



Libraries and Learning Services

University of Auckland Research Repository, ResearchSpace

Version

This is the publisher's version. This version is defined in the NISO recommended practice RP-8-2008 <http://www.niso.org/publications/rp/>

Suggested Reference

Muelbert, M., Harding, J. E., & Bloomfield, F. H. (2018). Exposure to the smell and taste of milk to accelerate feeding in preterm infants (Protocol). *Cochrane Database of Systematic Reviews*, 2018(5). doi: [10.1002/14651858.CD013038](https://doi.org/10.1002/14651858.CD013038)

Copyright

Items in ResearchSpace are protected by copyright, with all rights reserved, unless otherwise indicated. Previously published items are made available in accordance with the copyright policy of the publisher.

This Protocol of a Cochrane Review was published in the *Cochrane Database of Systematic Reviews* 2018, 2. Cochrane Protocols and Reviews are regularly updated as new evidence emerges and in response to feedback, and the Cochrane Database of Systematic Reviews should be consulted for the most recent version of the Protocol.

For more information, see [General copyright](#), [Publisher copyright](#), [SHERPA/RoMEO](#).



Cochrane
Library

Cochrane Database of Systematic Reviews

Exposure to the smell and taste of milk to accelerate feeding in preterm infants (Protocol)

Muelbert M, Harding JE, Bloomfield FH

Muelbert M, Harding JE, Bloomfield FH.

Exposure to the smell and taste of milk to accelerate feeding in preterm infants.

Cochrane Database of Systematic Reviews 2018, Issue 5. Art. No.: CD013038.

DOI: 10.1002/14651858.CD013038.

www.cochranelibrary.com

TABLE OF CONTENTS

HEADER	1
ABSTRACT	1
BACKGROUND	1
OBJECTIVES	2
METHODS	3
ACKNOWLEDGEMENTS	6
REFERENCES	6
APPENDICES	7
CONTRIBUTIONS OF AUTHORS	12
DECLARATIONS OF INTEREST	12
SOURCES OF SUPPORT	12

[Intervention Protocol]

Exposure to the smell and taste of milk to accelerate feeding in preterm infants

Mariana Muelbert¹, Jane E Harding¹, Frank H Bloomfield¹

¹Liggins Institute, University of Auckland, Auckland, New Zealand

Contact address: Jane E Harding, Liggins Institute, University of Auckland, 85 Park Road, Grafton, Auckland, 1023, New Zealand. j.harding@auckland.ac.nz.

Editorial group: Cochrane Neonatal Group.

Publication status and date: New, published in Issue 5, 2018.

Citation: Muelbert M, Harding JE, Bloomfield FH. Exposure to the smell and taste of milk to accelerate feeding in preterm infants. *Cochrane Database of Systematic Reviews* 2018, Issue 5. Art. No.: CD013038. DOI: 10.1002/14651858.CD013038.

Copyright © 2018 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

ABSTRACT

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

To determine whether exposure to the taste or smell (or both) of milk administered with tube feedings can accelerate progress to full sucking feeds without adverse effects in preterm infants. We will also assess these effects in subgroups with different modes of administration, gestational age, birthweight, and type of milk.

BACKGROUND

Description of the condition

Because of immaturity of neurologic and digestive systems, preterm infants (born before 37 weeks' gestation) are often unable to co-ordinate sucking, swallowing, and breathing in order to feed. Initial nutrition is usually provided intravenously and via a tube which goes through the nose or mouth into the stomach, with a gradual transition to sucking feeds as co-ordination improves (Toce 1987). Usually, enteral feeds (feeds provided via the gut) start at small volumes and are increased slowly until full enteral feeds are tolerated.

Feeding intolerance is defined as the inability to digest enteral feedings in association with increased gastric residuals (fluid remaining in the stomach after tube feeds), abdominal distension or vomiting, or both (Moore 2011). It often leads to a delay in attainment of full enteral feeds and prolonged intravenous nutrition

(Fanaro 2013). Prolonged intravenous nutrition can increase the risk of: infection; cholestasis (impaired bile flow) (Gargasz 2012); impaired development of the gut mucosa; necrotising enterocolitis (severe intestinal inflammation) (Fanaro 2013); and increased morbidity and mortality (The SIFT Investigators Group 2013).

