

# BMJ Open

BMJ Open is committed to open peer review. As part of this commitment we make the peer review history of every article we publish publicly available.

When an article is published we post the peer reviewers' comments and the authors' responses online. We also post the versions of the paper that were used during peer review. These are the versions that the peer review comments apply to.

The versions of the paper that follow are the versions that were submitted during the peer review process. They are not the versions of record or the final published versions. They should not be cited or distributed as the published version of this manuscript.

BMJ Open is an open access journal and the full, final, typeset and author-corrected version of record of the manuscript is available on our site with no access controls, subscription charges or pay-per-view fees (<http://bmjopen.bmj.com>).

If you have any questions on BMJ Open's open peer review process please email [info.bmjopen@bmj.com](mailto:info.bmjopen@bmj.com)

# BMJ Open

## Sex-specific effects of nutritional supplements in infants born early or small: Protocol for an individual participant data meta-analysis (ESSENCE IPD-MA)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-033438
Article Type:	Protocol
Date Submitted by the Author:	05-Aug-2019
Complete List of Authors:	Lin, Luling; The University of Auckland Liggins Institute, Crowther, Caroline; The University of Auckland Liggins Institute Gamble, Greg; The University of Auckland Liggins Institute Bloomfield, Frank; The University of Auckland Liggins Institute Harding, Jane; University of Auckland Liggins Institute
Keywords:	Preterm, Small-for-gestational-age, Development, Metabolic, Individual participant data meta-analysis

SCHOLARONE™  
Manuscripts

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# Sex-specific effects of nutritional supplements in infants born early or small: Protocol for an individual participant data meta-analysis (ESSENCE IPD-MA)

Luling Lin (0000-0002-8448-1504)<sup>1</sup>, <luling.lin@auckland.ac.nz>

Caroline A. Crowther<sup>1</sup>, <c.crowther@auckland.ac.nz>

Gregory D. Gamble (0000-0003-0412-3203)<sup>1</sup>, <gd.gamble@auckland.ac.nz>

Frank H. Bloomfield<sup>1</sup>, <f.bloomfield@auckland.ac.nz>

Jane E. Harding (0000-0003-2697-1422)<sup>1</sup>, <j.harding@auckland.ac.nz>

for the ESSENCE IPD-MA Group<sup>2</sup>

<sup>1</sup> Liggins Institute, University of Auckland, Auckland, New Zealand

<sup>2</sup> Membership of the ESSENCE IPD-MA Group is listed in the Contribution section

Corresponding author

Jane E. Harding

Liggins Institute, University of Auckland

Building 503, Level 2, 85 Park Road, Auckland P Private Bag 92019, Auckland 1142, New Zealand

E-mail: j.harding@auckland.ac.nz

Telephone: +6499236439

**Word count: 2675**

## ABSTRACT

### Introduction

Preterm and small for gestational age (SGA) infants are at increased risk of poor growth, disability and delayed development. While growing up they are also at increased risk of obesity, diabetes and later heart disease. The risk of such adverse outcomes may be altered by how preterm and SGA infants are fed after birth. Faltering postnatal growth is common due to failure to achieve recommended high energy and protein intakes, and thus preterm and SGA infants are often provided with supplemental nutrition soon after birth. Enhanced nutrition has been associated with improved early growth and better cognitive development. However, limited evidence suggests that faster growth may increase the risk for later adiposity, metabolic and cardiovascular disease, and that such risks may differ between girls and boys.

### Methods and analysis

We will search OvidMedline, Embase, Cochrane CENTRAL, Cochrane Database of Systematic Reviews, controlled-trials.com, clinicaltrials.gov and anzctr.org.au for randomised trials that studied the effects of macronutrient supplements for preterm and SGA infants on developmental, metabolic and growth outcomes after hospital discharge. The co-primary outcomes will be cognitive impairment and metabolic risk. Individual participant data (IPD) from all available trials will be included using an intention-to-treat approach. A one-stage procedure for IPD meta-analysis (MA) will be used, accounting for clustering of participants within studies. Exploratory subgroup analyses will further investigate sources of heterogeneity, including sex and size of infants, different timing, duration and type of supplements.

**Ethics and dissemination:** This IPD-MA is approved by the University of Auckland Human Participants Ethics Committee (reference number: 019874). Individual studies have approval from relevant local ethics committees. Results will be disseminated in a peer-reviewed journal and presented at international conferences.

**PROSPERO registration number:** CRD42017072683

### Strengths and limitations of this study

- This IPD-MA will synthesise data from multiple randomised clinical trials using uniformly defined relevant outcomes for all available trials.
- Subgroup analyses may allow detection of potential sex differences that could not be achieved through aggregate analyses.
- This IPD-MA will explore the interactions between treatment and participant-level characteristics.
- A potential limitation is that the analyses planned will depend on obtaining the relevant individual participant data.
- There may be considerable heterogeneity as interventions are likely to be very varied and the trials performed over several decades.

## INTRODUCTION

Infants born preterm or small for gestational age (SGA) are at increased risk of poor growth, disability and delayed development.<sup>1-3</sup> As adults, they are at increased risk of obesity, diabetes and later heart disease.<sup>4</sup> How infants born small are fed after birth may alter the risk of these adverse outcomes. Providing preterm and SGA infants with enhanced nutrition soon after birth is associated with improved early growth and better cognitive development,<sup>5-7</sup> but observational data suggest that early faster growth may increase the risk for later adiposity, metabolic and cardiovascular disease.<sup>8</sup>

It has been recognised for centuries that girls and boys grow differently, experience different metabolic and endocrine milieux, and have different cognitive and health outcomes. Little attention has been paid to improving outcomes following preterm birth by treating girls and boys differently, although it is well recognised that preterm boys compared to girls have higher mortality and morbidity,<sup>9</sup> and are more likely to have adverse developmental and educational outcomes.<sup>10</sup> There is substantial evidence that perinatal insults can result in different adult phenotypes in males and females.<sup>11</sup> For example, animal studies across many different species after a wide variety of prenatal insults show that males are more likely than females to exhibit adverse effects such as impaired renal function, hypertension, insulin resistance, altered hypothalamic-pituitary-adrenal (HPA) axis function and altered growth in later life.<sup>12</sup> The reasons for this sex difference in vulnerability to early environmental perturbations are not well understood, but may include faster growth and hence greater substrate demands in males, altered tempo of maturation, different exposure to sex steroids and sex-specific epigenetic mechanisms.<sup>12</sup> Unfortunately, most clinical studies have not reported findings separately by sex and are not adequately powered to do so. Further, because the majority of animal experiments are done in polytocous species, prenatal and postnatal sex effects cannot be separated in mixed-sex litters. There is little reliable evidence about how best to feed preterm babies to optimise both short- and long-term health outcomes, and almost none about targeting nutrition by sex.

### Hypotheses

The effects of early nutritional supplements on post-discharge development, markers of metabolic risk and growth are different in girls and boys.

### Need for individual participant data meta-analysis

Systematic reviews using aggregate data meta-analyses are limited due to within-trial variation in gestational age of the infants at birth, co-morbidities of the infant, starting time and duration of the intervention, macronutrient content of the intervention and control groups. Outcomes within aggregate meta-analyses such as cerebral palsy, motor dysfunction or hearing loss also include a range of severity of disability. Aggregate meta-analyses tend to vary in completeness and in the definitions used for the outcomes. Not all trials combine the same outcomes in composite outcomes or use the same measures of neuro-developmental outcome. Few trials describe multiple subgroups, making meta-analysis of data almost impossible. Importantly, few trials to date have provided the sex of the infant as a subgroup variable.

One method to ameliorate some of the limitations of aggregate data meta-analysis is to combine the large volume of individual trial data available to perform an individual participant data (IPD) meta-analysis (MA). The estimates of treatment effects with an IPD-MA often differ from aggregate meta-analyses.<sup>13</sup> IPD-MA allows the inclusion of additional unpublished data provided by the trialists, and allows consistent re-categorisation of definitions of outcomes and populations in order to answer the clinical questions of interest. Further, IPD-MA may allow more detailed meta-analysis of key outcomes, taking into account both subject-level and study-level sources of heterogeneity in treatment effects. Thus, IPD-MA offers the potential to help clarify the sex-specific effects of early macronutrient supplements provided to preterm and SGA infants.

## METHODS AND ANALYSIS

This study will use an IPD-MA approach and follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>14</sup>

### Aims

To assess, using IPD-MA, the effects of macronutrient supplements in nutrition of preterm and SGA infants on developmental, metabolic and growth outcomes after hospital discharge, and in particular, whether these effects differ in girls and boys.

### Criteria for inclusion and exclusion

We will include published and unpublished randomised and quasi-randomised trials without restrictions on date of publication or language. Trials that studied infants born preterm (< 37 weeks' gestation) or born small (birthweight <2.5 kg or < 10<sup>th</sup> centile for gestational age) and in which the intervention was intended to increase the intake of one or more macronutrients (protein, carbohydrate, fat, energy content or protein to energy ratio), with the primary aim of improving growth and development will be included.

Interventions can be enteral or parenteral or a combination, commence at any time during the hospitalisation or after discharge from hospital, and must be provided for a minimum duration of one week. Trials that report on comparisons between un-supplemented nutrition and supplemented nutrition with parenteral supplements, human breast milk supplements, formula milk or other macronutrients will be eligible for inclusion, for example: 1) Parenteral formulation A versus parenteral formulation B with different macronutrient composition; 2) Human milk (mother's own or donor) versus supplemented human milk (mother's own or donor); 3) Human milk (mother's own or donor) versus formula milk (term or preterm); 4) Supplemented human milk (mother's own or donor) versus formula (term or preterm); 5) Supplemented human milk A (mother's own or donor) versus supplemented human milk B (mother's own or donor); 6) Formula A versus formula B with different macronutrient composition (including preterm versus term formula, brand A versus brand B). We will exclude trials that examine the timing of the introduction of nutrition (early versus delayed feeding); that compare macronutrients of different composition (e.g. different types of lipids or proteins); studies whose outcomes focus on gastrointestinal development rather than growth and development; and studies reporting on variations in composition of



1  
2  
3 micronutrients (including sodium, potassium, calcium, phosphorus, vitamins, other minerals,  
4 amino acids, fatty acids).  
5  
6

7 Outcome data must be reported beyond term equivalent age ( $\geq 37$  weeks' post-menstrual age)  
8 or following discharge from hospital after birth. Where the data are available, the outcomes  
9 will be categorised and evaluated in toddlers (less than 3 years), childhood (3 to 8 years),  
10 adolescence (9 to 18 years) and adulthood (more than 18 years).  
11  
12  
13

14 The co-primary outcomes will be 1) Cognitive impairment: below -1 SD on standard tests of  
15 development (toddlers) or cognition/intelligence quotient (later ages) and 2) Metabolic risk  
16 (*See Appendix 1 for definitions*): any of overweight/obese; increased waist circumference;  
17 increased fat mass or fat mass percentage; elevated plasma triglyceride concentrations; low  
18 high-density lipoprotein (HDL) concentrations; elevated low-density lipoprotein (LDL)  
19 concentrations; elevated fasting plasma glucose concentrations; insulin resistance; impaired  
20 glucose tolerance; diagnosis of type 2 diabetes; high blood pressure and impaired flow-  
21 mediated vasodilatation.  
22  
23  
24  
25  
26  
27  
28

29 The secondary outcomes will be (*See Appendix 2 for definitions*): 1) Composite of survival  
30 free of any disability (including death, cerebral palsy, motor development delay or  
31 impairment, cognition/intelligence delay or impairment, language delay, visual impairment,  
32 hearing impairment); 2) Cognition/intelligence delay or impairment; 3)  
33 Cognition/intelligence scores; 4) Motor delay or impairment; 5) Motor scores; 6) Cerebral  
34 palsy (any); 7) Severity of cerebral palsy; 8) Visual impairment; 9) Hearing impairment; 10)  
35 School performance; 11) Measures of psychological well-being; 12) Metabolic outcomes:  
36 waist circumference, overweight/obese, type-2 diabetes, blood lipid concentrations  
37 (triglycerides, HDL, LDL, HDL:LDL), fasting blood glucose concentration, insulin  
38 concentration, insulin resistance (HOMA), glucose tolerance, IGF-1 concentration; 13)  
39 Cardiovascular risk outcomes: blood pressure (systolic blood pressure (SBP), diastolic blood  
40 pressure (DBP), mean arterial pressure (MAP)), flow-mediated vasodilatation, measures of  
41 sympathetic and parasympathetic tone, cardiac size and structure; 14) Brain development:  
42 whole brain, white matter and grey matter volumes and volumes of individual brain regions,  
43 brain maturation measured using MRI (white matter tracts, measures of diffusivity,  
44 myelination, surface folding), functional brain imaging; 15) Growth outcomes: weight (raw  
45 data and z scores); length/height (raw data and z scores); head circumference (raw data and z  
46 scores); Ponderal index; body mass index (BMI), body composition (fat mass, lean mass, as  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

1  
2  
3 measured by bioimpedance or Dual-energy X-ray absorptiometry (DXA) or skin fold  
4 thickness or air displacement plethysmography or other method); 16) Bone development:  
5 bone mineral content; volumetric bone mineral density and fractures; 17) Health outcomes:  
6 allergies (eczema, asthma, hayfever), respiratory function, hospitalisation (duration), health  
7 care utilisation; 18) Nutrition: feeding tolerance; intake (milk, energy), appetite, breast  
8 feeding; 19) Death (neonatal or later death up to the time of follow-up and cause of death);  
9 20) Quality of life; 21) General health and use of healthcare resources; 22) Adverse Events;  
10 23) Cost.  
11  
12  
13  
14  
15  
16  
17  
18  
19

### 20 **Search strategy**

21 We will search OvidMedline, Embase, Cochrane Library Central Registry of Controlled  
22 Trials (CENTRAL), and Cochrane Database of Systematic Review from inception to identify  
23 eligible trials. We will also search for registered trials in Current Controlled Trials  
24 ([www.controlled-trials.com](http://www.controlled-trials.com)), Clinical Trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and Australian and  
25 New Zealand Clinical Trials Registry ([www.anzctr.org.au](http://www.anzctr.org.au)) to identify eligible ongoing  
26 studies. The full search strategy and search terms are available as online supplementary  
27 material (Appendix 1). Experts in the field and trialists will be asked if they can identify other  
28 published or ongoing trials. Potentially eligible trials that are not yet completed will not be  
29 included in this IPD-meta analysis, but will be noted for inclusion in future updates.  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39

### 40 **Identify studies**

41 The eligibility of trials will be assessed by two researchers. Discrepancies will be resolved by  
42 discussion. If IPD are unavailable from any eligible trial it will be included in the IPD-MA  
43 using aggregate data for sensitivity analysis where possible.  
44  
45  
46  
47  
48  
49

### 50 **Contact Authors**

51 Authors of eligible studies will be invited to join the ESSENCE IPD-MA Collaborative  
52 group. We will identify contact information from the published trials. An initial email will be  
53 sent to the main trial author (corresponding author) providing them with the summary IPD-  
54 MA protocol. Another investigator from the study will be contacted if initial emails fail to  
55 receive a response, followed by phone calls if needed.  
56  
57  
58  
59  
60

### Quality assessment

We will assess the quality of the eligible trials using the methods specified in the Cochrane Handbook for Systematic Reviews of Interventions:<sup>15</sup> random sequence generation (selection bias); allocation concealment (selection bias); blinding of participants, personnel, and outcome assessment (performance and detection bias); incomplete outcome data (attrition bias); selective reporting (reporting bias); (6) Other bias (checking for bias due to problems not covered by (1) to (5) above).

