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Breastfeeding in infants diagnosed with phenylketonuria (Protocol)

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[Intervention Protocol]

Breastfeeding in infants diagnosed with phenylketonuria

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the effects of breastfeeding (exclusive or partial) compared to low-Phe formula feeding in the first six months after birth in infants diagnosed with PKU.

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BACKGROUND

Description of the condition

Phenylketonuria (PKU) is the most common inherited disease of amino acid metabolism, with an incidence of approximately 1 in every 8000 births across Europe (Loeber 2007). It is an autosomal recessive genetic disorder of phenylalanine (Phe) metabolism that is characterised by insufficient activity of the enzyme phenylalanine hydroxylase (PAH) (ACOG 2020). PAH is responsible for converting Phe to tyrosine, and the lack of this enzyme causes elevated levels of Phe (Jervis 1953). This results in a spectrum of disorders, primarily affecting foetal brain, heart, and nervous system development in the newborn infant (Huttenlocher 2000). Phe is an amino acid that is present in many protein-rich foods. The cornerstone of treatment for this disorder is the dietary restriction of Phe. Infants diagnosed with PKU via a newborn screening test are treated with a low-Phe diet, which involves restricting protein intake by lowering the amount of milk containing Phe, such as breast milk or standard infant formula, and supplementing the diet with low-Phe protein substitutes (Pinto 2018).

Maternal PKU (i.e. the condition where the mother has PKU, but the infant is not affected) also impacts foetal development with a high risk of intellectual disability and microcephaly in the offspring if the mother is not on a low-Phe diet (Lee 2005). This review will not include studies that investigate the effect of maternal PKU on the unaffected foetus or newborn infant and will be restricted to studies that investigate infant feeding in infants with PKU whose mothers do not have PKU.

Description of the intervention

Exclusive breastfeeding means that the infant receives only breast milk. No other liquids or solids are given - not even water - except oral rehydration solutions, or drops or syrups of vitamins, minerals, or medicines (WHO 2008). The World Health Organization (WHO) recommends that infants should be exclusively breastfed for the first six months of life to achieve optimal growth, development, and health. Thereafter, to meet their evolving nutritional requirements, infants should receive nutritionally adequate and safe complementary foods, while continuing to breastfeed for up to two years or beyond.

Partial breastfeeding means that an infant continues to breastfeed but is also receiving other milk. In an attempt to achieve consistency in defining what is meant by breastfeeding, in 1988 the Interagency Group for Action on Breastfeeding defined levels of breastfeeding as high (more than 80% breastfeeds), medium (between 20% and 80% breastfeeds), and low (minimal, occasional, irregular breastfeeds) (Labbok 1990). In addition, they also categorise "token breast feeding" where minimal, occasional, irregular breastfeeds are given to an infant who is predominantly fed other foods.

These definitions are based on “what the infant is fed” and not how or who the milk comes from (Noel-Weiss 2012). Breast milk includes all human breast milk, i.e. an infant’s own mother’s milk and milk from a donor mother (or “wet nurse”). This milk may be fed to the infants in any way including direct feeding on the breast or expressed milk given by a bottle, gastric tube, or other methods.

In PKU, although natural protein restriction is important, Phe is an essential amino acid and must be provided in an amount that supports growth and tissue repair while keeping plasma Phe concentrations within recommended ranges. In addition, to ensure that the natural protein restriction does not cause protein deficit in the diet, the provision of a suitable Phe-free protein replacement or substitute is often recommended to optimise metabolic control. In infants, specialised Phe-free infant formulae (providing non-Phe amino acids with other essential nutrients) are available for such supplementation.

How the intervention might work

The European guidelines on phenylketonuria recommend that individuals with PKU maintain blood Phe levels from 120 to 360 µmol/L, whilst maintaining a tyrosine level in the normal range (van Wegberg 2017). There is no universal approach to feeding infants with PKU and no clear guidance is given in the UK NICE guidelines or in the European guidelines (NICE 2021; van Wegberg 2017) .

The amino acid profile of breast milk varies with lactational stage and geographic region, but Phe concentrations are low and rarely exceed 50 µmol/L (Zhang 2013). Breastfeeding is optimal for infant growth and development and has other advantages, such as lower risk of sudden infant death, fewer infections (such as otitis media), as well as long-term benefits of lower risk of obesity, diabetes, and an association with higher performance in intelligence tests (Rollins 2016). In addition, breastfeeding benefits mother-infant bonding and may help with reduction in parental anxiety during the difficult time of diagnosis.