Taste and smell are important for the appreciation of food but also have a significant role in nutrition. In response to sensory cues, a sequence of pre-absorptive physiological responses is triggered by the brain, collectively referred to as cephalic phase responses (Smeets 2010).

The cephalic phase response plays an important role in the activation of physiological processes at multiple sites to optimise digestion, including increased salivation, increased peristaltic movements, and increased secretion of digestive enzymes and digestive-related hormones, all of which are active in the newborn (Lipchock 2011; Mattes 1997; Zolotukhin 2013).

The pathways underlining the cephalic phase response to taste and smell stimulation are diverse and stimulate different parts of the

digestive system. First, the increase in salivation starts the process of digestion as a result of the presence of salivary enzymes (such as α -amylase and lingual lipase), salivary insulin, and the moistening of the digestive bolus to assist swallowing. Further down the gastrointestinal tract, the cephalic phase response initiates the release of gastric secretions containing gastrin, gastric acid, trypsin and gut peptides. It also initiates the release of hormones such as ghrelin, glucagon-like peptide-1, leptin and somatostatin, as well as increasing gut motility. Smell and taste also are known to stimulate gastric emptying by increasing contraction of segments of the gastrointestinal tract. Lastly, the release of pancreatic secretions that are rich in digestive enzymes such as lipase, amylase and cholecystokinin assist further digestion of nutrients. In addition to the pancreatic secretions released in the gut, the pancreas also releases insulin and glucagon into the bloodstream in response to sensory stimulation.

All of the responses described above contribute to food digestion and absorption (Mattes 1997; Zolotukhin 2013). However, little is known about the effects of taste and smell stimulation in preterm infants, despite the presence of functional taste receptors from 18 weeks' gestation and flavour perception from around 24 weeks' gestation (Lipchock 2011).

Fetal swallowing of amniotic fluid starts by the end of the first trimester and reaches up to 750 mL/day by 34 weeks' gestation (Dasgupta 2016). Thus, fetal smell and taste receptors are exposed to the components of amniotic fluid for many weeks before birth and at equivalent gestations to those of infants born preterm (Bloomfield 2017), suggesting that the first sensory experiences happen *in utero*.

Distinct olfactory reflexes have been demonstrated in neonates after 32 weeks of gestation, with infants presenting different responses to the smell of substances such as amniotic fluid, colostrum or peppermint oil, varying from sucking response alone to a combination of sucking and arousal-withdrawal reflex (Bingham 2003; Marlier 1998; Sarnat 1978). These findings suggest that the olfactory system is fully functional in preterm infants after 32 weeks of gestational age.

Tube feedings bypass the oral and nasal cavities, so tube-fed infants have limited exposure to the taste and smell of their feeds. Therefore, there is little stimulation of the cephalic phase response of digestion, which is important for digestion and tolerance of feeds. The provision of smell and taste exposure to preterm infants receiving tube feedings is currently being applied in the care of some preterm infants based on the assumption that there is biological plausibility for a possible benefit, despite lack of evidence to support this practice. More importantly, potential adverse effects have not been assessed; these could include risks such as aspiration, gagging or choking, bradycardia, desaturations or increase in oxygen requirement.

Description of the intervention

The intervention consists of placing a few drops of the milk with which the infant is being fed on the infant's lips and tongue in order to provide the taste of milk, and placing a cotton bud or gauze soaked with a few drops of milk close to the infant's nostril to provide the smell of milk. The exposure should be done before starting the tube feed in order to stimulate the cephalic phase response of digestion.

How the intervention might work

Preterm infants being fed via gastric tube have limited exposure to the taste and smell stimulation which trigger the cephalic phase response of digestion, and this might contribute to feeding intolerance and prolonged intravenous nutrition.

Exposure to the taste and smell of milk before tube feeding may stimulate the cephalic phase response of digestion and assist digestion by increasing salivation, triggering peristaltic movements of gut, secretion of digestive enzymes and release of digestion-related hormones such as ghrelin, leptin, gastrin, insulin and others (Power 2008).