### Development of the database

We will develop a set of pre-specified and defined variables for IPD-MA at both the outcome, participant and trial level (Appendix 3). We will seek data on all randomised infants which will be coded for anonymity (date of birth, study centre); baseline data for narrative purposes (birthweight, gestational age at birth, plurality, sex); details of the intervention and comparator (date of randomisation, allocated intervention, type and composition of intervention and comparator, enteral or parenteral administration, age at start of intervention, weight at start of intervention, duration of intervention) and the outcomes listed above.

Trialists will provide de-identified data in any format which will be recoded as required, verified and checked for consistency with published data and stored on a secure, password protected file on the University of Auckland servers. Data will only be accessible by authorised personnel in the ESSENCE Data Management Group.

Methodological details of the individual trials will be cross-checked against published reports, trial registration (where available) and trial data collection forms. Where inconsistencies are identified, discussions will be held with individual trial groups to attempt to resolve these. Each trial final dataset to be used in the IPD-MA will be returned to the trialists for verification. Trials will then be analysed individually using IPD-MA pre-specified variables and outcomes and the results returned to the trialists for verification. The individual trial datasets will then be combined to form the ESSENCE-IPD dataset and the IPD meta-analysis undertaken.

### Data synthesis and statistical analysis

A detailed statistical analysis plan will be prepared and agreed on by the ESSENCE-IPD team.

We will use a one-stage approach to the analysis of each outcome so that the IPD from all eligible trials are included in a single model. We will make an assessment of heterogeneity to decide if combining data from trials is appropriate or if heterogeneity, if significant, can be explained.

Binary outcomes will be analysed using log binomial regression models and data will be reported as Risk Ratio (RR) with 95% Confidence Intervals (CI) and associated 2-sided p values. Continuous data will be analysed using linear regression models and data will be reported as mean differences (MD) with 95% Confidence Intervals (CI) and associated 2-sided p values.

A large number of outcomes are being investigated in this study. This increases the chance of observing false positive results. The overall probability of a type 1 error will be maintained at 5% for the two co-primary outcomes by testing each at 0.025 (i.e. splitting the critical p value evenly). No further adjustment for multiplicity is planned for comparisons made in secondary and exploratory analyses.

We will explore the effects of the sex of the infants by presenting data separately for each sex as pre-specified subgroups, and by testing a treatment by sex interaction term within the model.

Where data are missing, those infants will be removed from the analysis and, where possible, the reasons for missing data will be explored. It is not proposed to impute missing data since the assumption of 'missing at random' is unlikely to be met. Where there are large amounts of missing data or trials are unable to provide IPD we will conduct sensitivity analyses to explore the effect of removing such trials from the analysis.

Statistical analyses will be performed using SAS (v.9.4, SAS Institute, Cary, NC, USA).

### Planned subgroup analysis

Where data are available, we will conduct subgroup analyses to explore whether the effects of supplements differ between subgroups and test for interaction terms.

1. Sex of infant (boys vs girls);
2. Size of infant at birth ( $\leq 1$  kg vs  $>1$  kg at birth);
3. Size for gestation of the infant ( $\leq 10^{\text{th}}$  centile vs  $> 10^{\text{th}}$  centile);
4. Gestational age of infant at birth ( $\leq 28$  completed weeks vs 29 to 32 completed weeks vs 33 to 36 weeks).
5. Timing of supplement:  
In hospital nutrition: the intervention was commenced in hospital or on average ended at 42 weeks' postmenstrual age or earlier;  
Post-discharge nutrition: the intervention was commenced after discharge or on average started at or after 36 weeks' postmenstrual age;  
Both in hospital and post-discharge nutrition: the intervention was commenced in the hospital and continued post-discharge.
6. Type of supplement (protein vs carbohydrate vs fat vs multicomponent and their interactions).
7. Breast milk vs formula as primary milk feed.
8. Duration of supplement (1 to 2 weeks vs 3 to 6 weeks vs more than 7 weeks).
9. Different epochs (commenced up to the year of 2000 vs commenced in or after the year of 2001).

### Planned sensitivity analyses

We will perform sensitivity analyses to assess whether the results are robust to the trial design by excluding trials assessed as high risk of bias.

Where trials are unable to contribute data to the IPD we will assess the robustness of the inclusion or exclusion of these trials by combining their aggregate data with the IPD.

### Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research.

## DISCUSSION

This will be the first IPD-MA to investigate the effects of early macronutrient supplements on preterm and SGA infants. IPD meta-analysis has been described as the ‘gold standard’ of systematic review methodology as it allows for more powerful and flexible analysis of both subgroups and outcomes.<sup>16</sup> This IPD-MA, using existing data from the individual trials, may reveal the sex-specific effects of macronutrient supplement on preterm and SGA infants, and will allow assessment of important interactions that cannot be tested in standard, aggregate data meta-analysis.

## ETHICS AND DISSEMINATION

The shared data will be de-identified, the data files will be transferred by secure means, and stored in in a secure password protected area on a Auckland University server.

Final results will be presented to the ESSENCE IPD-MA collaborators prior to publication and public dissemination. Results of the study will be published in peer-reviewed journals and presented at national and international conferences.

**REFERENCE**

1. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an inevitable consequence of current recommendations in preterm infants? *Pediatrics* 2001;107(2):270-3.
2. Hay WW, Jr. Nutritional requirements of extremely low birthweight infants. *Acta Paediatr Suppl* 1994;402:94-9.
3. Cooke RW. Conventional birth weight standards obscure fetal growth restriction in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2007;92(3):F189-92. doi: 10.1136/adc.2005.089698
4. Luu TM, Katz SL, Leeson P, et al. Preterm birth: risk factor for early-onset chronic diseases. *Can Med Assoc J* 2016;188(10):736-40. doi: 10.1503/cmaj.150450
5. Lucas A, Fewtrell MS, Morley R, et al. Randomized outcome trial of human milk fortification and developmental outcome in preterm infants. *Am J Clin Nutr* 1996;64(2):142-51.
6. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later intelligence quotient. *BMJ* 1998;317(7171):1481-7.
7. Lucas A, Morley R, Cole TJ, et al. A randomised multicentre study of human milk versus formula and later development in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 1994;70(2):F141-6.
8. Peacock JL, Marston L, Marlow N, et al. Neonatal and infant outcome in boys and girls born very prematurely. *Pediatr Res* 2012;71(3):305-10. doi: 10.1038/pr.2011.50
9. Glass HC, Costarino AT, Stayer SA, et al. Outcomes for extremely premature infants. *Anesth Analg* 2015;120(6):1337-51. doi: 10.1213/ANE.0000000000000705
10. Ong KK, Kennedy K, Castaneda-Gutierrez E, et al. Postnatal growth in preterm infants and later health outcomes: a systematic review. *Acta Paediatr* 2015;104(10):974-86. doi: 10.1111/apa.13128
11. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease. *Reprod Toxicol* 2011;31(3):363-73. doi: 10.1016/j.reprotox.2010.12.055
12. Aiken CE, Ozanne SE. Sex differences in developmental programming models. *Reproduction* 2013;145(1):R1-13. doi: 10.1530/REP-11-0489
13. Smith CT, Marcucci M, Nolan SJ, et al. Individual participant data meta-analyses compared with meta-analyses based on aggregate data. *Cochrane Db Syst Rev* 2016(9) doi: ARTN MR00000710.1002/14651858.MR000007.pub3
14. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097. doi: 10.1371/journal.pmed.1000097 [published Online First: 2009/07/22]
15. Higgins JPT, Green S (editors). Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated March 2011]. *The Cochrane Collaboration, 2011 Available from www.cochrane-handbook.org* 2011

- 1  
2  
3 16. Tierney JF, Vale C, Riley R, et al. Individual participant data (IPD) meta-analyses of randomised  
4 controlled trials: guidance on their use. *PLoS Med* 2015;12(7) doi: ARTN  
5 e100185510.1371/journal.pmed.1001855  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



## DECLARATIONS

### Acknowledgements

We would like to acknowledge Dr Julie Brown for help with developing the draft protocol and search strategies, Mariana Muelbert for her help with the communication with trialists from Brazil, and Laura Galante for her help with the communication with trialists from Italy.

### Ethical approval and consent to participate

The ESSENCE-IPD project has been approved by University Of Auckland Human Participants Ethics Committee.

Participants in the individual trials have previously given informed consent to participate in their respective trials. The data for these projects are to be used for the purpose for which they were originally collected and are available through an agreement between all trialists of the collaborative group. These trialists remain custodians of their original trial data at all times. A data sharing agreement will be signed by a representative of the institution that owns the data and a representative of University of Auckland.

### Consent for publication

Not applicable

### Availability of data and material

Not applicable

### Competing interests

The authors declare that they have no competing interests.

### Funding

The ESSENCE-IPD project is supported by the Health Research Council (HRC) of New Zealand (16/605). The analysis will be included as part of the doctoral thesis of Luling Lin, who is supported by Agnes Paykel PhD Scholarship. None of the funders are involved in any other aspect of the project, such as the design of the protocol and analysis plan, the collection and analysis of the data, or the interpretation and publication of the study results.

### Authors' contributions

The Chair of the ESSENCE-IPD Project Team (J.E. Harding) wrote the first draft of the ESSENCE-IPD protocol. L Lin revised the subsequent versions of the ESSENCE-IPD protocol and prepared the initial draft of the manuscript. The ESSENCE-IPD Project Team

1  
2  
3 and the ESSENCE-IPD Management Group participated in the protocol development and  
4 commented on all drafts of the manuscript. The ESSENCE-IPD Trialist Group participated in  
5 the development of the IPD protocol and have read and approved the final draft of the  
6 manuscript.  
7  
8  
9

## 10 **Contributors**

### 11 **The ESSENCE IPD-MA Group**

12 **ESSENCE-IPD Project Team:** This is the project Steering Group which is responsible for  
13 the day-to-day management of the IPD. This group has drafted the IPD protocol, will liaise  
14 with trialists and prepare the draft publications. J.E. Harding (chair of ESSENCE-IPD  
15 project); L Lin; C.A. Crowther; F.H. Bloomfield; and G Gamble.  
16  
17  
18  
19  
20  
21

22 **ESSENCE-IPD Management Group:** This group is convened by the Chair of the Project  
23 Team and comprises the IPD-MA statistician and data manager who will be responsible for  
24 the collection, checking, storage and analyses of data. J.E. Harding (chair of ESSENCE-IPD  
25 project); L Lin; C.A. Crowther; and G Gamble.  
26  
27  
28  
29

30 **ESSENCE-IPD Trialist Group:** This group includes investigators from all eligible trials  
31 who have agreed to share their data for the IPD.  
32

33 M Agosti<sup>1</sup>; S.A. Atkinson<sup>2</sup>; A Biasini<sup>3</sup>; R.D.S Da Cunha<sup>4</sup>; N.D. Embleton<sup>5</sup>; M Faraz<sup>2</sup>; M.S  
34 Fewtrell<sup>6</sup>; F Lamy Filho<sup>7</sup>; C. Fusch<sup>2,8</sup>; M.L. Gianni<sup>9</sup>; H.G. Kanmaz<sup>10</sup>; W.WK. Koo<sup>11</sup>; I  
35 Litmanovitz<sup>12</sup>; A Lucas<sup>13</sup>; C Morgan<sup>14</sup>; K Mukhopadhyay<sup>15</sup>; E Neri<sup>16</sup>; J Picaud<sup>17</sup>; E.V  
36 Rafael<sup>18</sup>; P Roggero<sup>9</sup>; A Singhal<sup>19</sup>; K Stroemmen<sup>20</sup>; M.J. Tan<sup>21</sup>; F.M. Tandoi<sup>1</sup>; C.L. Wood<sup>22</sup>;  
37 G Zachariassen<sup>23</sup>  
38  
39  
40  
41  
42

43 <sup>1</sup> Division of Neonatology and Neonatal Intensive Care Unit, “F. Del Ponte” Hospital,  
44 Varese, Italy  
45  
46

47 <sup>2</sup> Department of Pediatrics, Faculty of Health Sciences, McMaster University, Hamilton,  
48 Ontario, Canada.  
49  
50

51 <sup>3</sup> Donor Human Milk Bank Italian Association (AIBLUD), Milan, Italy  
52  
53

54 <sup>4</sup> Hospital Universitário da Universidade Federal do Maranhão - Brasil  
55

56 <sup>5</sup> Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK  
57  
58  
59  
60

1  
2  
3 <sup>6</sup> Childhood Nutrition Research Centre, UCL Great Ormond Street Institute of Child Health,  
4 London, UK  
5

6  
7 <sup>7</sup> Departamento de Medicina, Universidade Federal do Maranhão (UFMA), São Luís, MA,  
8 Brazil  
9

10  
11 <sup>8</sup> Department of Pediatrics, Nuremberg General Hospital, Paracelsus Medical University,  
12 90471 Nuremberg, Germany  
13

14  
15 <sup>9</sup> Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, via Commenda 12, 20122  
16 Milan, Italy  
17

18  
19 <sup>10</sup> Department of Neonatology, NICU, Zekai Tahir Burak Education and Research Hospital,  
20 Ankara, Turkey  
21

22  
23 <sup>11</sup> Department of Nutrition and Food Science, Wayne State University, Detroit, MI, USA  
24

25  
26 <sup>12</sup> Department of Neonatology, Meir Medical Center, Kfar Saba, Israel  
27

28  
29 <sup>13</sup> MRC Childhood Nutrition Research Centre, Institute of Child Health, University College  
30 London, London, UK  
31

32  
33 <sup>14</sup> Department of Neonatology, Liverpool Women's Hospital, Liverpool, UK  
34

35  
36 <sup>15</sup> Department of Pediatrics, Post Graduate Institute of Medical Education and Research  
37 (PGIMER), Chandigarh, India.  
38

39  
40 <sup>16</sup> Department of Psychology, University of Bologna, Bologna, Italy  
41

42  
43 <sup>17</sup> Division of Neonatology, Hôpital de la Croix-Rousse, Lyon, France  
44

45  
46 <sup>18</sup> Departamento de Enfermagem da Universidade Federal do Maranhão, Brasil  
47

48  
49 <sup>19</sup> Department of Nutrition, Institute of Child Health, London, UK  
50

51  
52 <sup>20</sup> Department of Neonatal Intensive Care, Division of Pediatric and Adolescent Medicine,  
53 Rikshospitalet, Oslo University Hospital, Oslo, Norway  
54