The aim of this review is to investigate the effects of exclusive or partial breastfeeding in infants with PKU as compared to feeding low-Phe infant formula in the first six months after birth. Infants born to mothers who have PKU will not be included, whether or not the infants themselves have PKU.

Why it is important to do this review

Despite PKU being a research model for therapeutic strategies and long-term outcomes in inherited metabolic disorders (Thiele 2017), there is a lack of consensus on whether exclusive breastfeeding infants with PKU is acceptable. While breastfeeding is undisputedly the optimal feeding strategy for most infants (WHO 2008), infants diagnosed with PKU are often offered low-Phe specialised infant formula as a substitute to ensure that their Phe intake can be controlled.

Although many parents choose to continue breastfeeding after their infants' diagnosis of PKU (Banta-Wright 2014), mothers who exclusively breastfeed often experience a higher degree of stress than those who opt for formula feeding (Schulpis 2019), perhaps due to the unmeasured amounts of Phe in breast milk. Conversely, many mothers feel that breastfeeding is the healthiest choice and continuing to breastfeed helped them feel that their infants were healthy, despite the diagnosis of PKU (Banta-Wright 2015).

Since breastfeeding in PKU is not well studied, national and international guidelines do not give clear recommendations on infant feeding choices in the first six months after birth. It is important to understand the effects of continuing breastfeeding, either exclusive or partial, after an infant is diagnosed with PKU to inform families and empower them to make the correct choices such that they can enjoy the benefits of breastfeeding without

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incurring the risks of increased Phe levels. This review will collate existing evidence comparing exclusive or partial breastfeeding with formula feeding in infants with PKU to provide a summary of the evidence to enable such guidance and design of further research.

OBJECTIVES

To assess the effects of breastfeeding (exclusive or partial) compared to low-Phe formula feeding in the first six months after birth in infants diagnosed with PKU.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised controlled trials (RCTs) or quasi-RCTs, including those where baseline characteristics and outcome measurements were dissimilar (i.e. statistically significantly different) between both groups. We will not include non-randomised trials, such as retrospective studies or case reports. We will also only include articles with published full texts or abstracts that have sufficient information to meet the inclusion criteria.

Types of participants

We will include infants diagnosed with PKU, either by newborn screening or later, but within the first six months of life, and their mothers.

We will not include infants born to mothers who have PKU, whether or not the infants themselves have PKU.

Types of interventions

We will include studies that compare exclusive or partial breastfeeding with low-Phe formula feeding in infants up to six months of age.

The experimental intervention will consist of continuation of breastfeeding after the diagnosis of PKU. This will include both exclusive and partial breastfeeding as defined above (Labbok 1990; WHO 2008).

The comparator intervention will include groups fed infant formula without any breastfeeding after the diagnosis of PKU. This will include feeding infant formula that is specialised to be low-Phe.

Types of outcome measures

Primary outcomes

1. Blood Phe levels
   a. at six months after birth
   b. at 12 months after birth

Secondary outcomes

1. Growth rates (weight gain, linear growth, and head growth) in the first two years of life
   a. change in weight-for-age z scores
   b. change in height-for-age z scores
   c. head circumference-for- age z scores
   d. change in weight-for height z scores
2. Neurodevelopmental scores in children aged 12 months or older based on validated assessment tools, such as the Bayley Scale Index III (Bayley 2006)*
3. Any adverse psychological effects in the child due to the intervention
4. Infant quality of life as measured by standardised methods such as the Infant and Toddler Quality of Life Questionnaire (ITQOL) (Bowling 2004)
5. Mother-infant bonding measured using standardised methods such as the Postpartum Bonding Questionnaire (PBQ)

*results are considered abnormal if the Bayley III Mental Developmental Index is less than 70, if the Psychomotor Developmental Index is less than 70, or if there was visual impairment or hearing impairment, or both; neurological examination will be considered abnormal if motor or sensory functions, or both, are reported as impaired.

Search methods for identification of studies

We will search for all relevant published and unpublished studies without restrictions on language, year or publication status using criteria and standard methods as described by Cochrane.

Electronic searches

The Cochrane Cystic Fibrosis and Genetic Disorders Group's Information Specialist will conduct a search of the Group's Inborn Errors of Metabolism Trials Register for relevant trials using relevant terms:pku:kw AND (breast* OR chest* OR lactat* OR milk).