Why it is important to do this review

Prolonged exposure to intravenous nutrition increases the risk of late-onset sepsis, prolonging hospital stay and increasing health costs. In addition, delayed enteral feeding can result in degeneration of gastrointestinal mucosa and increase the risk of necrotising enterocolitis once the tube feedings start, impacting significantly on infant survival and hospital costs (Johnson 2014). Thus any interventions that accelerate transition to enteral feedings, and then to sucking feedings, would be of considerable potential benefit to infants, their families and the healthcare system.

It is increasingly common for staff in neonatal nurseries to include exposure to the smell or taste (or both) of milk in the process for tube feeding preterm infants. This is largely based on the belief that this must be beneficial, which could lead to performance bias when assessing the effects of the intervention. Furthermore, this additional intervention requires staff time (and therefore cost), and there is also the potential for adverse effects such as choking or aspiration. Reliable evidence is required on the benefits as well as possible risks of this intervention.

OBJECTIVES

To determine whether exposure to the taste or smell (or both) of milk administered with tube feedings can accelerate progress to full sucking feeds without adverse effects in preterm infants. We will also assess these effects in subgroups with different modes of administration, gestational age, birthweight, and type of milk.

METHODS

Criteria for considering studies for this review

Types of studies

We will include any published or unpublished randomised or quasi-randomised trials where the unit of randomisation is the infant, or cluster-randomised trials where the neonatal unit or hospital is the unit of randomisation. We will exclude cross-over trials and non-randomised trials such as controlled before-and-after studies.

Types of participants

Preterm infants (born before 37 weeks' gestation) of both sexes and all ethnicities who are receiving any enteral feeds and have not yet reached full sucking feeds.

Types of interventions

We will include studies that report the exposure to the taste or smell (or both) of breast milk or formula milk, immediately before or at the time of tube feedings.

For smell stimulation, we will include in this review interventions that consist of delivering the smell of milk to preterm infants using a gauze with a few drops of milk placed in the cot/incubator close to the infants' nose, or using a cotton bud soaked with milk or other forms of administration of the smell of milk (eg. using an olfactometer adapted to a pacifier).

For taste stimulation, we will include in this review studies that report placing a few drops of milk on the infant's lips or tongue using a syringe, or other forms of oral administration of a small amount of milk (eg. using a pacifier dipped in milk).

We will explore the following comparisons.

1. Exposure to the smell and taste of milk with tube feeds versus no exposure
2. Exposure to the smell of milk with tube feeds versus no exposure
3. Exposure to the taste of milk with tube feeds versus no exposure

Types of outcome measures

Primary outcomes

1. Time to reach full sucking feeds (defined as the removal of the feeding tube), measured in days.
2. Adverse effects related to the intervention, such as aspiration, gagging/choking, bradycardia, desaturations or increase in oxygen requirement during the intervention period.

Secondary outcomes

1. Duration of parenteral nutrition (defined as the removal of intravenous nutrition line), measured in days.
2. Time to reach full enteral feedings (150 ml/Kg/day, or as defined by the trialists), measured in days.
3. Feed intolerance (resulting in cessation or reduction in enteral feeding), during the period of hospitalisation.
4. Necrotising enterocolitis (Bell's stage 2 or more) (Walsh 1986), during the period of hospitalisation.
5. Late infection (bacterial or fungal infection confirmed by presence of blood or cerebrospinal fluid infection with initiation of symptoms beyond 48 hours after birth) (ANZNN 2015), during the period of hospitalisation..
6. Growth from birth to discharge (weight, height/length, head circumference and z-scores; gain in these parameters from birth to 36 weeks' postmenstrual age or to term equivalent age; body composition).
7. Exclusive breastfeeding at time of discharge (WHO 2008).
8. Time to first discharge home, measured in days.

Search methods for identification of studies

We will use the criteria and standard methods of Cochrane and Cochrane Neonatal (see [the Cochrane Neonatal search strategy for specialized register](#)). We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review. We will not limit the search to any particular geographical region, language or timing of publication.

Electronic searches

We will conduct a comprehensive search of databases, including: Cochrane Central Register of Controlled Trials (CENTRAL, current issue) in the Cochrane Library; MEDLINE via PubMed (1996 to current); Embase (1980 to current); and CINAHL (1982 to current), using search terms unique to the review topic, plus database-specific limiters for randomised controlled trials (RCTs) and neonates (see [Appendix 1](#) for the full search strategies for each database). We will search clinical trials registries for protocols of ongoing or recently completed trials (clinicaltrials.gov; [ICTRP](#); [ANZCTR](#) and the [ISRCTN Registry](#)). We will search using both English and American spelling. We will not apply language restrictions.