55  
56 <sup>21</sup> Department of Developmental Paediatrics, Alder Hey Children's NHS Foundation Trust,  
57 Liverpool, UK  
58

59  
60 <sup>22</sup> Institute of Genetic Medicine, Newcastle University, Newcastle, UK

1  
2  
3 <sup>23</sup> H.C. Andersen Children's Hospital, Odense University Hospital and University of  
4 Southern Denmark, Odense, Denmark  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

1  
2  
3 **Sex-specific effects of nutritional supplements in infants born**  
4 **early or small: protocol for an individual participant data meta-**  
5 **analysis (ESSENCE-IPD)**  
6  
7  
8  
9

10  
11  
12  
13  
14  
15  
16  
17  
18 **Supplement document**  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

### Appendix 1. Definitions for Primary Outcome of Metabolic Risk

Measurement	Guideline/ Equipment	Age	Abnormal	Notes
Size for gestation at birth	INTERGROWTH 21 Charts <sup>1</sup>	≤ 6 months	≤ 10th centile vs > 10th centile	INTERGROWTH 21 charts for babies younger than 6 months <sup>1</sup>
Overweight/obese	WHO Growth Charts <sup>2 3</sup>	<5 years <sup>2</sup>	Overweight: weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; Obesity: weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median.	Charts and tables: WHO child growth standards for children aged under 5 years <sup>2</sup>
		5-19 years <sup>3</sup>	Overweight: BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; Obesity: greater than 2 standard deviations above the WHO Growth Reference median.	Charts and tables: WHO growth reference for children aged between 5–19 years <sup>2</sup>
Waist Circumference	NHANES 2011-2014 <sup>4</sup>	2- 60 years	≥90 <sup>th</sup> percentile <sup>5</sup>	
Fat mass (FM)	DEXA-NHANES <sup>6</sup>	≥8 years	Fat Mass Index (kg/m <sup>2</sup> ) classification ranges for sex	
	BIA <sup>7</sup>	5-18 years	≥85 <sup>th</sup> percentile (%FM)	
	ADP- BodPod <sup>7</sup>	5-18 years	≥85 <sup>th</sup> percentile (%FM)	
	ADP- PedPod <sup>8</sup>	0.5-24 months	%FM greater than 1 standard deviation above the reference mean	
	skinfolds- NHES II, NHES III, NHANES I, NHANES II and NHANES III <sup>9</sup>	1.5-19 years	≥85 <sup>th</sup> percentile <sup>9</sup>	
	Multicomponent model	0.5- 24 month <sup>8</sup>	%FM greater than 1 standard deviation above the reference mean	

Measurement	Guideline/ Equipment	Age	Abnormal	Notes
		5-20 years <sup>10</sup>	FM greater than 1 standard deviation above the reference mean	Fat mass reference data for males and females by Z-score or percentile <sup>10</sup>
Blood pressure	NHBPEP <sup>11</sup>	1 to 17 years	≥90 <sup>th</sup> centile <sup>5</sup> (age, sex and height specific) Charts and tables: WHO Child growth standards for length/height	Compared with Jackson LV 2007 <sup>12</sup> , although the NHBPEP is older, it contains the appropriate age range and reported the actual numbers at each cut point.
Triglycerides	NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton <sup>13</sup>	4-18 years	≥90 <sup>th</sup> centile <sup>14</sup>	Compared to NHANES III, NCEP, and NGHS, this includes a wider age range.
	NHANES	>18 years	≥150mg/dL (8.3 mmol/L) <sup>13</sup>	
HDL-C	NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton <sup>13</sup>	4-18 years	≤10 <sup>th</sup> centile <sup>14</sup>	Compared to NHANES III, NCEP, and NGHS, this includes a wider age range.
	NHANES <sup>13</sup>	>18 years	<40 mg/dL (2.2 mmol/L) <sup>13</sup> for male <50 mg/dL (2.8 mmol/L) <sup>13</sup> for female	
LDL-C	NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton <sup>13</sup>	4-18 years	≥90 <sup>th</sup> centile <sup>13</sup>	Compared to NHANES III, this includes a wider age range.
	NCEP ATP III	>18 years	>130 mg/dL (7.2 mmol/L) <sup>13</sup>	
Fasting plasma glucose concentration	ADA criterion <sup>15</sup> (increased risk for diabetes or prediabetes)		FPG ≥100 mg/dL (5.6 mmol/L)	
Impaired glucose tolerance	ADA criterion <sup>15</sup> (increased risk for diabetes or prediabetes)		2-h PG ≥140mg/dL (7.8 mmol/L) during a 75g OGTT	
<b>Abbreviation</b> WHO: World Health Organisation NHANES: National Health and Nutrition Examination Survey BIA: Bioelectrical impedance analysis DEXA: Dual-energy X-ray absorptiometry FM: Fat mass				

Measurement	Guideline/ Equipment	Age	Abnormal	Notes
ADP: Air displacement plethysmography	NHBPEP: National High Blood Pressure Education Program	NCEP: National Cholesterol Education Program	NGHS: National Lung, Heart and Blood Institute's Growth and Health Study	HDL-C: High triglyceride concentration
LDL-C: Low triglyceride concentration	ATP III: Adult Treatment Panel III	ADA: American Diabetes Association		

For peer review only

bmjopen-2019-033438 on 8 January 2020. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2021 by guest. Protected by copyright.

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46



**Appendix 2. Definitions for Secondary outcomes**

Term	Classification	Definition	Note
Cerebral palsy		<p>1. Cerebral palsy is a physical disability that affects movement and posture.</p> <p>Any definition that includes the following five key elements:</p> <p>(1) is an umbrella term for a group of disorders</p> <p>(2) is a condition that is permanent but not unchanging</p> <p>(3) involves a disorder of movement and/or posture and of motor function</p> <p>(4) is due to a non-progressive interference, lesion or abnormality, and</p> <p>(5) the interference, lesion or abnormality originates in the immature brain</p> <p>2. As defined by investigators</p>	Australian cerebral palsy register report - CP Register <sup>16</sup>
Severity of cerebral palsy	GMFCS Level I	Children walk at home, school, outdoors and in the community. They can climb stairs without the use of a railing. Children perform gross motor skills such as running and jumping, but speed, balance and coordination are limited.	Gross Motor Function Classification System (GMFCS) <sup>17</sup>
	GMFCS Level II	Children walk in most settings and climb stairs holding onto a railing. They may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded areas or confined spaces. Children may walk with physical assistance, a handheld mobility device or used wheeled mobility over long distances. Children have only minimal ability to perform gross motor skills such as running and jumping.	
	GMFCS Level III	Children walk using a hand-held mobility device in most indoor settings. They may climb stairs holding onto a railing with supervision or assistance. Children use wheeled mobility when traveling long distances and may self-propel for shorter distances.	
	GMFCS Level IV	Children use methods of mobility that require physical assistance or powered mobility in most settings. They may walk for short distances at home with physical assistance or use powered mobility or a body support walker when positioned. At school, outdoors and in the community children are transported in a manual wheelchair or use powered mobility.	
	GMFCS Level V	Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control leg and arm movements.	
Developmental delay or intellectual	Mild	A score on scale from 2 SD to <1 SD below test mean	Scores were obtained relative to the mean and standard deviation (SD)
	Moderate	A score on scale from 3 SD to <2 SD below test mean	

impairment	Severe	A score on scale 3 SD below test mean	for the normal birth weight population. <sup>18</sup>
Visual impairment	None	Presenting visual acuity 6/18 or better in the better eye.	WHO Definition of visual impairment <sup>19</sup>
	Moderate/ low vision	Can see a toy and able to follow a toy. Presenting visual acuity worse than 6/18, equal to or better than 6/60 in the better eye in the better eye.	
	Severe/ no useful vision	Able to see light or gross movement up close (within 40cm). Presenting visual acuity worse than 6/60, equal to or better than 1/60 in the better eye	Visual Standards- Aspects and Ranges of Vision Loss <sup>20</sup>
	Blindness/ no light perception	No useful vision. Presenting visual acuity worse than 1/60 in the better eye or no light perception.	
	Legal blindness	Medically diagnosed central visual acuity of 20/200 (6/60) or less in the better eye with the best possible correction, and/or a visual field of 20 degrees or less	
Hearing impairment (Classification 1)	None	None diagnosed	WHO Grades of hearing impairment- Prevention of blindness and deafness <sup>22</sup>
	Mild	Hearing level in decibels: 26-40dB A child with this level of hearing loss will have trouble hearing and understanding soft speech, speech from a distance or speech against a background of noise	
	Moderate	Hearing level in decibels: 41-60db A child with this level of hearing loss will have difficulty hearing regular speech, even at close distance	
	Severe	Hearing level in decibels: 61-80dB A child with this level of hearing loss may only hear very loud speech or loud sounds in the environment, such as a fire truck siren or a door slamming. Most conversational speech is not heard.	
	Profound	Hearing level in decibels: over 81dB A child with this level of hearing loss may perceive loud sounds as vibrations.	
Motor dysfunction	mild impairment	Test score between 5th and 15th centile on the Movement ABC / A score from 2 SD to <1 SD below the population mean on the BOTMP	Movement Assessment Battery for Children (Movement ABC) Bruininks–Oseretsky Test of Motor Proficiency (BOTMP) <sup>23</sup>
	moderate to severe impairment	Test score less than 5th centile on the Movement ABC / more than 2 SD below the population mean on the BOTMP	
School performance	Defined by teachers based on their observation and academic scores; at or above vs below expected performance/level for age		Poor school performance <sup>24</sup>

/bmjopen-2019-033438 on 8 January 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2021 by guest. Protected by copyright.

Growth Z-scores	WHO Growth Charts	Charts and tables: WHO child growth standards for children <sup>2</sup>
<p>Abbreviation:  CP: Cerebral palsy  GMFCS: Gross Motor Function Classification System  SD: Standard deviation  Movement ABC: Movement Assessment Battery for Children  BOTMP: Bruininks–Oseretsky Test of Motor Proficiency</p>		

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

### Appendix 3. Data items to be collected

#### Trial level information

- Protocols of each individual trial
- Data forms or case report forms (CRFs) of each individual trial
- Country
- Setting (neonatal intensive care unit (NICU), hospital, or home)
- Dates of start and end of trial
- Number of infants randomised
- Informed consent procedures
- Methods of random allocation
- Methods of allocation concealment
- Blinding of outcome assessment
- Blinding of researchers/ caregivers
- Stratification factors used
- Purpose of intervention
- Planned intervention
- Specific details of the planned nutrition in the experimental and control arms of the trial (including composition, whether given as sole feed or in addition to breast milk and duration)
- Outcomes collected (primary and secondary)

#### Participant level information: Infant characteristics at trial entry

- Unique identification code
- Gestational age at birth
- Age at trial entry
- Birthweight
- Weight, length and head circumference at trial entry
- Sex
- Single/multiple (if multiple order of birth)

#### Participant level information: After trial entry

- Actual intervention or comparison received
- Age at commencement of nutritional supplement
- Age at ceasing the nutritional supplement
- Receipt of breast milk and whether mother's own or donor/banked
- Size at discharge or term-equivalent age (36-42 weeks' post-menstrual age)- including weight, length, head circumference, and measures of body composition e.g. skinfolds, bioimpedance, plethysmography

#### Appendix 4. Search strategies

Embase from 1980	
#	Search strategies
1	exp prematurity/
2	exp low birth weight/
3	exp small for date infant/
4	exp very low birth weight/
5	(prematu* adj2 infant*).tw.
6	(prematu* adj2 newborn*).tw.
7	(prematu* adj2 neonate*).tw.
8	preterm.tw.
9	low birth weight.tw.
10	low birthweight.tw.
11	VLBW.tw.
12	LBW.tw.
13	ELBW.tw.
14	small for gestation*.tw.
15	SGA.tw.
16	(less than adj6 g).tw.
17	(less than adj3 32 weeks).tw.
18	birth weight below.tw.
19	(gestation* adj2 less than).tw.
20	or/1-19
21	exp breast feeding/
22	exp infant nutrition/
23	exp protein intake/
24	exp dietary supplement/
25	exp omega 3 fatty acid/ct, ad, dt, ig, pa [Clinical Trial, Drug Administration, Drug Therapy, Intragastric Drug Administration, Parenteral Drug Administration]
26	exp arachidonic acid/ae, ct, ad, dt, ig, pa, th [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Therapy, Intragastric Drug Administration, Parenteral Drug Administration, Therapy]
27	exp unsaturated fatty acid/ct, dt, pa, th [Clinical Trial, Drug Therapy, Parenteral Drug Administration, Therapy]
28	exp fat intake/ae, ad, dt [Adverse Drug Reaction, Drug Administration, Drug Therapy]
29	exp enteric feeding/
30	exp parenteral nutrition/
31	exp artificial milk/
32	exp breast milk/
33	exp fortified food/
34	exp elemental diet/
35	exp baby food/
36	(breast milk or human milk).tw.
37	formula.tw.
38	PUFA supplement*.tw.
39	feed* regimen*.tw.
40	(protein* adj2 concentration*).tw.
41	probiotic\$.tw.
42	parenteral*.tw.
43	enteral*.tw.
44	maternal milk.tw.
45	multinutrient supplement*.tw.