The Inborn Errors of Metabolism Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated with each new issue of the Cochrane Library), weekly searches of MEDLINE and the prospective hand searching of one journal (Journal of Inherited Metabolic Disease). Unpublished work is identified by searching through the abstract books of the Society for the Study of Inborn Errors of Metabolism conference and the SHS Inborn Error Review Series. For full details of all searching activities for the register, please see the relevant section of the Cochrane Cystic Fibrosis and Genetic Disorders Group's website.

We will search the following databases and trial registries:

1. MEDLINE Ovid (1946 to present);
2. Embase Ovid (1974 to present);
3. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
4. WHO International Clinical Trials Registry Platform (trialsearch.who.int/).

For details of our search strategies, please see Appendix 1.

Searching other resources

We will check the bibliographies of included studies and any relevant systematic reviews identified for further references to relevant trials. We will also contact experts in the field to obtain additional information on relevant trials.

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Data collection and analysis

Selection of studies

We will remove duplicates using Covidence software prior to title and abstract screening (Covidence), and remove any additional duplicates during the screening process. Two review authors (LC and JK) will screen the title and abstract of studies and potentially relevant reports identified from the above search using Covidence. The same two review authors will retrieve and read the full texts of potentially relevant articles to determine their eligibility for inclusion in the review. We will document all exclusions, with reasons.

The two review authors will ask a third review author (NC or SO) to arbitrate if they are unable to resolve disagreements regarding inclusion or exclusion.

Data extraction and management

Two review authors (LC and JK) will independently extract data from each included study using a structured and pilot-tested data collection form for details of design, methodology, participants, interventions, and outcomes.

The data collection form will include:

1. article information (author, date, language, author contact details);
2. study information (age at recruitment, method of diagnosis, duration of follow-up, sample size, study limitations);
3. population description including demographics (e.g. mothers' age, ethnicity), birth characteristics (birth weight, gestational age), socioeconomic factors (mothers' educational attainment, family income, deprivation index) and any baseline differences in population characteristics;
4. methods (study design, setting, deviations from the study protocol, randomisation, blinding, statistical methods);
5. intervention (description, co-interventions and comparator, timing, context);
6. outcomes and time points (those collected and those reported, unit measurements, how outcome measures were defined);
7. results (impacts on outcomes summary data, any adverse effects reported and how they were measured);
8. data relevant for risk of bias assessment using the Cochrane Risk of Bias 2 (RoB2) tool including deviations from intended interventions; and
9. other information (funding, conclusions, references of relevant studies, additional comments).

We will cross-check information and resolve any discrepancies by discussion until agreement is reached. We will contact study authors if additional information is required.

Assessment of risk of bias in included studies

We will use the Cochrane RoB2 tool to assess the risks of bias in the included trials (Sterne 2019). Two review authors (LC and JK) will independently assess the risks of bias and resolve any disagreements by discussion with a third review author (NC or SO). We will obtain additional information, as necessary, from study authors to clarify methodology.

We will assess the risks of bias for the following outcomes (which we will also include in the summary of findings (GRADE) tables):

1. blood Phe levels measured during the first six months after birth (the primary outcome);
2. weight gain (z score) in the first two years of life;
3. linear growth (z score) in the first two years of life;
4. head circumference growth (z score) in the first two years of life;
5. neurodevelopmental scores in children aged 12 months or older; and
6. mother-infant bonding measures.

We will assess the effect of the feeding strategy on outcomes as per the assignment to the intervention at baseline, regardless of whether the infant was fed as intended ("intention-to-treat" analysis). It is likely that, in some studies at least, there will be significant deviation from the assigned intervention, which is more likely to be in the breastfeeding group. As parents and families may be more interested in the effect of adhering to breastfeeding, we will undertake a "per-protocol" effect analysis if sufficient data are available.

Risk of bias assessment will include the following domains:

1. bias arising from the randomisation process;
2. bias due to deviations from intended interventions;
3. bias due to missing outcome data;
4. bias in measurement of the outcome; and
5. bias in selection of the reported result.

