variables in a pre/post-operative patient group (Clement et al., 2019). Previous publications have used the SF-12 MCS in the perinatal population and provided evidence of validity (Mogos et al., 2013). The differing findings for the EPDS/STAI-state and SF12 mental function scores may reflect the focus of the latter on capturing emotion, accomplishment and energy, and their impact on daily function, along with non-specific psychological distress (Yu et al., 2015; Kessler et al., 2002) rather than simply mood and anxiety symptoms per se.

The intervention contained a standard amount of myo-inositol, enhanced amounts of vitamins B6, B12 and riboflavin compared to that typical of prenatal supplements available over-the-counter, recommended daily allowance amounts in the UK for pregnant women of vitamin D, zinc, folic acid and iodine, minimal amounts of iron, β-carotene, calcium and probiotics (*Lactobacillus rhamnosus* NCC 4007 (CGMCC 1.3724) also known as LPR and *Bifidobacterium animalis* sp. *lactis* NCC 2818 (CNCM I-3446) also known as Bl818) (Godfrey et al., 2017). It remains to be determined which ingredients in the intervention account for effects on mental health functioning and it is plausible that the beneficial effect may be a result of a combination of nutrients and probiotics. Additionally, longitudinal assessments of changes in the levels of the nutrients and other components of the intervention may suggest pathways of effect and inform further trials in this field.

Diets that are healthy can modulate the gut-brain axis and potentially prevent and treat some mental health disorders (Jacka, 2019). It is possible that the microbiome may modulate the effects of diet on the brain and mood (Hughes et al., 2019; Berding et al., 2021). However, microbiome data were not available to confirm viability of the probiotic in participant samples. Good adherence to the intervention is supported by high intake of the supplements by sachet counts (96.6 % took >60 % of sachets averaged across preconception and pregnancy) and additionally by higher plasma 25-hydroxyvitamin D concentrations in the intervention group at 28 weeks' gestation (Godfrey et al., 2017; Godfrey et al., 2021).

Strengths of this study include its randomised controlled trial design and the use of validated instruments to assess mental wellbeing. Maternal history of mental ill-health and medication use for mental health problems at recruitment were balanced between the control and intervention groups. Limitations of the study are that mental wellbeing was a secondary outcome of the trial and the numbers of participants with high scores suggestive of depression or high anxiety were modest as we were not studying a population at high risk of perinatal mental ill-health. Consequently, the study had only modest power to detect a robust change in high EPDS or STAI scores. Generalisability may be limited by the lack of other ethnic backgrounds, by our trial being conducted in high-resource settings and by participants in the 1st-3rd deciles of within-country income being under-represented in our sample. Additionally, we are not able to disentangle the effects of individual ingredients in the intervention.

In conclusion, we found some evidence of an improvement in mental health functioning assessed by the SF-12 MCS in association with the nutritional supplement trialled, but no impact was found on mood and anxiety scores. This data provides preliminary support for a role of nutrition in maintaining mental health functioning during pregnancy and postpartum, but highlights the need for further detailed studies into the effects of individual nutrients and probiotics.

CRediT authorship contribution statement

Sarah El-Heis: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Sheila J. Barton:** Conceptualization, Data curation, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **Hsin Fang Chang:** Methodology, Writing – review & editing. **Heidi Nield:** Project administration. **Vanessa Cox:** Data curation. **Sevasti Galani:** Formal analysis. **Wayne Cutfield:** Funding acquisition, Methodology, Supervision, Writing – review & editing. **Shiao-Yng Chan:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing. **Keith M. Godfrey:** Conceptualization, Formal analysis, Funding acquisition, Methodology, Supervision, Writing – review & editing.

Declaration of competing interest

KG, YSC, WC and SC report grants from Société Des Produits Nestlé S. A. during the conduct of the study, and are co-inventors on patent filings by Nestlé S.A. relating to the NiPPeR intervention or its components. KG, SB, YSC, WC and SC are part of an academic consortium that has received grants from Nestlé S.A. and BenevolentAI Bio Ltd outside the submitted work. All other authors declare no competing interests

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Supplementary materials

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