1	
2	
3	
4	
5	
6	
7	
8	
9	
10	
11	
12	
13	
14	
15	
16	
17	
18	
19	
20	
21	
22	
23	
24	
25	
26	
27	
28	
29	
30	
31	
32	
33	
34	
35	
36	
37	
38	
39	
40	
41	
42	
43	
44	
45	
46	
47	
48	
49	
50	
51	
52	
53	
54	
55	
56	
57	
58	
59	
60	
46	(breast fed or breastfed).tw.
47	prebiotic*.tw.
48	diet* supplement*.tw.
49	nutrient enriched.tw.
50	Docosahexaenoic Acid*.tw.
51	arachidonic acid*.tw.
52	(glutamine adj2 supplement*).tw.
53	(taurine adj2 supplement*).tw.
54	(calcium adj2 supplement*).tw.
55	palm olein.tw.
56	palmitic acid.tw.
57	(fortification or fortified).tw.
58	fatty acids.tw.
59	supplement* feed*.tw.
60	complementary feed*.tw.
61	nutrition*.tw.
62	Hydrolysed liquid.tw.
63	Hydrolyzed liquid.tw.
64	gamma-linoleic acid.tw.
65	(diet* adj3 protein*).tw.
66	or/21-65
67	20 and 66
68	Clinical Trial/
69	Randomized Controlled Trial/
70	exp randomization/
71	Single Blind Procedure/
72	Double Blind Procedure/
73	Crossover Procedure/
74	Placebo/
75	Randomized controlled trial\$.tw.
76	Rct.tw.
77	random allocation.tw.
78	randomly.tw.
79	randomly allocated.tw.
80	allocated randomly.tw.
81	(allocated adj2 random).tw.
82	Single blind\$.tw.
83	Double blind\$.tw.
84	((treble or triple) adj blind\$.tw.
85	placebo\$.tw.
86	prospective study/
87	or/68-86
88	case study/
89	case report.tw.
90	abstract report/ or letter/
91	or/88-90
92	87 not 91
93	67 and 92

## References

1. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014;384(9946):857-68. doi: 10.1016/S0140-6736(14)60932-6
2. Assessing Growth Using the WHO Growth Charts [Available from: [https://www.cdc.gov/nccdphp/dnpao/growthcharts/who/using/assessing\\_growth.htm](https://www.cdc.gov/nccdphp/dnpao/growthcharts/who/using/assessing_growth.htm).
3. Growth reference 5-19 years World Health Organization [updated January 16, 2019; cited 2019 January 16]. Available from: [https://www.who.int/growthref/who2007\\_bmi\\_for\\_age/en/](https://www.who.int/growthref/who2007_bmi_for_age/en/) accessed May 05 2019.
4. Fryar CD, Gu Q, Ogden CL, et al. Anthropometric Reference Data for Children and Adults: United States, 2011-2014. *Vital Health Stat* 3 2016(39):1-46.
5. Zimmet P, George K, Alberti MM, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatr Diabetes* 2007;8(5):299-306. doi: DOI 10.1111/j.1399-5448.2007.00271.x
6. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-ray absorptiometry body composition reference values from NHANES. *PLoS One* 2009;4(9) doi: ARTN e703810.1371/journal.pone.0007038
7. McCarthy HD, Cole TJ, Fry T, et al. Body fat reference curves for children. *Int J Obes* 2006;30(4):598-602. doi: 10.1038/sj.ijo.0803232
8. Butte NF, Hopkinson JM, Wong WW, et al. Body composition during the first 2 years of life: An updated reference. *Pediatr Res* 2000;47(5):578-85. doi: Doi 10.1203/00006450-200005000-00004
9. Addo OY, Himes JH. Reference curves for triceps and subscapular skinfold thicknesses in US children and adolescents. *Am J Clin Nutr* 2010;91(3):635-42. doi: 10.3945/ajcn.2009.28385
10. Wells JC, Williams JE, Chomtho S, et al. Body-composition reference data for simple and reference techniques and a 4-component model: a new UK reference child. *Am J Clin Nutr* 2012;96(6):1316-26. doi: 10.3945/ajcn.112.036970
11. Falkner B, Daniels SR, Loggie JMH, et al. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A Working Group Report from the National High Blood Pressure Education Program. *Pediatrics* 1996;98(4):649-58.
12. Jackson LV, Thalange NKS, Cole TJ. Blood pressure centiles for Great Britain. *Arch Dis Child* 2007;92(4):298-303. doi: 10.1136/adc.2005.081216
13. Cook S, Auinger P, Huang TT. Growth curves for cardio-metabolic risk factors in children and adolescents. *J Pediatr* 2009;155(3):S6 e15-26. doi: 10.1016/j.jpeds.2009.04.051
14. Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4-19 years: Data from the third National Health and Nutrition Examination Survey. *Prev Med* 1998;27(6):879-90. doi: DOI 10.1006/pmed.1998.0376
15. criterion. A. 2. Classification and Diagnosis of Diabetes Diabetes Care American Diabetes Association; 2015 [updated 2015 Jan. American Diabetes Association ]. Available from: [http://care.diabetesjournals.org/content/38/Supplement\\_1/S8](http://care.diabetesjournals.org/content/38/Supplement_1/S8) accessed Nov 27 2017.
16. The Australian Cerebral Palsy Register Group. Australian cerebral palsy register report 2016 Cerebral Palsy Alliance [Available from: [https://www.cpreregister.com/pubs/pdf/ACPR-Report\\_Web\\_2016.pdf](https://www.cpreregister.com/pubs/pdf/ACPR-Report_Web_2016.pdf).

17. Palisano RJ, Rosenbaum P, Bartlett D, et al. Content validity of the expanded and revised Gross Motor Function Classification System. *Dev Med Child Neurol* 2008;50(10):744-50. doi: 10.1111/j.1469-8749.2008.03089.x
18. Doyle LW, Roberts G, Anderson PJ, et al. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. *J Pediatr* 2010;156(1):49-U84. doi: 10.1016/j.jpeds.2009.07.013
19. IAPB, VISION 2020, WHO. Global Initiative for the elimination of avoidable blindness- Action plan 2006-2011 [Available from: [http://www.who.int/blindness/Vision2020\\_report.pdf](http://www.who.int/blindness/Vision2020_report.pdf).
20. International Council of Ophthalmology. Visual standards- Aspects and ranges of vision loss with emphasis on population surveys 2002 [Available from: <http://www.icoph.org/downloads/visualstandardsreport.pdf>.
21. American Foundation for the Blind. Key definitions of statistical terms- vision terms 2017 [Available from: <http://www.afb.org/info/blindness-statistics/key-definitions-of-statistical-terms/25>.
22. WHO. Prevention of blindness and deafness- hearing loss grades [Available from: [http://www.who.int/pbd/deafness/hearing\\_impairment\\_grades/en/](http://www.who.int/pbd/deafness/hearing_impairment_grades/en/).
23. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev Med Child Neurol* 2010;52(3):232-37. doi: 10.1111/j.1469-8749.2009.03544.x
24. Siqueira CM, Gurgel-Giannetti J. Poor school performance: an updated review. *Rev Assoc Med Bras (1992)* 2011;57(1):78-87.



# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	n/a

## 1 Registration

2  
3  
4 [#2](#) If registered, provide the name of the registry (such as 2  
5 PROSPERO) and registration number  
6  
7  
8

## 9 Authors

10  
11  
12  
13 Contact [#3a](#) Provide name, institutional affiliation, e-mail address of all 1  
14 protocol authors; provide physical mailing address of  
15 corresponding author  
16  
17  
18

19  
20 Contribution [#3b](#) Describe contributions of protocol authors and identify the 16  
21 guarantor of the review  
22  
23  
24

## 25 Amendments

26  
27  
28  
29 [#4](#) If the protocol represents an amendment of a previously n/a  
30 completed or published protocol, identify as such and list  
31 changes; otherwise, state plan for documenting important  
32 protocol amendments  
33  
34  
35  
36  
37

## 38 Support

39  
40  
41  
42 Sources [#5a](#) Indicate sources of financial or other support for the review 15  
43  
44

45 Sponsor [#5b](#) Provide name for the review funder and / or sponsor 15  
46  
47

48 Role of sponsor or [#5c](#) Describe roles of funder(s), sponsor(s), and / or institution(s), 15  
49 funder if any, in developing the protocol  
50  
51  
52

## 53 Introduction

54  
55  
56 Rationale [#6](#) Describe the rationale for the review in the context of what is 4-5  
57  
58  
59

1		already known	
2			
3			
4	Objectives	<a href="#">#7</a> Provide an explicit statement of the question(s) the review	6
5			
6		will address with reference to participants, interventions,	
7			
8		comparators, and outcomes (PICO)	
9			
10			
11	<b>Methods</b>		
12			
13			
14	Eligibility criteria	<a href="#">#8</a> Specify the study characteristics (such as PICO, study	6-8
15			
16		design, setting, time frame) and report characteristics (such	
17			
18		as years considered, language, publication status) to be	
19			
20		used as criteria for eligibility for the review	
21			
22			
23			
24	Information	<a href="#">#9</a> Describe all intended information sources (such as electronic	8
25			
26	sources	databases, contact with study authors, trial registers or other	
27			
28		grey literature sources) with planned dates of coverage	
29			
30			
31			
32	Search strategy	<a href="#">#10</a> Present draft of search strategy to be used for at least one	Appendix
33			
34		electronic database, including planned limits, such that it	4
35			
36		could be repeated	
37			
38			
39	Study records -	<a href="#">#11a</a> Describe the mechanism(s) that will be used to manage	9
40			
41	data management	records and data throughout the review	
42			
43			
44			
45	Study records -	<a href="#">#11b</a> State the process that will be used for selecting studies (such	8
46			
47	selection process	as two independent reviewers) through each phase of the	
48			
49		review (that is, screening, eligibility and inclusion in meta-	
50			
51		analysis)	
52			
53			
54			
55	Study records -	<a href="#">#11c</a> Describe planned method of extracting data from reports	8-9
56			
57	data collection	(such as piloting forms, done independently, in duplicate),	
58			Appendix
59			
60			

1	process		any processes for obtaining and confirming data from	3
2			investigators	
3				
4				
5				
6	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	6-8
7			(such as PICO items, funding sources), any pre-planned data	
8			assumptions and simplifications	Appendix
9				1-2
10				
11				
12				
13				
14	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	7-8
15	prioritization		including prioritization of main and additional outcomes, with	
16			rationale	
17				
18				
19				
20				
21				
22	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	9
23	individual studies		individual studies, including whether this will be done at the	
24			outcome or study level, or both; state how this information	
25			will be used in data synthesis	
26				
27				
28				
29				
30				
31				
32	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be quantitatively	10
33			synthesised	
34				
35				
36				
37	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	10
38			planned summary measures, methods of handling data and	
39			methods of combining data from studies, including any	
40			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
41				
42				
43				
44				
45				
46				
47	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	11
48			sensitivity or subgroup analyses, meta-regression)	
49				
50				
51				
52	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the type	11
53			of summary planned	
54				
55				
56				
57				
58	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	n/a
59				
60				

1 publication bias across studies, selective reporting within  
2  
3 studies)  
4

5  
6 Confidence in [#17](#) Describe how the strength of the body of evidence will be n/a  
7  
8 cumulative assessed (such as GRADE)  
9  
10 evidence  
11  
12

13 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution  
14 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool  
15  
16 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

# BMJ Open

## Sex-specific effects of nutritional supplements in infants born early or small: Protocol for an individual participant data meta-analysis (ESSENCE IPD-MA)

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2019-033438.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Nov-2019
Complete List of Authors:	Lin, Luling; The University of Auckland Liggins Institute, Crowther, Caroline; The University of Auckland Liggins Institute Gamble, Greg; The University of Auckland Liggins Institute Bloomfield, Frank; The University of Auckland Liggins Institute Harding, Jane; University of Auckland Liggins Institute
<b>Primary Subject Heading</b>:	Paediatrics
Secondary Subject Heading:	Paediatrics, Nutrition and metabolism
Keywords:	Preterm, Small-for-gestational-age, Development, Metabolic, Individual participant data meta-analysis

SCHOLARONE™  
Manuscripts

1  
2  
3  
4 1 **Sex-specific effects of nutritional supplements in infants born**  
5  
6 2 **early or small: Protocol for an individual participant data meta-**  
7  
8 3 **analysis (ESSENCE IPD-MA)**  
9

10  
11 4  
12  
13 5  
14  
15 6 Luling Lin (0000-0002-8448-1504)<sup>1</sup>, <luling.lin@auckland.ac.nz>

16  
17  
18 7 Caroline A. Crowther<sup>1</sup>, <c.crowther@auckland.ac.nz>

19  
20 8 Gregory D. Gamble (0000-0003-0412-3203)<sup>1</sup>, <gd.gamble@auckland.ac.nz>

21  
22 9 Frank H. Bloomfield<sup>1</sup>, <f.bloomfield@auckland.ac.nz>

23  
24  
25 10 Jane E. Harding (0000-0003-2697-1422)<sup>1</sup>, <j.harding@auckland.ac.nz>

26  
27 11 for the **ESSENCE IPD-MA Group**<sup>2</sup>

28  
29  
30 12 <sup>1</sup> Liggins Institute, University of Auckland, Auckland, New Zealand

31  
32 13 <sup>2</sup> Membership of the ESSENCE IPD-MA Group is listed in the Contribution section

33  
34 14

35  
36  
37 15 Corresponding author

38  
39 16 Jane E. Harding

40  
41 17 Liggins Institute, University of Auckland

42  
43  
44 18 Building 503, Level 2, 85 Park Road, Auckland P Private Bag 92019, Auckland 1142, New  
45  
46 19 Zealand

47  
48 20 E-mail: j.harding@auckland.ac.nz

49  
50 21 Telephone: +6499236439

51  
52  
53 22

54  
55 23 **Word count: 2846**  
56  
57  
58  
59  
60

## 24 **ABSTRACT**

### 25 **Introduction**

26 Preterm and small for gestational age (SGA) infants are at increased risk of poor growth,  
27 disability and delayed development. While growing up they are also at increased risk of  
28 obesity, diabetes and later heart disease. The risk of such adverse outcomes may be altered by  
29 how preterm and SGA infants are fed after birth. Faltering postnatal growth is common due  
30 to failure to achieve recommended high energy and protein intakes, and thus preterm and  
31 SGA infants are often provided with supplemental nutrition soon after birth. Enhanced  
32 nutrition has been associated with improved early growth and better cognitive development.  
33 However, limited evidence suggests that faster growth may increase the risk for later  
34 adiposity, metabolic and cardiovascular disease, and that such risks may differ between girls  
35 and boys.

### 36 **Methods and analysis**

37 We will search OvidMedline, Embase, Cochrane CENTRAL, Cochrane Database of  
38 Systematic Reviews, controlled-trials.com, clinicaltrials.gov and anzctr.org.au for  
39 randomised trials that studied the effects of macronutrient supplements for preterm and SGA  
40 infants on i) developmental and metabolic and ii) growth outcomes after hospital discharge.  
41 The outcomes will be i) cognitive impairment and metabolic risk (co-primary) and ii) body  
42 mass index. Individual participant data (IPD) from all available trials will be included using  
43 an intention-to-treat approach. A one-stage procedure for IPD meta-analysis (MA) will be  
44 used, accounting for clustering of participants within studies. Exploratory subgroup analyses  
45 will further investigate sources of heterogeneity, including sex and size of infants, different  
46 timing, duration and type of supplements.

47 **Ethics and dissemination:** This IPD-MA is approved by the University of Auckland Human  
48 Participants Ethics Committee (reference number: 019874). Individual studies have approval  
49 from relevant local ethics committees. Results will be disseminated in a peer-reviewed  
50 journal and presented at international conferences.