For each domain, we will use the "signalling questions" to assess risk of bias as "Yes" or "probably yes" to indicate a low or high risk of bias (depending on the way the question is framed) and "no" or "probably no", similarly. We will use the option of "No information" when either insufficient details are reported to permit a response of "Yes", "Probably yes", "No" or "Probably no", or when in the absence of these details it would be unreasonable to respond "Probably yes" or "Probably no" given the circumstances of the study. We will judge the implications of "No information" according to the purpose of the question. If the question seeks to identify the evidence of a problem then "No information" will correspond to no evidence of the problem. If the question relates to an item which we expect to be reported, we will judge the lack of information as a cause for potential risk of bias. In addition, we will use the option of "Not applicable" for signalling questions that we do not consider necessary for that particular study or outcome.

After we have answered the signalling questions, we will determine our judgement for the risk of bias and assign one of three levels to each domain:

1. low risk of bias;
2. some concerns; or
3. high risk of bias.

We will use the algorithm in the RoB2 tool to map responses to the signalling questions to a proposed risk-of-bias judgement for each domain. We will revise the judgements proposed by the algorithm to include a consideration of "risk of material bias" i.e. concerns will be expressed only about issues that are likely to affect the ability to draw reliable conclusions from the study.

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We will present supporting information in free-text boxes.

Where possible, we will judge the overall and domain-specific direction of the bias. This is may be applicable in studies where there is lack of adherence to the intervention in one arm (e.g. infants assigned to exclusive breastfeeding going on to receive formula feeding) leading to a potential reduction in the observed difference between the groups and resulting in the estimated effect of adhering to intervention being biased towards the null. Where we are unable to judge the direction of the bias, we will leave the response blank.

We will present a full risk-of-bias table, including responses to each signalling question within each domain, risk of bias judgement, and text to support each judgement.

We will include studies in the analyses irrespective of their risk of bias assessments. Where meta-analysis is possible, we will present the risk of bias judgements alongside the results of each study included in the meta-analysis. If a sufficient number of studies are available and there are many studies with a high risk of bias, we will perform a sensitivity analysis to assess the effects of restricting the analysis to RCTs with overall “low” or “low/some concerns”.

We will generate bar graphs and present these to illustrate the relative contributions of studies with each of risk-of-bias judgement (low risk of bias, some concerns, and high risk of bias).

We will make summary judgements about the risk of bias for the results within the studies and across the studies using the RoB2 tool and will judge the certainty of the body of evidence using the GRADE system. Our decisions and rationale will be stored in the Nottingham Research Data Management Repository, and will be publicly available.

Measures of treatment effect

We will analyse the effects of breastfeeding versus formula feeding in the individual studies using RevMan Web (RevMan Web 2020). We will report both the risk ratio (RR) and the risk difference (RD) for dichotomous data and the mean difference (MD) for continuous data, with respective 95% confidence intervals (CIs). For analyses with a statistically significant difference in the RD, we will also report the number needed to treat for an additional beneficial outcome (NNTB) or number needed to treat for an additional harmful outcome (NNTH). For categorical outcomes, we will calculate typical estimates for relative risk, RD, NNTB, and NNTH. We will use 95% CIs.

Unit of analysis issues

The unit of analysis will be the participating infant or mother in individually randomised studies. We will consider an infant only once in an analysis. We will exclude infants with multiple enrolments from the analysis, unless we obtain data from the report or investigators relating to the first episode of randomisation. If we can not identify these data, we will exclude the study as we will not be able to address the unit of analysis issues that arise from multiple enrolments of the same infant. We will include infants from multiple births. We intend to conduct intention-to-treat analyses. We will handle outcomes with repeated measurements by determining clinically meaningful time points. If we include studies with multiple treatment groups, we will include relevant pair-wise comparisons, by combining the intervention groups and creating a single pair-wise comparison to avoid double counting the comparator group when included in the same analysis. We will make the final decisions prior to analysis.

The participating health organisation will be the unit of analysis in cluster-RCTs. We will analyse these trials using an estimate of the intra-cluster correlation coefficient (ICC) derived from the study (if possible), or from another source, as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). For cluster-RCTs, we will conduct the analysis at the same level as the allocation using a summary measurement from each cluster, which will be the unit of analysis.

Dealing with missing data

If data are missing or reported unclearly, we will request additional data on important outcomes from the study authors. Where data are still missing, we will examine the impact on effect size estimates in sensitivity analyses using the 'best-worst case scenario' technique.