Searching other resources

Additionally, we will review the reference lists of all identified articles for relevant articles not identified in the primary search. We will also approach well-known researchers in this area to identify any unpublished or ongoing research.

Data collection and analysis

We will follow the standard data collection methods of the Cochrane Neonatal Group.

Selection of studies

Two authors will independently evaluate and appraise the retrieved studies, following the steps below.

1. Screen titles and abstracts to select relevant reports and exclude studies not relevant for this review
2. Access the full text of potentially relevant reports
3. Use a reference software management to combine search results and remove duplicate records of the same report and combine multiple reports of the same study
4. Examine full-text studies for compliance with the eligibility criteria determined for this review
5. Where appropriate, corresponded with study authors in order to elucidate any issue regarding selected studies, such as request for missing results or complementary information
6. Make final decisions on study inclusion and proceed to data collection

We will resolve disagreements by discussion and if necessary, a third review author will mediate for differences in interpretation. We will record the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009), and 'Characteristics of excluded studies' table.

Data extraction and management

We will develop a data extraction form to extract data from eligible studies. Two review authors will independently extract data from each eligible study. Information extracted will include, but not be limited to: source details, eligibility assessment, methodological details, characteristics of participants, details of intervention and outcomes reported. Any disagreement will be resolved by discussion and if necessary in discussion with a third review author. We will enter details from the data extraction form into Review Manager 5 (Review Manager 2014). Where review authors are authors of an included trial, we will ensure that those authors are excluded from any decision-making regarding inclusion of the trial in this review, and they will not be involved in data extraction or quality assessment relating to that trial.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias (low, high, or unclear) of all included trials using the Cochrane 'Risk of bias' tool (Higgins 2017). We will assess the risk of bias the following domains.

1. Sequence generation (selection bias)
2. Allocation concealment (selection bias)
3. Blinding of participants and personnel (performance bias)

4. Blinding of outcome assessment (detection bias)
5. Incomplete outcome data (attrition bias)
6. Selective reporting (reporting bias)
7. Any other bias

Any disagreements will be resolved by discussion or by a third assessor. See Appendix 2 for a more detailed description of risk of bias for each domain. We will enter the assessed risk of bias into Review Manager 5 (Review Manager 2014).

Measures of treatment effect

We will use the numbers of events in the control and intervention groups of each study to calculate risk ratios (RRs) for dichotomous data. We will calculate mean differences (MDs) between treatment groups where outcomes are measured in the same way for continuous data. Where outcomes are measured differently we will report data as standardised mean differences (SMDs). We will report risk differences (RDs), and where a significant effect is found we will calculate the numbers needed to treat to benefit (NNTB) or the numbers needed to treat to harm (NNTH). We will report 95% confidence intervals (CIs) for all outcomes.

Unit of analysis issues

The unit of analysis will be the participating infant in individually randomised trials and an infant will be considered only once in the analysis. The participating neonatal unit or section of a neonatal unit or hospital will be the unit of analysis in cluster randomised trials. We will analyse them using an estimate of the intra-cluster correlation coefficient (ICC) derived from the trial (if possible), or from a similar trial or from a study with a similar population as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). If we use ICCs from a similar trial or from a study with a similar population we will report this and conduct a sensitivity analysis to investigate the effect of variation in the ICC.

If we identify both cluster-randomised trials and individually randomised trials, we will only combine the results from both if there is little heterogeneity between the study designs, and the interaction between the effect of the intervention and the choice of randomisation unit is considered to be unlikely.

Any possible heterogeneity in the randomisation unit will be acknowledged and a sensitivity analysis will be performed to investigate possible effects of the randomisation unit.

Dealing with missing data

We intend to carry out analysis on an intention-to-treat basis for all outcomes, where feasible. We will analyse all participants in the treatment group to which they were randomised, regardless of the actual treatment received, whenever possible. If important missing data (in the outcomes) or unclear data are identified, we will request the missing data by contacting the original investigators.