51 **PROSPERO registration number:** CRD42017072683

52



1  
2  
3 **53 Strengths and limitations of this study**  
4

- 5 54 • This IPD-MA will synthesise data from multiple randomised clinical trials using  
6 uniformly defined relevant outcomes for all available trials.  
7 55  
8 56 • Subgroup analyses may allow detection of potential sex differences that could not be  
9 achieved through aggregate analyses.  
10 57  
11 58 • This IPD-MA will explore the interactions between treatment and participant-level  
12 characteristics.  
13 59  
14 60 • A potential limitation is that the analyses planned will depend on obtaining the  
15 relevant individual participant data.  
16 61  
17 62 • There may be considerable heterogeneity as interventions are likely to be very varied  
18 and the trials performed over several decades.  
19 63  
20  
21  
22  
23 64  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

## 65 INTRODUCTION

66 Infants born preterm or small for gestational age (SGA) are at increased risk of poor growth,  
67 disability and delayed development.<sup>1-3</sup> As adults, they are at increased risk of obesity,  
68 diabetes and later heart disease.<sup>4</sup> How infants born small are fed after birth may alter the risk  
69 of these adverse outcomes. Providing preterm and SGA infants with enhanced nutrition soon  
70 after birth is associated with improved early growth and better cognitive development,<sup>5-7</sup> but  
71 observational data suggest that early faster growth may increase the risk for later adiposity,  
72 metabolic and cardiovascular disease.<sup>8</sup>

73  
74 It has been recognised for centuries that girls and boys grow differently, experience different  
75 metabolic and endocrine milieux, and have different cognitive and health outcomes. Little  
76 attention has been paid to improving outcomes following preterm birth by treating girls and  
77 boys differently, although it is well recognised that preterm boys compared to girls have  
78 higher mortality and morbidity,<sup>9</sup> and are more likely to have adverse developmental and  
79 educational outcomes.<sup>10</sup> There is substantial evidence that perinatal insults can result in  
80 different adult phenotypes in males and females.<sup>11</sup> For example, animal studies across many  
81 different species after a wide variety of prenatal insults show that males are more likely than  
82 females to exhibit adverse effects such as impaired renal function, hypertension, insulin  
83 resistance, altered hypothalamic-pituitary-adrenal (HPA) axis function and altered growth in  
84 later life.<sup>12</sup> The reasons for this sex difference in vulnerability to early environmental  
85 perturbations are not well understood, but may include faster growth and hence greater  
86 substrate demands in males, altered tempo of maturation, different exposure to sex steroids  
87 and sex-specific epigenetic mechanisms.<sup>12</sup>

88  
89 There is limited evidence from human studies that these effects may also be important in  
90 babies. Preterm boys have been reported to have higher protein and calorie requirements to  
91 maintain growth than girls.<sup>13</sup> Preterm boys also were more vulnerable than girls to the  
92 adverse effects of delayed early nutrition<sup>14</sup>, whereas enhanced nutrition improved cognitive  
93 outcomes for preterm boys, but had no effect on girls.<sup>15</sup> Unfortunately, most clinical studies  
94 have not reported findings separately by sex and are not adequately powered to do so.  
95 Further, because the majority of animal experiments are done in polytocous species, prenatal  
96 and postnatal sex effects cannot be separated in mixed-sex litters. There is little reliable

1  
2  
3 97 evidence about how best to feed preterm babies to optimise both short- and long-term health  
4 98 outcomes, and almost none about targeting nutrition by sex.

5  
6 99

## 8 100 **Hypotheses**

9 101 The effects of early nutritional supplements on post-discharge development, markers of  
10 102 metabolic risk and growth are different in girls and boys.

11  
12 103

## 13 14 104 **Need for individual participant data meta-analysis**

15 105 Systematic reviews using aggregate data meta-analyses are limited due to within-trial  
16 106 variation in gestational age of the infants at birth, co-morbidities of the infant, starting time  
17 107 and duration of the intervention, macronutrient content of the intervention and control groups.  
18 108 Outcomes within aggregate meta-analyses such as cerebral palsy, motor dysfunction or  
19 109 hearing loss also include a range of severity of disability. Aggregate meta-analyses tend to  
20 110 vary in completeness and in the definitions used for the outcomes. Not all trials combine the  
21 111 same outcomes in composite outcomes or use the same measures of neuro-developmental  
22 112 outcome. Few trials describe multiple subgroups, making meta-analysis of data almost  
23 113 impossible. Importantly, few trials to date have provided the sex of the infant as a subgroup  
24 114 variable.

25  
26 115

27 116 One method to ameliorate some of the limitations of aggregate data meta-analysis is to  
28 117 combine the large volume of individual trial data available to perform an individual  
29 118 participant data (IPD) meta-analysis (MA). The estimates of treatment effects with an IPD-  
30 119 MA often differ from aggregate meta-analyses.<sup>16</sup> IPD-MA allows the inclusion of additional  
31 120 unpublished data provided by the trialists, and allows consistent re-categorisation of  
32 121 definitions of outcomes and populations in order to answer the clinical questions of interest.  
33 122 Further, IPD-MA may allow more detailed meta-analysis of key outcomes, taking into  
34 123 account both subject-level and study-level sources of heterogeneity in treatment effects.  
35 124 Thus, IPD-MA offers the potential to help clarify the sex-specific effects of early  
36 125 macronutrient supplements provided to preterm and SGA infants.

37  
38 126

39  
40 127

## 128 **METHODS AND ANALYSIS**

129 This study will use an IPD-MA approach and follow the Preferred Reporting Items for  
130 Systematic Reviews and Meta-Analyses (PRISMA) guidelines.<sup>17</sup>

131

### 132 **Aims**

133 To assess, using IPD-MA, the effects of macronutrient supplements in nutrition of preterm  
134 and SGA infants on developmental, metabolic and growth outcomes after hospital discharge,  
135 and in particular, whether these effects differ in girls and boys.

136

### 137 **Criteria for inclusion and exclusion**

138 We will include published and unpublished randomised and quasi-randomised trials without  
139 restrictions on date of publication or language. Trials that studied infants born preterm (< 37  
140 weeks' gestation) or born small (birthweight <2.5 kg or < 10<sup>th</sup> centile for gestational age) and  
141 in which the intervention was intended to increase the intake of one or more macronutrients  
142 (protein, carbohydrate, fat, energy content or protein to energy ratio), with the primary aim of  
143 improving growth and development will be included.

144 Interventions can be enteral or parenteral or a combination, commence at any time during the  
145 hospitalisation or after discharge from hospital, and must be provided for a minimum  
146 duration of one week. Trials that report on comparisons between un-supplemented nutrition  
147 and supplemented nutrition with parenteral supplements, human breast milk supplements,  
148 formula milk or other macronutrients will be eligible for inclusion, for example: 1) Parenteral  
149 formulation A versus parenteral formulation B with different macronutrient composition; 2)  
150 Human milk (mother's own or donor) versus supplemented human milk (mother's own or  
151 donor); 3) Human milk (mother's own or donor) versus formula milk (term or preterm); 4)  
152 Supplemented human milk (mother's own or donor) versus formula (term or preterm); 5)  
153 Supplemented human milk A (mother's own or donor) versus supplemented human milk B  
154 (mother's own or donor); 6) Formula A versus formula B with different macronutrient  
155 composition (including preterm versus term formula, brand A versus brand B). We will  
156 exclude trials that examine the timing of the introduction of nutrition (early versus delayed  
157 feeding); that compare macronutrients of different composition (e.g. different types of lipids  
158 or proteins); studies whose outcomes focus on gastrointestinal development rather than  
159 growth and development; and studies reporting on variations in composition of

1  
2  
3 160 micronutrients (including sodium, potassium, calcium, phosphorus, vitamins, other minerals,  
4 161 amino acids, fatty acids).

7 162 Outcome data must be reported beyond term equivalent age (> 37 weeks' post-menstrual age)  
8  
9 163 or following discharge from hospital after birth. Where the data are available, the outcomes  
10  
11 164 will be categorised and evaluated in toddlers (less than 3 years), childhood (3 to 8 years),  
12  
13 165 adolescence (9 to 18 years) and adulthood (more than 18 years).

15 166 We plan to report the findings as two reviews, one reporting developmental and metabolic  
16  
17 167 outcomes, and the other reporting growth outcomes.

18  
19 168 1. Developmental and metabolic outcomes:

21 169 The co-primary outcomes will be 1) Cognitive impairment: below -1 SD on standard tests of  
22  
23 170 development (toddlers) or cognition/intelligence quotient (later ages) and 2) Metabolic risk  
24  
25 171 (*See Appendix 1 for definitions*): any of overweight/obese; increased waist circumference;  
26  
27 172 increased fat mass or fat mass percentage; elevated plasma triglyceride concentrations; low  
28  
29 173 high-density lipoprotein (HDL) concentrations; elevated low-density lipoprotein (LDL)  
30  
31 174 concentrations; elevated fasting plasma glucose concentrations; insulin resistance; impaired  
32  
33 175 glucose tolerance; diagnosis of type 2 diabetes; high blood pressure and impaired flow-  
34  
35 176 mediated vasodilatation.

36 177 The secondary outcomes will be (*See Appendix 2 for definitions*): 1) Composite of survival  
37  
38 178 free of any disability (including death, cerebral palsy, motor development delay or  
39  
40 179 impairment, cognition/intelligence delay or impairment, language delay, visual impairment,  
41  
42 180 hearing impairment); 2) Cognition/intelligence delay or impairment; 3)  
43  
44 181 Cognition/intelligence scores; 4) Motor delay or impairment; 5) Motor scores; 6) Cerebral  
45  
46 182 palsy (any); 7) Severity of cerebral palsy; 8) Visual impairment; 9) Hearing impairment; 10)  
47  
48 183 School performance; 11) Measures of psychological well-being; 12) Metabolic outcomes:  
49  
50 184 waist circumference, overweight/obese, type-2 diabetes, blood lipid concentrations  
51  
52 185 (triglycerides, HDL, LDL, HDL:LDL), fasting blood glucose concentration, insulin  
53  
54 186 concentration, insulin resistance, glucose tolerance, IGF-1 concentration; 13) Cardiovascular  
55  
56 187 risk outcomes: blood pressure (systolic blood pressure (SBP), diastolic blood pressure (DBP),  
57  
58 188 mean arterial pressure (MAP)), flow-mediated vasodilatation, measures of sympathetic and  
59  
60 189 parasympathetic tone, cardiac size and structure; 14) Brain development: whole brain, white  
190  
191 matter and grey matter volumes and volumes of individual brain regions, brain maturation

1  
2  
3 191 measured using MRI (white matter tracts, measures of diffusivity, myelination, surface  
4 192 folding), functional brain imaging; 15) Health outcomes: allergies (eczema, asthma,  
5 193 hayfever), respiratory function, hospitalisation (duration), health care utilisation; 16)  
6 194 Nutrition: feeding tolerance; intake (milk, energy), appetite, breast feeding; 17) Death  
7 195 (neonatal or later death up to the time of follow-up and cause of death); 18) Quality of life;  
8 196 19) General health and use of healthcare resources; 20) Adverse Events; 21) Cost.

## 14 197 2. Growth outcomes:

16 198 The primary outcome will be body mass index (BMI) in childhood (3 to 8 years).

18 199 The secondary outcomes will be (1) Growth assessments: weight (raw data and z scores),  
20 200 length/height (raw data and z scores), head circumference (raw data and z scores), Ponderal  
21 201 Index, body mass index (BMI), body composition (fat mass, fat free mass, measured by  
22 202 bioimpedance or DEXA or skinfold thickness or other method); (2) Bone development: bone  
23 203 mineral content, volumetric bone mineral density, bone fractures; (3) Nutrition: feeding  
24 204 tolerance; intake (protein, energy); appetite; breastfeeding and duration.

25 205

## 30 206 **Search strategy**

32 207 We will search OvidMedline, Embase, Cochrane Library Central Registry of Controlled  
33 208 Trials (CENTRAL), and Cochrane Database of Systematic Review from inception to identify  
34 209 eligible trials. We will also search for registered trials in Current Controlled Trials  
35 210 ([www.controlled-trials.com](http://www.controlled-trials.com)), Clinical Trials ([www.clinicaltrials.gov](http://www.clinicaltrials.gov)) and Australian and  
36 211 New Zealand Clinical Trials Registry ([www.anzctr.org.au](http://www.anzctr.org.au)) to identify eligible ongoing  
37 212 studies. The full search strategy and search terms are available as online supplementary  
38 213 material (Appendix 1). Experts in the field and trialists will be asked if they can identify other  
39 214 published or ongoing trials. Potentially eligible trials that are not yet completed will not be  
40 215 included in this IPD-meta analysis, but will be noted for inclusion in future updates.

41 216

## 46 217 **Identify studies**

48 218 The eligibility of trials will be assessed by two researchers. Discrepancies will be resolved by  
49 219 discussion. If IPD are unavailable from any eligible trial it will be included in the IPD-MA  
50 220 using aggregate data for sensitivity analysis where possible.

51 221

## 222 **Contact Authors**

223 Authors of eligible studies will be invited to join the ESSENCE IPD-MA Collaborative  
224 group. We will identify contact information from the published trials. An initial email will be  
225 sent to the main trial author (corresponding author) providing them with the summary IPD-  
226 MA protocol. Another investigator from the study will be contacted if initial emails fail to  
227 receive a response, followed by phone calls if needed.

## 229 **Quality assessment**

230 We will assess the quality of the eligible trials using the methods specified in the Cochrane  
231 Handbook for Systematic Reviews of Interventions:<sup>18</sup> random sequence generation (selection  
232 bias); allocation concealment (selection bias); blinding of participants, personnel, and  
233 outcome assessment (performance and detection bias); incomplete outcome data (attrition  
234 bias); selective reporting (reporting bias); (6) Other bias (checking for bias due to problems  
235 not covered by (1) to (5) above).

## 237 **Development of the database**

238 We will develop a set of pre-specified and defined variables for IPD-MA at both the  
239 outcome, participant and trial level (Appendix 3). We will seek data on all randomised infants  
240 which will be coded for anonymity (date of birth, study centre); baseline data for narrative  
241 purposes (birthweight, gestational age at birth, plurality, sex); details of the intervention and  
242 comparator (date of randomisation, allocated intervention, type and composition of  
243 intervention and comparator, enteral or parenteral administration, age at start of intervention,  
244 weight at start of intervention, duration of intervention) and the outcomes listed above.

245  
246 Trialists will provide de-identified data in any format which will be recoded as required,  
247 verified and checked for consistency with published data and stored on a secure, password  
248 protected file on the University of Auckland servers. Data will only be accessible by  
249 authorised personnel in the ESSENCE Data Management Group.

250  
251 Methodological details of the individual trials will be cross-checked against published  
252 reports, trial registration (where available) and trial data collection forms. Where  
253 inconsistencies are identified, discussions will be held with individual trial groups to attempt

1  
2  
3 254 to resolve these. Each trial final dataset to be used in the IPD-MA will be returned to the  
4  
5 255 trialists for verification. Trials will then be analysed individually using IPD-MA pre-specified  
6  
7 256 variables and outcomes and the results returned to the trialists for verification. The individual  
8  
9 257 trial datasets will then be combined to form the ESSENCE-IPD dataset and the IPD meta-  
10  
11 258 analysis undertaken.

12 259

### 14 260 **Data synthesis and statistical analysis**

15  
16 261 A detailed statistical analysis plan will be prepared and agreed on by the ESSENCE-IPD  
17  
18 262 team.

19  
20 263 We will use a one-stage approach to the analysis of each outcome so that the IPD from all  
21  
22 264 eligible trials are included in a single model. We will make an assessment of heterogeneity to  
23  
24 265 decide if combining data from trials is appropriate or if heterogeneity, if significant, can be  
25  
26 266 explained.

27 267

28  
29 268 Binary outcomes will be analysed using log binomial regression models and data will be  
30  
31 269 reported as Risk Ratio (RR) with 95% Confidence Intervals (CI) and associated 2-sided p  
32  
33 270 values. Continuous data will be analysed using linear regression models and data will be  
34  
35 271 reported as mean differences (MD) with 95% Confidence Intervals (CI) and associated 2-  
36  
37 272 sided p values.