Assessment of heterogeneity

We will examine the intervention effects of individual studies and heterogeneity between study results by inspecting the forest plots. We will consider the I^2 statistic which quantifies inconsistency across studies and describes the percentage of variability in effect estimates that may be due to heterogeneity rather than to sampling error. We will classify the degree of heterogeneity according to the I^2 statistic:

1. below 25% - no heterogeneity;
2. 25% to 49% - low heterogeneity;
3. 50% to74% - moderate heterogeneity; and
4. 75% or above - high heterogeneity.

In addition, we will employ a Chi^2 test of homogeneity to determine the strength of evidence that heterogeneity is genuine.

Assessment of reporting biases

If we include more than 10 studies in a meta-analysis, we will use a funnel plot to assess potential reporting bias.

Data synthesis

We will assess the appropriateness of undertaking a meta-analysis based on the variation in PICO (participant, intervention, comparator, and outcome) characteristics across the eligible studies. If there is limited evidence for comparisons - including lack of eligible studies, incomplete reporting of outcomes, clinical and methodological heterogeneity - we may not perform meta-analyses. We will give the reason(s) for the decision and present the results of included studies that we considered ineligible for meta-analyses in a narrative format. We will summarise these results for each outcome.

We will use the random-effects model for meta-analyses, given the heterogeneity of the populations, studies and their approach to data collection, particularly maternal biodata. We will synthesise data using RR, RD, NNTB, NNTH, MD, and 95% CIs. Where substantial heterogeneity exists, we will investigate the potential causes using subgroup and sensitivity analyses.

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Subgroup analysis and investigation of heterogeneity

If sufficient studies meet the inclusion criteria, we will perform a subgroup analysis comparing exclusively breastfed infants (defined as infants who feed on mother's own milk only and do not receive any supplemental feeds for at least up to four months of age) to infants who are partially breastfed (defined as infants who receive any volume of mother's own breast milk supplemented with specialised formula milk).

Sensitivity analysis

We will perform sensitivity analyses to determine if the findings are affected by including only studies of adequate methodology (overall low risk of bias) as described above.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach, as outlined in the GRADE Handbook to assess the certainty of evidence for the following (clinically relevant) outcomes (Schünemann 2013):

1. level of Phe in blood during the first six months after birth;
2. weight gain (z score) in the first two years of life;
3. linear growth (z score) in the first two years of life;
4. head circumference growth (z score) in the first two years of life;
5. neurodevelopmental scores in children aged 12 months or older measured by the Bayley Scale Index III, which include adverse and psychological effects;
6. infant quality of life (as measured by standardised methods, such as the ITQOL questionnaire); and
7. mother-infant bonding measures (as measured by standardised methods, such as the PBQ questionnaire).

Two review authors will independently assess the certainty of evidence for each of the outcomes listed above as per the GRADE recommendations. We will consider evidence from RCTs as high certainty but downgrade evidence by one level for serious (or two levels for very serious) limitations based upon the following:

1. design (risk of bias)*;
2. consistency across studies;
3. directness of evidence;
4. precision of estimates; and
5. presence of publication bias.

*We will not downgrade if the risk of bias is limited to allocation concealment and non-blinding of the participants as mothers who breastfeed cannot be blinded to the intervention. However, we will downgrade if the outcome assessors are non-blinded. We will downgrade the quality of the evidence if more than 20% of participants are unaccounted for.

We will use the GRADEpro GDT Guideline Development Tool to create a summary of findings table to report the certainty of evidence. The GRADE approach results in an assessment of the certainty of a body of evidence according to one of four grades:

1. high certainty: further research is very unlikely to change our confidence in the estimate of effect.
2. moderate certainty: further research is likely to have an important impact on our confidence in the estimate of elect and may change the estimate.
3. low certainty: further research is very likely to have an important impact on our confidence in the estimate of elect and is likely to change the estimate.
4. very low certainty: we are very uncertain about the estimate.

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APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms	Date searched
MEDLINE Ovid (1946 onwards)	#1 ((breast or chest) and (feed* or fed)).tw. #2 (breastfeed* or breastfed or chestfeed* or chestfed or breastmilk or chestmilk or milk or lactat*).tw. #3 exp Breast Feeding/ #4 exp Lactation/ #5 Milk, Human/ #6 1 or 2 or 3 or 4 or 5 #7 phenylketonuria.tw. #8 PKU.tw. #9 phenylalanine hydroxylase defici*.tw. #10 (hyperphenylalaninaemia or hyperphenylalaninemia).tw. #11 (PAH and deficien*).tw. #12 exp Phenylketonurias/ #13 7 or 8 or 9 or 10 or 11 or 12 #14 6 and 13 #15 randomized controlled trial.pt. #16 controlled clinical trial.pt. #17 randomized.ab. #18 placebo.ab. #19 drug therapy.fs. #20 randomly.ab. #21 trial.ab. #22 groups.ab.	