We will make explicit the assumptions of any methods used to deal with missing data. We may perform sensitivity analyses to assess how sensitive results are to reasonable changes in the assumptions that are made. We will address the potential impact of missing data on the findings of the review in the 'Discussion' section.

Assessment of heterogeneity

We will observe the clinical and methodological characteristics of the included studies in order to assess if the studies are sufficiently similar for meta-analysis to provide a clinically meaningful summary. We will do this by inspecting the forest plots and assessing statistical heterogeneity using the Chi^2 test and the I^2 statistic, considering the guidelines recommended by the Cochrane Neonatal Group for interpretation of results. We will consider an I^2 value of less than 25% to represent no heterogeneity; 25% to 49% to represent low heterogeneity; 50% to 74% to represent moderate heterogeneity; and more than 75% to represent high heterogeneity.

We will consider an I^2 value greater than 50% and a low P value (less than 0.10) in the Chi^2 test for heterogeneity to indicate substantial heterogeneity (Deeks, 2017). If we detect substantial heterogeneity, we will explore possible explanations in sensitivity/subgroup analyses. We will take statistical heterogeneity into account when interpreting the results, especially if there is any variation in the direction of effect.

Assessment of reporting biases

We intend to conduct a comprehensive search for eligible studies and we will be alert for duplication of data. If 10 or more trials are identified for meta-analysis, we will assess possible publication bias by inspection of a funnel plot. If we uncover reporting bias that could, in the opinion of the authors, introduce serious bias, we plan to conduct a sensitivity analysis to determine the effect of including and excluding these studies in the analysis.

Data synthesis

We will evaluate studies for potential clinical diversity and restrict meta-analysis to situations where clinical consistency is apparent. Where substantial heterogeneity is detected, we will test the potential causes in subgroup and sensitivity analysis. We will use a fixed-effect model to combine data where it is reasonable to assume that studies were estimating the same underlying treatment effect. If there is evidence of clinical heterogeneity we will try to explain this based on the different study characteristics and subgroup analyses.

Quality of evidence

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, as outlined in the

GRADE Handbook (Schünemann 2013), to assess the quality of evidence for the following (clinically relevant) outcomes.

1. Time to reach full sucking feeds (defined as the removal of the feeding tube), measured in days
2. Time to reach full enteral feedings (150 ml/Kg/day, or as defined by the trialists), measured in days
3. Feed intolerance (resulting in cessation or reduction in enteral feeding)
4. Duration of parenteral nutrition (defined as the removal of the intravenous nutrition line), measured in days
5. Necrotising enterocolitis (Bell's stage 2 or more) (Walsh 1986)
6. Late infection (bacterial or fungal infection confirmed by presence of blood or cerebrospinal fluid infection with initiation of symptoms beyond 48 hours after birth) (ANZNN 2015)
7. Adverse effects related to intervention such as aspiration, gagging/choking, bradycardia, desaturations or increase in oxygen requirement

Two review authors will independently assess the quality of the evidence for each of the outcomes above. We will consider evidence from randomised controlled trials as high quality, but downgrade the evidence by one level for serious (or two levels for very serious) limitations based upon the following: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias. We will use GRADEpro GDT to create a 'Summary of findings' table to report the quality of the evidence for these specified outcomes.

The GRADE approach results in an assessment of the quality of a body of evidence in one of the four following grades.

1. High: we are very confident that the true effect lies close to that of the estimate of the effect.
2. Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
3. Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
4. Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Subgroup analysis and investigation of heterogeneity

Where we identify sufficient data, we plan to carry out the following subgroup analyses using a fixed-effect model.

1. Type of administration of smell exposure (cotton swab or similar soaked with milk placed close to infants' nostril versus placed by the infant's side)
2. Type of administration of taste (cotton swab or similar soaked with milk placed on infant's lips and tongue versus syringe administration of milk directly onto the infant's lips and tongue versus use of pacifier to deliver taste of milk)

3. Type of exposure (provision of smell and taste versus provision of taste only versus provision of smell only)
4. Gestational age (less than 28 weeks' versus 28 to less than 32 weeks' versus 32 to less than 37 weeks' postmenstrual age)
5. Type of diet (exclusively human milk versus formula versus human milk + formula)
6. Intrauterine growth restricted or small for gestational age (less than 10th centile or as defined by the trialists) versus appropriately grown at birth

We will investigate whether the results of subgroup analyses are significantly different by examining the overlap of confidence intervals and performing the test for subgroup differences available in Review Manager 5 software (Review Manager 2014).