38 273

39 274 A large number of outcomes are being investigated in this study. This increases the chance of  
40  
41 275 observing false positive results. The overall probability of a type 1 error will be maintained at  
42  
43 276 5% for each review. For the review of developmental and metabolic outcomes, the p value  
44  
45 277 will be split equally between the co-primary outcomes by testing each at  $p = 0.025$ . For the  
46  
47 278 review of growth outcomes,  $p < 0.05$  will denote statistical significance for the primary  
48  
49 279 outcome. No further adjustment for multiplicity is planned for comparisons made in  
50  
51 280 secondary and exploratory analyses.

52 281

53 282 We will explore the effects of the sex of the infants by presenting data separately for each sex  
54  
55 283 as pre-specified subgroups, and by testing a treatment by sex interaction term within the  
56  
57 284 model.

58 285

59  
60



286 Where data are missing, those infants will be removed from the analysis and, where possible,  
287 the reasons for missing data will be explored. It is not proposed to impute missing data since  
288 the assumption of ‘missing at random’ is unlikely to be met. Where there are large amounts  
289 of missing data or trials are unable to provide IPD we will conduct sensitivity analyses to  
290 explore the effect of removing such trials from the analysis.

292 Statistical analyses will be performed using SAS (v.9.4, SAS Institute, Cary, NC, USA).

### 294 **Planned subgroup analysis**

295 Where data are available, we will conduct subgroup analyses to explore whether the effects  
296 of supplements differ between subgroups and test for interaction terms.

- 297 1. Sex of infant (boys vs girls);
- 298 2. Size of infant at birth ( $\leq 1$  kg vs  $>1$  kg at birth);
- 299 3. Size for gestation of the infant ( $\leq 10^{\text{th}}$  centile vs  $> 10^{\text{th}}$  centile);
- 300 4. Gestational age of infant at birth ( $\leq 28$  completed weeks vs 29 to 32 completed weeks vs  
301 33 to 36 weeks).
- 302 5. Timing of supplement:  
303 In hospital nutrition: the intervention was commenced in hospital or on average ended at  
304 42 weeks’ postmenstrual age or earlier;  
305 Post-discharge nutrition: the intervention was commenced after discharge or on average  
306 started at or after 36 weeks’ postmenstrual age;  
307 Both in hospital and post-discharge nutrition: the intervention was commenced in the  
308 hospital and continued post-discharge.
- 309 6. Type of supplement (protein vs carbohydrate vs fat vs multicomponent and their  
310 interactions).
- 311 7. Breast milk vs formula as primary milk feed.
- 312 8. Duration of supplement (1 to 2 weeks vs 3 to 6 weeks vs more than 7 weeks).
- 313 9. Different epochs (commenced up to the year of 2000 vs commenced in or after the year  
314 of 2001).

315

1  
2  
3 316 **Planned sensitivity analyses**  
4

5 317 We will perform sensitivity analyses to assess whether the results are robust to the trial  
6  
7 318 design by excluding trials assessed as high risk of bias.

8  
9 319 Where trials are unable to contribute data to the IPD we will assess the robustness of the  
10  
11 320 inclusion or exclusion of these trials by combining their aggregate data with the IPD.

12  
13 321

14  
15 322 **Patient and Public Involvement**  
16

17  
18 323 It was not appropriate or possible to involve patients or the public in the design, or conduct,  
19  
20 324 or reporting, or dissemination of our research.

21  
22 325  
23

24  
25 326 **DISCUSSION**  
26

27 327 This will be the first IPD-MA to investigate the effects of early macronutrient supplements on  
28  
29 328 preterm and SGA infants. IPD meta-analysis has been described as the ‘gold standard’ of  
30  
31 329 systematic review methodology as it allows for more powerful and flexible analysis of both  
32  
33 330 subgroups and outcomes.<sup>19</sup> This IPD-MA, using existing data from the individual trials, may  
34  
35 331 reveal the sex-specific effects of macronutrient supplement on preterm and SGA infants, and  
36  
37 332 will allow assessment of important interactions that cannot be tested in standard, aggregate  
38  
39 333 data meta-analysis.

40  
41 334

42 335 **ETHICS AND DISSEMINATION**  
43

44 336 The shared data will be de-identified, the data files will be transferred by secure means, and  
45  
46 337 stored in a secure password protected area on an Auckland University server.

47  
48 338 Final results will be presented to the ESSENCE IPD-MA collaborators prior to publication  
49  
50 339 and public dissemination. Results of the study will be published in peer-reviewed journals  
51  
52 340 and presented at national and international conferences.

53  
54 341 The ESSENCE-IPD project has been approved by University of Auckland Human  
55  
56 342 Participants Ethics Committee (reference number: 019874). Individual studies have approval  
57  
58 343 from relevant local ethics committees.

59  
60 344

345 **REFERENCE**

- 346 1. Embleton NE, Pang N, Cooke RJ. Postnatal malnutrition and growth retardation: an  
347 inevitable consequence of current recommendations in preterm infants? *Pediatrics*  
348 2001;107(2):270-3.
- 349 2. Hay WW, Jr. Nutritional requirements of extremely low birthweight infants. *Acta Paediatr*  
350 *Suppl* 1994;402:94-9.
- 351 3. Cooke RW. Conventional birth weight standards obscure fetal growth restriction in  
352 preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2007;92(3):F189-92. doi:  
353 10.1136/adc.2005.089698
- 354 4. Luu TM, Katz SL, Leeson P, et al. Preterm birth: risk factor for early-onset chronic  
355 diseases. *Can Med Assoc J* 2016;188(10):736-40. doi: 10.1503/cmaj.150450
- 356 5. Lucas A, Fewtrell MS, Morley R, et al. Randomized outcome trial of human milk  
357 fortification and developmental outcome in preterm infants. *Am J Clin Nutr*  
358 1996;64(2):142-51.
- 359 6. Lucas A, Morley R, Cole TJ. Randomised trial of early diet in preterm babies and later  
360 intelligence quotient. *BMJ* 1998;317(7171):1481-7.
- 361 7. Lucas A, Morley R, Cole TJ, et al. A randomised multicentre study of human milk versus  
362 formula and later development in preterm infants. *Arch Dis Child Fetal Neonatal Ed*  
363 1994;70(2):F141-6.
- 364 8. Peacock JL, Marston L, Marlow N, et al. Neonatal and infant outcome in boys and girls  
365 born very prematurely. *Pediatr Res* 2012;71(3):305-10. doi: 10.1038/pr.2011.50
- 366 9. Glass HC, Costarino AT, Stayer SA, et al. Outcomes for extremely premature infants.  
367 *Anesth Analg* 2015;120(6):1337-51. doi: 10.1213/ANE.0000000000000705
- 368 10. Ong KK, Kennedy K, Castaneda-Gutierrez E, et al. Postnatal growth in preterm infants  
369 and later health outcomes: a systematic review. *Acta Paediatr* 2015;104(10):974-86.  
370 doi: 10.1111/apa.13128
- 371 11. Perera F, Herbstman J. Prenatal environmental exposures, epigenetics, and disease.  
372 *Reprod Toxicol* 2011;31(3):363-73. doi: 10.1016/j.reprotox.2010.12.055
- 373 12. Aiken CE, Ozanne SE. Sex differences in developmental programming models.  
374 *Reproduction* 2013;145(1):R1-13. doi: 10.1530/REP-11-0489
- 375 13. Alur P. Sex differences in nutrition, growth, and metabolism in preterm infants. *Front*  
376 *Pediatr* 2019;7 doi: 10.3389/fped.2019.00022

- 1  
2  
3 377 14. Poindexter BB, Langer JC, Dusick AM, et al. Early provision of parenteral amino acids in  
4 378 extremely low birth weight infants: relation to growth and neurodevelopmental  
5 379 outcome. *J Pediatr* 2006;148(3):300-05. doi: 10.1016/j.jpeds.2005.10.038 [published  
6 380 Online First: 2006/04/18]
- 7 381 15. Lin L, Amissah E, Gamble GD, et al. Impact of macronutrient supplements for children  
8 382 born preterm or small for gestational age on developmental and metabolic outcomes:  
9 383 A systematic review and meta-analysis. *PLoS Med* 2019;16(10):e1002952. doi:  
10 384 10.1371/journal.pmed.1002952 [published Online First: 2019/10/31]
- 11 385 16. Smith CT, Marcucci M, Nolan SJ, et al. Individual participant data meta-analyses  
12 386 compared with meta-analyses based on aggregate data. *Cochrane Db Syst Rev*  
13 387 2016(9):MR000007. doi: 10.1002/14651858.MR000007.pub3
- 14 388 17. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews  
15 389 and meta-analyses: the PRISMA statement. *PLoS Med* 2009;6(7):e1000097. doi:  
16 390 10.1371/journal.pmed.1000097 [published Online First: 2009/07/22]
- 17 391 18. Higgins JPT, Green S (editors), The Cochrane Collaboration. Cochrane handbook for  
18 392 systematic reviews of interventions version 5.1.0 [updated March 2011] 2011 [cited  
19 393 09/04/2019 09/04/2019]. Available from: [www.cochrane-handbook.org](http://www.cochrane-handbook.org) accessed Apr  
20 394 9 2019.
- 21 395 19. Tierney JF, Vale C, Riley R, et al. Individual participant data (IPD) meta-analyses of  
22 396 randomised controlled trials: guidance on their use. *PLoS Med* 2015;12(7):e1001855  
23 397 doi: 10.1371/journal.pmed.1001855
- 24 398

1  
2  
3 399 **DECLARATIONS**  
4

5 400 **Acknowledgements**

7 401 We would like to acknowledge Dr Julie Brown for help with developing the draft protocol  
8  
9 402 and search strategies, Mariana Muelbert for her help with the communication with trialists  
10  
11 403 from Brazil, and Laura Galante for her help with the communication with trialists from Italy.  
12

13  
14 404 **Ethical approval and consent to participate**

15 405 The ESSENCE-IPD project has been approved by University Of Auckland Human  
16  
17 406 Participants Ethics Committee.

18  
19 407 Participants in the individual trials have previously given informed consent to participate in  
20  
21 408 their respective trials. The data for these projects are to be used for the purpose for which  
22  
23 409 they were originally collected and are available through an agreement between all trialists of  
24  
25 410 the collaborative group. These trialists remain custodians of their original trial data at all  
26  
27 411 times. A data sharing agreement will be signed by a representative of the institution that owns  
28  
29 412 the data and a representative of University of Auckland.  
30

31 413 **Consent for publication**

32 414 Not applicable  
33

34 415 **Availability of data and material**

35 416 Not applicable  
36  
37  
38

39 417 **Competing interests**

40 418 The authors declare that they have no competing interests.  
41  
42

43 419 **Funding**

44 420 The ESSENCE-IPD project is supported by the Health Research Council (HRC) of New  
45  
46 421 Zealand (16/605). The analysis will be included as part of the doctoral thesis of Luling Lin,  
47  
48 422 who is supported by Agnes Paykel PhD Scholarship. None of the funders are involved in any  
49  
50 423 other aspect of the project, such as the design of the protocol and analysis plan, the collection  
51  
52 424 and analysis of the data, or the interpretation and publication of the study results.  
53

54 425 **Authors' contributions**

55 426 The Chair of the ESSENCE-IPD Project Team (J.E. Harding) wrote the first draft of the  
56  
57 427 ESSENCE-IPD protocol. L Lin revised the subsequent versions of the ESSENCE-IPD  
58  
59 428 protocol and prepared the initial draft of the manuscript. The ESSENCE-IPD Project Team  
60

1  
2  
3 429 and the ESSENCE-IPD Management Group participated in the protocol development and  
4  
5 430 commented on all drafts of the manuscript. The ESSENCE-IPD Trialist Group participated in  
6  
7 431 the development of the IPD protocol and have read and approved the final draft of the  
8  
9 432 manuscript.

### 10 433 **Contributors**

#### 11 434 **The ESSENCE IPD-MA Group**

12  
13  
14  
15 435 **ESSENCE-IPD Project Team:** This is the project Steering Group which is responsible for  
16  
17 436 the day-to-day management of the IPD. This group has drafted the IPD protocol, will liaise  
18  
19 437 with trialists and prepare the draft publications. J.E. Harding (chair of ESSENCE-IPD  
20  
21 438 project); L Lin; C.A. Crowther; F.H. Bloomfield; and G Gamble.

22  
23 439 **ESSENCE-IPD Management Group:** This group is convened by the Chair of the Project  
24  
25 440 Team and comprises the IPD-MA statistician and data manager who will be responsible for  
26  
27 441 the collection, checking, storage and analyses of data. J.E. Harding (chair of ESSENCE-IPD  
28  
29 442 project); L Lin; C.A. Crowther; and G Gamble.

30 443 **ESSENCE-IPD Trialist Group:** This group includes investigators from all eligible trials  
31  
32 444 who have agreed to share their data for the IPD.

33  
34 445 M Agosti<sup>1</sup>; S.A. Atkinson<sup>2</sup>; A Biasini<sup>3</sup>; R.D.S Da Cunha<sup>4</sup>; N.D. Embleton<sup>5</sup>; M Faraz<sup>2</sup>; M.S  
35  
36 446 Fewtrell<sup>6</sup>; F Lamy Filho<sup>7</sup>; C. Fusch<sup>2,8</sup>; M.L. Gianni<sup>9</sup>; H.G. Kanmaz<sup>10</sup>; W.WK. Koo<sup>11</sup>; I  
37  
38 447 Litmanovitz<sup>12</sup>; A Lucas<sup>13</sup>; C Morgan<sup>14</sup>; K Mukhopadhyay<sup>15</sup>; E Neri<sup>16</sup>; J Picaud<sup>17</sup>; E.V  
39  
40 448 Rafael<sup>18</sup>; P Roggero<sup>9</sup>; A Singhal<sup>19</sup>; K Stroemmen<sup>20</sup>; M.J. Tan<sup>21</sup>; F.M. Tandoi<sup>1</sup>; C.L. Wood<sup>22</sup>;  
41  
42 449 G Zachariassen<sup>23</sup>

43 450 <sup>1</sup> Division of Neonatology and Neonatal Intensive Care Unit, “F. Del Ponte” Hospital,  
44  
45 451 Varese, Italy

46  
47 452 <sup>2</sup> Department of Pediatrics, Faculty of Health Sciences, McMaster University, Hamilton,  
48  
49 453 Ontario, Canada.