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	#23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 #24 exp animals/ not humans.sh. #25 23 not 24 #26 14 and 25 NOTE: Search lines #15 - #25 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2008 revision); Ovid format (page 62 training.cochrane.org/handbook/version-6/chapter-4-tech-suppl)
Embase Ovid (1974 onwards)	1. ((breast or chest) and (feed* or fed)).tw. 2. (breastfeed* or breastfed or chestfeed* or chestfed or breastmilk or chestmilk or milk or lactat*).tw. 3. exp infant feeding/ 4. lactation/ 5. breast milk/ 6. 1 or 2 or 3 or 4 or 5 7. phenylketonuria.tw. 8. PKU.tw. 9. phenylalanine hydroxylase defici*.tw. 10. (hyperphenylalaninaemia or hyperphenylalaninemia).tw. 11. (PAH and deficien*).tw. 12. phenylketonuria/ 13. hyperphenylalaninemia/ 14. 7 or 8 or 9 or 10 or 11 or 12 or 13 15. ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)).ti,ab. 16. (assigned or allocated).ti,ab. 17. (controlled adj7 (study or design or trial)).ti,ab. 17. (volunteer or volunteers).ti,ab. 18. human experiment/ 19. trial.ti. 20. or/16-33 21. 34 not 48 22. 15 and 49 23. 6 and 14 24. Randomized controlled trial/ 25. Controlled clinical study/ 26. random$.ti,ab. 27. randomization/ 28. intermethod comparison/ 29. placebo.ti,ab. 30. (compare or compared or comparison).ti. 31. ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab. 32. (open adj label).ti,ab. 33. ((double or single or doubly or singly) adj (blind or blinded or blindly)).ti,ab. 34. double blind procedure/ 35. parallel group$1.ti,ab. 36. (crossover or cross over).ti,ab.

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	37.random$ adj sampl$ adj7 (“cross section$” or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.) 38.Cross-sectional study/ not (randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group $1.ti,ab.) 39.(((case adj control$) and random$) not randomi?ed controlled).ti,ab. 40.(Systematic review not (trial or study)).ti. 41.(nonrandom$ not random$).ti,ab. 42.“Random field$”.ti,ab. 43.(random cluster adj3 sampl$).ti,ab. 44.(review.ab. and review.pt.) not trial.ti. 45.“we searched”.ab. and (review.ti. or review.pt.) 46.“update review”.ab. 47.(databases adj4 searched).ab. 48.(rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/ 49.Animal experiment/ not (human experiment/ or human/) 50.or/35-47 NOTE: Search lines #16 - #49 are the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in Embase: (2018 revision); Ovid format (Glanville et al 2019b) (page 64 -65 training.cochrane.org/handbook/version-6/chapter-4-tech-suppl)
ClinicalTrials.gov (www.clinicaltrials.gov)	[Advanced Search] Condition or disease: PKU OR phenylketonuria OR PAH OR hyperphenylalaninemia OR phenylalanine hydroxylase deficiency Other terms: breast OR breastfeed OR breastfeeding OR breastfed OR “chest feed” OR “chest feeding” OR “chest fed” OR chestfeed OR chestfeeding OR chestfed OR milk Study type: Interventional Studies (Clinical Trials)
World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch)	phenylketonuria AND breastmilk OR breastfeeding OR chestfeeding OR chestmilk

CONTRIBUTIONS OF AUTHORS

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Task	Author(s)
Draft the protocol	LC and JK
Develop and run the search strategy	LC and JK with input from Information Specialists
Obtain copies of studies	LC and JK
Select which studies to include (2 people)	LC and JK
Extract data from studies (2 people)	LC and JK
Enter data into RevMan	LC and JK
Carry out the analysis	LC and JK
Interpret the analysis	LC, JK, NC, SO
Draft the final review	LC, JK, NC, SO

DECLARATIONS OF INTEREST

Lydia Chong declares no potential conflicts of interest.

Jahnavi Kalvala declares no potential conflicts of interest.

Neil Chadborn declares no potential conflicts of interest.

Shalini Ojha declares no potential conflicts of interest.

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