Sensitivity analysis

Where we identify substantial heterogeneity, we will conduct sensitivity analysis to determine if the findings are affected by inclusion of only those trials considered of adequate methodology with a low risk of selection and performance bias. We will report results of sensitivity analyses for primary outcomes only.

ACKNOWLEDGEMENTS

We acknowledge the support of the Cochrane Neonatal Group editorial office.

The methods section of this protocol is based on a standard template used by Cochrane Neonatal.

REFERENCES

Additional references

ANZNN 2015

Australian and New Zealand Neonatal Network. ANZNN Data Dictionary. Available from <https://npsu.unsw.edu.au/sites/default/files/npsu/page/ANZNN%20Data%20dictionary%202015.pdf> (accessed 18 May 2018) December 2014:99.

Bingham 2003

Bingham PM, Abassi S, Sivieri E. A pilot study of milk odor effect on nonnutritive sucking by premature newborns. *Archives of Pediatrics & Adolescent Medicine* 2003;**157**(1):72–5. DOI: 10.1001/archpedi.157.1.72; PUBMED: 12517198

Bloomfield 2017

Bloomfield FH, Alexander T, Muelbert M, Beker F. Smell and taste in the preterm infant. *Early Human Development* 2017;**114**:31–4. DOI: 10.1016/j.earlhumdev.2017.09.012; PUBMED: 28899618

Dasgupta 2016

Dasgupta S, Arya S, Choudhary S, Jain SK. Amniotic fluid: Source of trophic factors for the developing intestine. *World Journal of Gastrointestinal Pathophysiology* 2016;**7**(1):38–47. DOI: 10.4291/wjgp.v7.i1.38; PUBMED: 26909227

Deeks, 2017

Deeks JJ, Higgins JPT, Altman DG G (editors) on behalf of the Cochrane Statistical Methods Group. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017).. Cochrane, 2017. Available from training.cochrane.org/handbook (accessed 18 May 2018).

Fanaro 2013

Fanaro S. Feeding intolerance in the preterm infant. *Early Human Development* 2013;**89**(Suppl 2):S13–20. DOI: 10.1016/j.earlhumdev.2013.07.013; PUBMED: 23962482

Gargasz 2012

Gargasz A. Neonatal and pediatric parenteral nutrition. *AACN Advanced Critical Care* 2012;**23**(4):451–64. DOI: 10.1097/NCI.0b013e31826e8f8b; PUBMED: 23095971

GRADEpro GDT [Computer program]

McMaster University (developed by Evidence Prime). GRADEpro GDT. Version accessed 19 January 2018. Hamilton (ON): McMaster University (developed by Evidence Prime), 2015.

Higgins 2011

Higgins JPT, Deeks JJ, Altman DG on behalf of the Cochrane Statistical Methods Group. Chapter 16: Special topics in statistics. In: 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 (accessed 18 May 2018).

Higgins 2017

Higgins JPT, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Churchill R, Chandler J, Cumpston MS (editors), *Cochrane Handbook for Systematic Reviews of Interventions* version 5.2.0 (updated June 2017), Cochrane, 2017. Available from training.cochrane.org/handbook (accessed 18 May 2018).

Johnson 2014

Johnson J, Patel AL, Bigger HR, Engstrom JL, Meier PP. Economic benefits and costs of human milk feedings: a strategy to reduce the risk of prematurity-related morbidities in very-low-birth-weight infants. *Advances in Nutrition* 2014;**5**(2):207–12. DOI: 10.3945/an.113.004788; PUBMED: 24618763

Lipchock 2011

Lipchock SV, Reed DR, Mennella J. The gustatory and olfactory systems during infancy: implications for development of feeding behaviors in the high-risk neonate. *Clinics in Perinatology* 2011;**38**(4):627–41. DOI: 10.1016/j.clp.2011.08.008; PUBMED: 22107894