50  
51 454 <sup>3</sup> Donor Human Milk Bank Italian Association (AIBLUD), Milan, Italy

52  
53 455 <sup>4</sup> Hospital Universitário da Universidade Federal do Maranhão - Brasil

54  
55 456 <sup>5</sup> Institute of Health and Society, Newcastle University, Newcastle upon Tyne, UK  
56  
57  
58  
59  
60

- 1  
2  
3 457 <sup>6</sup> Childhood Nutrition Research Centre, UCL Great Ormond Street Institute of Child Health,  
4 458 London, UK  
5  
6  
7 459 <sup>7</sup> Departamento de Medicina, Universidade Federal do Maranhão (UFMA), São Luís, MA,  
8 460 Brazil  
9  
10  
11 461 <sup>8</sup> Department of Pediatrics, Nuremberg General Hospital, Paracelsus Medical University,  
12 462 90471 Nuremberg, Germany  
13  
14  
15 463 <sup>9</sup> Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico, via Commenda 12, 20122  
16 464 Milan, Italy  
17  
18  
19 465 <sup>10</sup> Department of Neonatology, NICU, Zekai Tahir Burak Education and Research Hospital,  
20 466 Ankara, Turkey  
21  
22  
23 467 <sup>11</sup> Department of Nutrition and Food Science, Wayne State University, Detroit, MI, USA  
24  
25  
26 468 <sup>12</sup> Department of Neonatology, Meir Medical Center, Kfar Saba, Israel  
27  
28  
29 469 <sup>13</sup> MRC Childhood Nutrition Research Centre, Institute of Child Health, University College  
30 470 London, London, UK  
31  
32  
33 471 <sup>14</sup> Department of Neonatology, Liverpool Women's Hospital, Liverpool, UK  
34  
35  
36 472 <sup>15</sup> Department of Pediatrics, Post Graduate Institute of Medical Education and Research  
37 473 (PGIMER), Chandigarh, India.  
38  
39  
40 474 <sup>16</sup> Department of Psychology, University of Bologna, Bologna, Italy  
41  
42 475 <sup>17</sup> Division of Neonatology, Hôpital de la Croix-Rousse, Lyon, France  
43  
44 476 <sup>18</sup> Departamento de Enfermagem da Universidade Federal do Maranhão, Brasil  
45  
46  
47 477 <sup>19</sup> Department of Nutrition, Institute of Child Health, London, UK  
48  
49 478 <sup>20</sup> Department of Neonatal Intensive Care, Division of Pediatric and Adolescent Medicine,  
50 479 Rikshospitalet, Oslo University Hospital, Oslo, Norway  
51  
52  
53 480 <sup>21</sup> Department of Developmental Paediatrics, Alder Hey Children's NHS Foundation Trust,  
54 481 Liverpool, UK  
55  
56  
57 482 <sup>22</sup> Institute of Genetic Medicine, Newcastle University, Newcastle, UK  
58  
59  
60

1  
2  
3 483 <sup>23</sup> H.C. Andersen Children's Hospital, Odense University Hospital and University of  
4  
5 484 Southern Denmark, Odense, Denmark  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only



1  
2  
3 **Sex-specific effects of nutritional supplements in infants born**  
4 **early or small: protocol for an individual participant data meta-**  
5 **analysis (ESSENCE-IPD)**  
6  
7  
8  
9

10  
11  
12  
13  
14  
15  
16  
17  
18 **Supplement document**  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only

### Appendix 1. Definitions for Primary Outcome of Metabolic Risk

Measurement	Guideline/ Equipment	Age	Abnormal	Notes
Size for gestation at birth	INTERGROWTH 21 Charts <sup>1</sup>	≤ 6 months	≤ 10th centile vs > 10th centile	INTERGROWTH 21 charts for babies younger than 6 months <sup>1</sup>
Overweight/obese	WHO Growth Charts <sup>2,3</sup>	<5 years <sup>2</sup>	Overweight: weight-for-height greater than 2 standard deviations above WHO Child Growth Standards median; Obesity: weight-for-height greater than 3 standard deviations above the WHO Child Growth Standards median.	Charts and tables: WHO child growth standards for children aged under 5 years <sup>2</sup>
		5-19 years <sup>3</sup>	Overweight: BMI-for-age greater than 1 standard deviation above the WHO Growth Reference median; Obesity: greater than 2 standard deviations above the WHO Growth Reference median.	Charts and tables: WHO growth reference for children aged between 5–19 years <sup>2</sup>
Waist Circumference	NHANES 2011-2014 <sup>4</sup>	2- 60 years	≥90 <sup>th</sup> percentile <sup>5</sup>	
Fat mass (FM)	DEXA-NHANES <sup>6</sup>	≥8 years	Fat Mass Index (kg/m <sup>2</sup> ) classification ranges for sex	
	BIA <sup>7</sup>	5-18 years	≥85 <sup>th</sup> percentile (%FM)	
	ADP- BodPod <sup>7</sup>	5-18 years	≥85 <sup>th</sup> percentile (%FM)	
	ADP- PedPod <sup>8</sup>	0.5-24 months	%FM greater than 1 standard deviation above the reference mean	
	skinfolds- NHES II, NHES III, NHANES I, NHANES II and NHANES III <sup>9</sup>	1.5-19 years	≥85 <sup>th</sup> percentile <sup>9</sup>	
	Multicomponent model	0.5- 24 month <sup>8</sup>	%FM greater than 1 standard deviation above the reference mean	

Measurement	Guideline/ Equipment	Age	Abnormal	Notes
		5-20 years <sup>10</sup>	FM greater than 1 standard deviation above the reference mean	Fat mass reference data for males and females by Z-score or percentile <sup>10</sup>
Blood pressure	NHBPEP <sup>11</sup>	1 to 17 years	≥90 <sup>th</sup> centile <sup>5</sup> (age, sex and height specific) Charts and tables: WHO Child growth standards for length/height	Compared with Jackson LV 2007 <sup>12</sup> , although the NHBPEP is older, it contains the appropriate age range and reported the actual numbers at each cut point.
Triglycerides	NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton <sup>13</sup>	4-18 years	≥90 <sup>th</sup> centile <sup>14</sup>	Compared to NHANES III, NCEP, and NGHS, this includes a wider age range.
	NHANES	>18 years	≥150mg/dL (8.3 mmol/L) <sup>13</sup>	
HDL-C	NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton <sup>13</sup>	4-18 years	≤10 <sup>th</sup> centile <sup>14</sup>	Compared to NHANES III, NCEP, and NGHS, this includes a wider age range.
	NHANES <sup>13</sup>	>18 years	<40 mg/dL (2.2 mmol/L) <sup>13</sup> for male <50 mg/dL (2.8 mmol/L) <sup>13</sup> for female	
LDL-C	NHANES III, NHANES 1999–2004, Bogalusa, Muscatine, Fels, and Princeton <sup>13</sup>	4-18 years	≥90 <sup>th</sup> centile <sup>13</sup>	Compared to NHANES III, this includes a wider age range.
	NCEP ATP III	>18 years	>130 mg/dL (7.2 mmol/L) <sup>13</sup>	
Fasting plasma glucose concentration	ADA criterion <sup>15</sup> (increased risk for diabetes or prediabetes)		FPG ≥100 mg/dL (5.6 mmol/L)	
Impaired glucose tolerance	ADA criterion <sup>15</sup> (increased risk for diabetes or prediabetes)		2-h PG ≥140mg/dL (7.8 mmol/L) during a 75g OGTT	
<b>Abbreviation</b> WHO: World Health Organisation NHANES: National Health and Nutrition Examination Survey BIA: Bioelectrical impedance analysis DEXA: Dual-energy X-ray absorptiometry FM: Fat mass				

Measurement	Guideline/ Equipment	Age	Abnormal	Notes
ADP: Air displacement plethysmography NHBPEP: National High Blood Pressure Education Program NCEP: National Cholesterol Education Program NGHS: National Lung, Heart and Blood Institute's Growth and Health Study HDL-C: High triglyceride concentration LDL-C: Low triglyceride concentration ATP III: Adult Treatment Panel III ADA: American Diabetes Association				

/bmjopen-2019-033438 on 8 January 2020. Downloaded from <http://bmjopen.bmj.com/> on April 23, 2021 by guest. Protected by copyright.

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

## Appendix 2. Definitions for Secondary outcomes

Term	Classification	Definition	Note
Cerebral palsy		<p>1. Cerebral palsy is a physical disability that affects movement and posture.</p> <p>Any definition that includes the following five key elements:</p> <p>(1) is an umbrella term for a group of disorders</p> <p>(2) is a condition that is permanent but not unchanging</p> <p>(3) involves a disorder of movement and/or posture and of motor function</p> <p>(4) is due to a non-progressive interference, lesion or abnormality, and</p> <p>(5) the interference, lesion or abnormality originates in the immature brain</p> <p>2. As defined by investigators</p>	Australian cerebral palsy register report - CP Register <sup>16</sup>
Severity of cerebral palsy	GMFCS Level I	Children walk at home, school, outdoors and in the community. They can climb stairs without the use of a railing. Children perform gross motor skills such as running and jumping, but speed, balance and coordination are limited.	Gross Motor Function Classification System (GMFCS) <sup>17</sup>
	GMFCS Level II	Children walk in most settings and climb stairs holding onto a railing. They may experience difficulty walking long distances and balancing on uneven terrain, inclines, in crowded areas or confined spaces. Children may walk with physical assistance, a handheld mobility device or used wheeled mobility over long distances. Children have only minimal ability to perform gross motor skills such as running and jumping.	
	GMFCS Level III	Children walk using a hand-held mobility device in most indoor settings. They may climb stairs holding onto a railing with supervision or assistance. Children use wheeled mobility when traveling long distances and may self-propel for shorter distances.	
	GMFCS Level IV	Children use methods of mobility that require physical assistance or powered mobility in most settings. They may walk for short distances at home with physical assistance or use powered mobility or a body support walker when positioned. At school, outdoors and in the community children are transported in a manual wheelchair or use powered mobility.	
	GMFCS Level V	Children are transported in a manual wheelchair in all settings. Children are limited in their ability to maintain antigravity head and trunk postures and control leg and arm movements.	
	Mild	A score on scale from 2 SD to <1 SD below test mean	Scores were obtained relative to the mean and standard deviation (SD)
	Moderate	A score on scale from 3 SD to <2 SD below test mean	

Developmental delay or intellectual impairment	Severe	A score on scale 3 SD below test mean	for the normal birth weight population. <sup>18</sup>
Visual impairment	None	Presenting visual acuity 6/18 or better in the better eye.	WHO Definition of visual impairment <sup>19</sup>
	Moderate/ low vision	Can see a toy and able to follow a toy. Presenting visual acuity worse than 6/18, equal to or better than 6/60 in the better eye in the better eye.	
	Severe/ no useful vision	Able to see light or gross movement up close (within 40cm). Presenting visual acuity worse than 6/60, equal to or better than 1/60 in the better eye.	Visual Standards- Aspects and Ranges of Vision Loss <sup>20</sup>
	Blindness/ no light perception	No useful vision. Presenting visual acuity worse than 1/60 in the better eye or no light perception.	
	Legal blindness	Medically diagnosed central visual acuity of 20/200 (6/60) or less in the better eye with the best possible correction, and/or a visual field of 20 degrees or less	
Hearing impairment (Classification 1)	None	None diagnosed	WHO Grades of hearing impairment- Prevention of blindness and deafness <sup>22</sup>
	Mild	Hearing level in decibels: 26-40dB A child with this level of hearing loss will have trouble hearing and understanding soft speech, speech from a distance or speech against a background of noise	
	Moderate	Hearing level in decibels: 41-60db A child with this level of hearing loss will have difficulty hearing regular speech, even at close distance	
	Severe	Hearing level in decibels: 61-80dB A child with this level of hearing loss may only hear very loud speech or loud sounds in the environment, such as a fire truck siren or a door slamming. Most conversational speech is not heard.	
	Profound	Hearing level in decibels: over 81dB A child with this level of hearing loss may perceive loud sounds as vibrations.	
Motor dysfunction	mild impairment	Test score between 5th and 15th centile on the Movement ABC / A score from 2 SD to <1 SD below the population mean on the BOTMP	Movement Assessment Battery for Children (Movement ABC) Bruininks–Oseretsky Test of Motor Proficiency (BOTMP) <sup>23</sup>
	moderate to severe impairment	Test score less than 5th centile on the Movement ABC / more than 2 SD below the population mean on the BOTMP	
School performance	Defined by teachers based on their observation and academic scores;		Poor school performance <sup>24</sup>

/bmjopen-2019-033438 on 8 January 2020. Downloaded from http://bmjopen.bmj.com/ on April 23, 2021 by guest. Protected by copyright.

	at or above vs below expected performance/level for age	
Growth Z-scores	WHO Growth Charts	Charts and tables: WHO child growth standards for children <sup>2</sup>
Abbreviation: CP: Cerebral palsy GMFCS: Gross Motor Function Classification System SD: Standard deviation Movement ABC: Movement Assessment Battery for Children BOTMP: Bruininks–Oseretsky Test of Motor Proficiency		

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46

### Appendix 3. Data items to be collected

#### Trial level information

- Protocols of each individual trial
- Data forms or case report forms (CRFs) of each individual trial
- Country
- Setting (neonatal intensive care unit (NICU), hospital, or home)
- Dates of start and end of trial
- Number of infants randomised
- Informed consent procedures
- Methods of random allocation
- Methods of allocation concealment
- Blinding of outcome assessment
- Blinding of researchers/ caregivers
- Stratification factors used
- Purpose of intervention
- Planned intervention
- Specific details of the planned nutrition in the experimental and control arms of the trial (including composition, whether given as sole feed or in addition to breast milk and duration)
- Outcomes collected (primary and secondary)

#### Participant level information: Infant characteristics at trial entry

- Unique identification code
- Gestational age at birth
- Age at trial entry
- Birthweight
- Weight, length and head circumference at trial entry
- Sex
- Single/multiple (if multiple order of birth)

#### Participant level information: After trial entry

- Actual intervention or comparison received
- Age at commencement of nutritional supplement
- Age at ceasing the nutritional supplement
- Receipt of breast milk and whether mother's own or donor/banked
- Size at discharge or term-equivalent age (36-42 weeks' post-menstrual age)- including weight, length, head circumference, and measures of body composition e.g. skinfolds, bioimpedance, plethysmography



## References

1. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet* 2014;384(9946):857-68. doi: 10.1016/S0140-6736(14)60932-6
2. Assessing Growth Using the WHO Growth Charts [Available from: [https://www.cdc.gov/nccdphp/dnpao/growthcharts/who/using/assessing\\_growth.htm](https://www.cdc.gov/nccdphp/dnpao/growthcharts/who/using/assessing_growth.htm).
3. Growth reference 5-19 years World Health Organization [updated January 16, 2019; cited 2019 January 16]. Available from: [https://www.who.int/growthref/who2007\\_bmi\\_for\\_age/en/](https://www.who.int/growthref/who2007_bmi_for_age/en/) accessed May 05 2019.
4. Fryar CD, Gu Q, Ogden CL, et al. Anthropometric Reference Data for Children and Adults: United States, 2011-2014. *Vital Health Stat 3* 2016(39):1-46.
5. Zimmet P, George K, Alberti MM, et al. The metabolic syndrome in children and adolescents - an IDF consensus report. *Pediatr Diabetes* 2007;8(5):299-306. doi: DOI 10.1111/j.1399-5448.2007.00271.x
6. Kelly TL, Wilson KE, Heymsfield SB. Dual energy X-ray absorptiometry body composition reference values from NHANES. *PLoS One* 2009;4(9) doi: ARTN e703810.1371/journal.pone.0007038
7. McCarthy HD, Cole TJ, Fry T, et al. Body fat reference curves for children. *Int J Obes* 2006;30(4):598-602. doi: 10.1038/sj.ijo.0803232
8. Butte NF, Hopkinson JM, Wong WW, et al. Body composition during the first 2 years of life: An updated reference. *Pediatr Res* 2000;47(5):578-85. doi: Doi 10.1203/00006450-200005000-00004
9. Addo OY, Himes JH. Reference curves for triceps and subscapular skinfold thicknesses in US children and adolescents. *Am J Clin Nutr* 2010;91(3):635-42. doi: 10.3945/ajcn.2009.28385
10. Wells JC, Williams JE, Chomtho S, et al. Body-composition reference data for simple and reference techniques and a 4-component model: a new UK reference child. *Am J Clin Nutr* 2012;96(6):1316-26. doi: 10.3945/ajcn.112.036970
11. Falkner B, Daniels SR, Loggie JMH, et al. Update on the 1987 Task Force Report on High Blood Pressure in Children and Adolescents: A Working Group Report from the National High Blood Pressure Education Program. *Pediatrics* 1996;98(4):649-58.
12. Jackson LV, Thalange NKS, Cole TJ. Blood pressure centiles for Great Britain. *Arch Dis Child* 2007;92(4):298-303. doi: 10.1136/adc.2005.081216
13. Cook S, Auinger P, Huang TT. Growth curves for cardio-metabolic risk factors in children and adolescents. *J Pediatr* 2009;155(3):S6 e15-26. doi: 10.1016/j.jpeds.2009.04.051
14. Hickman TB, Briefel RR, Carroll MD, et al. Distributions and trends of serum lipid levels among United States children and adolescents ages 4-19 years: Data from the third National Health and Nutrition Examination Survey. *Prev Med* 1998;27(6):879-90. doi: DOI 10.1006/pmed.1998.0376
15. criterion. A. 2. Classification and Diagnosis of Diabetes Diabetes Care American Diabetes Association; 2015 [updated 2015 Jan. American Diabetes Association ]. Available from: [http://care.diabetesjournals.org/content/38/Supplement\\_1/S8](http://care.diabetesjournals.org/content/38/Supplement_1/S8) accessed Nov 27 2017.
16. The Australian Cerebral Palsy Register Group. Australian cerebral palsy register report 2016 Cerebral Palsy Alliance [Available from: [https://www.cpreregister.com/pubs/pdf/ACPR-Report\\_Web\\_2016.pdf](https://www.cpreregister.com/pubs/pdf/ACPR-Report_Web_2016.pdf).

17. Palisano RJ, Rosenbaum P, Bartlett D, et al. Content validity of the expanded and revised Gross Motor Function Classification System. *Dev Med Child Neurol* 2008;50(10):744-50. doi: 10.1111/j.1469-8749.2008.03089.x
18. Doyle LW, Roberts G, Anderson PJ, et al. Outcomes at age 2 years of infants < 28 weeks' gestational age born in Victoria in 2005. *J Pediatr* 2010;156(1):49-U84. doi: 10.1016/j.jpeds.2009.07.013
19. IAPB, VISION 2020, WHO. Global Initiative for the elimination of avoidable blindness- Action plan 2006-2011 [Available from: [http://www.who.int/blindness/Vision2020\\_report.pdf](http://www.who.int/blindness/Vision2020_report.pdf).
20. International Council of Ophthalmology. Visual standards- Aspects and ranges of vision loss with emphasis on population surveys 2002 [Available from: <http://www.icoph.org/downloads/visualstandardsreport.pdf>.
21. American Foundation for the Blind. Key definitions of statistical terms- vision terms 2017 [Available from: <http://www.afb.org/info/blindness-statistics/key-definitions-of-statistical-terms/25>].
22. WHO. Prevention of blindness and deafness- hearing loss grades [Available from: [http://www.who.int/pbd/deafness/hearing\\_impairment\\_grades/en/](http://www.who.int/pbd/deafness/hearing_impairment_grades/en/).
23. Williams J, Lee KJ, Anderson PJ. Prevalence of motor-skill impairment in preterm children who do not develop cerebral palsy: a systematic review. *Dev Med Child Neurol* 2010;52(3):232-37. doi: 10.1111/j.1469-8749.2009.03544.x
24. Siqueira CM, Gurgel-Giannetti J. Poor school performance: an updated review. *Rev Assoc Med Bras (1992)* 2011;57(1):78-87.

# Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-Reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

			Page Number
<b>Title</b>			
Identification	<a href="#">#1a</a>	Identify the report as a protocol of a systematic review	1
Update	<a href="#">#1b</a>	If the protocol is for an update of a previous systematic review, identify as such	n/a

1	<b>Registration</b>		
2			
3			
4		<a href="#">#2</a>	2
5		If registered, provide the name of the registry (such as	
6		PROSPERO) and registration number	
7			
8			
9			
10	<b>Authors</b>		
11			
12			
13	Contact	<a href="#">#3a</a>	1
14		Provide name, institutional affiliation, e-mail address of all	
15		protocol authors; provide physical mailing address of	
16		corresponding author	
17			
18			
19			
20	Contribution	<a href="#">#3b</a>	16
21		Describe contributions of protocol authors and identify the	
22		guarantor of the review	
23			
24			
25			
26	<b>Amendments</b>		
27			
28			
29		<a href="#">#4</a>	n/a
30		If the protocol represents an amendment of a previously	
31		completed or published protocol, identify as such and list	
32		changes; otherwise, state plan for documenting important	
33		protocol amendments	
34			
35			
36			
37			
38			
39	<b>Support</b>		
40			
41			
42	Sources	<a href="#">#5a</a>	15
43		Indicate sources of financial or other support for the review	
44			
45	Sponsor	<a href="#">#5b</a>	15
46		Provide name for the review funder and / or sponsor	
47			
48	Role of sponsor or	<a href="#">#5c</a>	15
49	funder	Describe roles of funder(s), sponsor(s), and / or	
50		institution(s), if any, in developing the protocol	
51			
52			
53	<b>Introduction</b>		
54			
55			
56			
57			
58			
59			
60			

1	Rationale	<a href="#">#6</a>	Describe the rationale for the review in the context of what	4-5
2			is already known	
3				
4				
5				
6	Objectives	<a href="#">#7</a>	Provide an explicit statement of the question(s) the review	6
7			will address with reference to participants, interventions,	
8			comparators, and outcomes (PICO)	
9				
10				
11				
12				
13				
14	<b>Methods</b>			
15				
16				
17	Eligibility criteria	<a href="#">#8</a>	Specify the study characteristics (such as PICO, study	6-8
18			design, setting, time frame) and report characteristics (such	
19			as years considered, language, publication status) to be	
20			used as criteria for eligibility for the review	
21				
22				
23				
24				
25				
26				
27	Information	<a href="#">#9</a>	Describe all intended information sources (such as	8
28			electronic databases, contact with study authors, trial	
29	sources		registers or other grey literature sources) with planned	
30			dates of coverage	
31				
32				
33				
34				
35				
36				
37	Search strategy	<a href="#">#10</a>	Present draft of search strategy to be used for at least one	Appendix
38			electronic database, including planned limits, such that it	4
39			could be repeated	
40				
41				
42				
43				
44				
45	Study records -	<a href="#">#11a</a>	Describe the mechanism(s) that will be used to manage	9
46			records and data throughout the review	
47	data management			
48				
49				
50	Study records -	<a href="#">#11b</a>	State the process that will be used for selecting studies	8
51			(such as two independent reviewers) through each phase	
52	selection process		of the review (that is, screening, eligibility and inclusion in	
53			meta-analysis)	
54				
55				
56				
57				
58				
59				
60				

1	Study records -	<a href="#">#11c</a>	Describe planned method of extracting data from reports	8-9
2				
3	data collection		(such as piloting forms, done independently, in duplicate),	Appendix
4				
5	process		any processes for obtaining and confirming data from	3
6				
7			investigators	
8				
9				
10				
11	Data items	<a href="#">#12</a>	List and define all variables for which data will be sought	6-8
12				
13			(such as PICO items, funding sources), any pre-planned	Appendix
14				
15			data assumptions and simplifications	1-2
16				
17				
18				
19	Outcomes and	<a href="#">#13</a>	List and define all outcomes for which data will be sought,	7-8
20				
21	prioritization		including prioritization of main and additional outcomes,	
22				
23			with rationale	
24				
25				
26				
27	Risk of bias in	<a href="#">#14</a>	Describe anticipated methods for assessing risk of bias of	9
28				
29	individual studies		individual studies, including whether this will be done at the	
30				
31			outcome or study level, or both; state how this information	
32				
33			will be used in data synthesis	
34				
35				
36				
37	Data synthesis	<a href="#">#15a</a>	Describe criteria under which study data will be	10
38				
39			quantitatively synthesised	
40				
41				
42	Data synthesis	<a href="#">#15b</a>	If data are appropriate for quantitative synthesis, describe	10
43				
44			planned summary measures, methods of handling data and	
45				
46			methods of combining data from studies, including any	
47				
48			planned exploration of consistency (such as I <sup>2</sup> , Kendall's $\tau$ )	
49				
50				
51				
52	Data synthesis	<a href="#">#15c</a>	Describe any proposed additional analyses (such as	11
53				
54			sensitivity or subgroup analyses, meta-regression)	
55				
56				
57				
58				
59				
60				

1	Data synthesis	<a href="#">#15d</a>	If quantitative synthesis is not appropriate, describe the	11
2				
3			type of summary planned	
4				
5				
6	Meta-bias(es)	<a href="#">#16</a>	Specify any planned assessment of meta-bias(es) (such as	n/a
7			publication bias across studies, selective reporting within	
8			studies)	
9				
10				
11				
12				
13				
14	Confidence in	<a href="#">#17</a>	Describe how the strength of the body of evidence will be	n/a
15	cumulative		assessed (such as GRADE)	
16	evidence			
17				
18				
19				
20				
21				

22 None The PRISMA-P checklist is distributed under the terms of the Creative Commons Attribution  
 23 License CC-BY 4.0. This checklist can be completed online using <https://www.goodreports.org/>, a tool  
 24 made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
 25  
 26  
 27  
 28  
 29  
 30  
 31  
 32  
 33  
 34  
 35  
 36  
 37  
 38  
 39  
 40  
 41  
 42  
 43  
 44  
 45  
 46  
 47  
 48  
 49  
 50  
 51  
 52  
 53  
 54  
 55  
 56  
 57  
 58  
 59  
 60

## Appendix. Search strategies

<b>Embase from 1980</b>	
#	Search strategies
1	exp prematurity/
2	exp low birth weight/
3	exp small for date infant/
4	exp very low birth weight/
5	(prematu* adj2 infant*).tw.
6	(prematu* adj2 newborn*).tw.
7	(prematu* adj2 neonate*).tw.
8	preterm.tw.
9	low birth weight.tw.
10	low birthweight.tw.
11	VLBW.tw.
12	LBW.tw.
13	ELBW.tw.
14	small for gestation*.tw.
15	SGA.tw.
16	(less than adj6 g).tw.
17	(less than adj3 32 weeks).tw.
18	birth weight below.tw.
19	(gestation* adj2 less than).tw.
20	or/1-19
21	exp breast feeding/
22	exp infant nutrition/
23	exp protein intake/
24	exp dietary supplement/
25	exp omega 3 fatty acid/ct, ad, dt, ig, pa [Clinical Trial, Drug Administration, Drug Therapy, Intra gastric Drug Administration, Parenteral Drug Administration]
26	exp arachidonic acid/ae, ct, ad, dt, ig, pa, th [Adverse Drug Reaction, Clinical Trial, Drug Administration, Drug Therapy, Intra gastric Drug Administration, Parenteral Drug Administration, Therapy]
27	exp unsaturated fatty acid/ct, dt, pa, th [Clinical Trial, Drug Therapy, Parenteral Drug Administration, Therapy]
28	exp fat intake/ae, ad, dt [Adverse Drug Reaction, Drug Administration, Drug Therapy]
29	exp enteric feeding/
30	exp parenteral nutrition/
31	exp artificial milk/
32	exp breast milk/
33	exp fortified food/
34	exp elemental diet/
35	exp baby food/
36	(breast milk or human milk).tw.
37	formula.tw.
38	PUFA supplement*.tw.
39	feed* regimen*.tw.
40	(protein* adj2 concentration*).tw.
41	probiotic\$.tw.
42	parenteral*.tw.



1	43	enteral*.tw.
2	44	maternal milk.tw.
3	45	multinutrient supplement*.tw.
4	46	(breast fed or breastfed).tw.
5	47	prebiotic*.tw.
6	48	diet* supplement*.tw.
7	49	nutrient enriched.tw.
8	50	Docosahexaenoic Acid*.tw.
9	51	arachidonic acid*.tw.
10	52	(glutamine adj2 supplement*).tw.
11	53	(taurine adj2 supplement*).tw.
12	54	(calcium adj2 supplement*).tw.
13	55	palm olein.tw.
14	56	palmitic acid.tw.
15	57	(fortification or fortified).tw.
16	58	fatty acids.tw.
17	59	supplement* feed*.tw.
18	60	complementary feed*.tw.
19	61	nutrition*.tw.
20	62	Hydrolysed liquid.tw.
21	63	Hydrolyzed liquid.tw.
22	64	gamma-linoleic acid.tw.
23	65	(diet* adj3 protein*).tw.
24	66	or/21-65
25	67	20 and 66
26	68	Clinical Trial/
27	69	Randomized Controlled Trial/
28	70	exp randomization/
29	71	Single Blind Procedure/
30	72	Double Blind Procedure/
31	73	Crossover Procedure/
32	74	Placebo/
33	75	Randomi?ed controlled trial\$.tw.
34	76	Rct.tw.
35	77	random allocation.tw.
36	78	randomly.tw.
37	79	randomly allocated.tw.
38	80	allocated randomly.tw.
39	81	(allocated adj2 random).tw.
40	82	Single blind\$.tw.
41	83	Double blind\$.tw.
42	84	((treble or triple) adj blind\$).tw.
43	85	placebo\$.tw.
44	86	prospective study/
45	87	or/68-86
46	88	case study/
47	89	case report.tw.
48	90	abstract report/ or letter/
49	91	or/88-90
50	92	87 not 91

93	67 and 92
----	-----------

For peer review only

1  
2  
3  
4  
5  
6  
7  
8  
9  
10  
11  
12  
13  
14  
15  
16  
17  
18  
19  
20  
21  
22  
23  
24  
25  
26  
27  
28  
29  
30  
31  
32  
33  
34  
35  
36  
37  
38  
39  
40  
41  
42  
43  
44  
45  
46  
47  
48  
49  
50  
51  
52  
53  
54  
55  
56  
57  
58  
59  
60

For peer review only