Marlier 1998

Marlier L, Schaal B, Soussignan R. Neonatal responsiveness to the odor of amniotic and lacteal fluids: a test of perinatal chemosensory continuity. *Child Development* 1998;**69**(3): 611–23. DOI: 10.1111/j.1467-8624.1998.tb06232.x; PUBMED: 9680675

Mattes 1997

Mattes RD. Physiologic responses to sensory stimulation by food: nutritional implications. *Journal of the American Dietetic Association* 1997; Vol. 97, issue 4:406–13. [10.1016/S0002-8223(97)00101-6; PUBMED: 9120195]

Moher 2009

Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Journal of Clinical Epidemiology* 2009;**62**(10):1006–12. [PUBMED: 19631508]

Moore 2011

Moore TA, Wilson ME. Feeding Intolerance. *Advances in Neonatal Care* 2011;**11**(3):149–54. DOI: 10.1097/ANC.0b013e31821ba28e; PUBMED: 21730906

Power 2008

Power ML, Schulkin J. Anticipatory physiological regulation in feeding biology: cephalic phase responses. *Appetite* 2008;**50**(2-3):194–206. DOI: 10.1016/j.appet.2007.10.006; PUBMED: 18045735

Review Manager 2014 [Computer program]

Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Sarnat 1978

Sarnat HB. Olfactory reflexes in the newborn infant. *The Journal of Pediatrics* 1978;**92**(4):624–6. DOI: 10.1016/S0022-3476(78)80307-2

Schünemann 2013

Schünemann H, Brożek J, Guyatt G, Oxman A, editor (s). Handbook for grading the quality of evidence and the strength of recommendations using the GRADE approach (updated October 2013). GRADE Working Group, 2013. Available from gdt.guidelinedevelopment.org/app/handbook/handbook.html (accessed 18 May 2018).

Smeets 2010

Smeets PA, Erkner A, De Graaf C. Cephalic phase responses and appetite. *Nutrition Reviews* 2010;**68**(11):643–55. DOI: 10.1111/j.1753-4887.2010.00334.x; PUBMED: 20961295

The SIFT Investigators Group 2013

SIFT Investigators Group. Early enteral feeding strategies for very preterm infants: current evidence from Cochrane reviews. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2013;**98**(6):F470–2. DOI: 10.1136/archdischild-2012-303260; PUBMED: 23766343

Toce 1987

Toce SS, Keenan WJ, Homan SM. Enteral feeding in very-low-birth-weight infants. A comparison of two nasogastric methods. *American Journal of Diseases of Children* 1987;**141**(4):439–44. DOI: 10.1001/archpedi.1987.04460040097025; PUBMED: 3105304

Walsh 1986

Walsh MC, Kliegman RM. Necrotizing enterocolitis: treatment based on staging criteria. *Pediatric Clinics of North America* 1986;**33**(1):179–201. DOI: 10.1016/S0031-3955(16)34975-6; PUBMED: 3081865

WHO 2008

World Health Organization. Indicators for assessing infant and young child feeding practices - part I: definition. Available from www.who.int/maternal_child_adolescent/documents/9789241596664/en/ (assessed 18 May 2018) 2008:1–19.

Zolotukhin 2013

Zolotukhin S. Metabolic hormones in saliva: origins and functions. *Oral Diseases* 2013;**19**(3):219–29. DOI: 10.1111/odi.12015; PUBMED: 22994880

* Indicates the major publication for the study

APPENDICES

Appendix I. Search strategies

PubMed:

```
(((((((((Taste[MeSH] OR Taste Perception[MeSH] OR Smell[Mesh] OR Olfactory Perception[Mesh] OR Odorants[MeSH])) OR ((taste*[tiab] OR tasting[tiab]))) OR gustat*[tiab] OR ((smell*[tiab] or smelt[tiab]))) OR olfact*[tiab] OR odor*[tiab])) AND (((Milk, Human[MeSH] OR Infant Formula[MeSH] OR Colostrum[MeSH])) OR ((milk*[tiab] or breastmilk*[tiab]))) OR formula*[tiab] OR ((colostrum[tiab] or colostr[tiab]))) AND (((infant, newborn[MeSH] OR newborn OR neonate OR neonatal OR premature OR low birth weight OR VLBW OR LBW or infan* or neonat*) AND (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh]))))
```

Embase:

1	exp taste/
2	(taste\$ or tasting).ti,ab.
3	gustat\$.ti,ab.
4	exp odor/
5	exp smelling/
6	(smell\$ or smelt).ti,ab.
7	olfact\$.ti,ab.
8	odo?r\$.ti,ab.
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp breast milk/
11	(milk\$ or breastmilk\$).ti,ab.
12	exp artificial milk/
13	formula\$.ti,ab.
14	exp colostrum/
15	(colostrum or colostr[al]).ti,ab.
16	10 or 11 or 12 or 13 or 14 or 15
17	(infan* or newborn or neonat* or premature or very low birth weight or low birth weight or VLBW or LBW).mp
18	exp infant/

(Continued)

19	17 or 18
20	(human not animal).mp.
21	(randomized controlled trial or controlled clinical trial or randomized or placebo or clinical trials as topic or randomly or trial or clinical trial).mp
22	19 and 20 and 21
23	9 and 16 and 22

CINAHL:

S1	(MH "Taste")
S2	TI (taste* OR tasting) OR AB (taste* OR tasting)
S3	TI gustat* OR AB gustat*
S4	(MH "Smell")
S5	(MH "Odors")
S6	TI (smell* OR smelt OR olfact* OR odor*) OR AB (smell* OR smelt OR olfact* OR odor*)
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	(MH "Milk, Human+")
S9	(MH "Infant Formula")
S10	(MH "Colostrum")
S11	TI (milk* OR breastmilk* OR formula* OR colostrum OR colostrals) OR AB (milk* OR breastmilk* OR formula* OR colostrum OR colostrals)
S12	S8 OR S9 OR S10 OR S11
S13	(infan* OR newborn OR neonat* OR premature OR low birth weight OR VLBW OR LBW) AND (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial OR PT clinical trial)
S14	S7 AND S12 AND S13

CRS Web:

1	MESH DESCRIPTOR Taste EXPLODE ALL AND CENTRAL:TARGET
2	MESH DESCRIPTOR Taste Perception EXPLODE ALL AND CENTRAL:TARGET
3	MESH DESCRIPTOR Smell EXPLODE ALL AND CENTRAL:TARGET
4	MESH DESCRIPTOR Olfactory Perception EXPLODE ALL AND CENTRAL:TARGET
5	MESH DESCRIPTOR Odorants EXPLODE ALL AND CENTRAL:TARGET
6	(taste* or tasting):ti,ab AND CENTRAL:TARGET
7	gustat*:ti,ab AND CENTRAL:TARGET
8	(smell* or smelt):ti,ab AND CENTRAL:TARGET
9	olfact*:.ti,ab AND CENTRAL:TARGET
10	odor*:ti,ab AND CENTRAL:TARGET
11	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12	MESH DESCRIPTOR Milk, Human EXPLODE ALL AND CENTRAL:TARGET
13	MESH DESCRIPTOR Infant Formula EXPLODE ALL AND CENTRAL:TARGET
14	MESH DESCRIPTOR Colostrum EXPLODE ALL AND CENTRAL:TARGET
15	(milk* or breastmilk*):ti,ab AND CENTRAL:TARGET
16	formula*:ti,ab AND CENTRAL:TARGET
17	(colostrum or colostr):ti,ab AND CENTRAL:TARGET
18	#12 OR #13 OR #14 OR #15 OR #16 OR #17
19	(infan* or newborn or neonat* or premature or preterm or very low birth weight or low birth weight or VLBW or LBW) AND CENTRAL:TARGET
20	#11 AND #18 AND #19

Appendix 2. Risk of bias tool

We will use the standard methods of Cochrane and Cochrane Neonatal to assess the methodological quality of the trials. For each trial, we will seek information regarding the method of randomisation, blinding and reporting of all outcomes of all the infants enrolled in the trial. We will assess each criterion as being at a low, high, or unclear risk of bias. Two review authors will separately assess each study. We will resolve any disagreement by discussion. We will add this information to the table Characteristics of included studies. We will evaluate the following issues and enter the findings into the risk of bias table:

1. Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we will categorise the method used to generate the allocation sequence as:

- low risk (any truly random process e.g. random number table; computer random number generator);
- high risk (any non-random process e.g. odd or even date of birth; hospital or clinic record number); or
- unclear risk.

2. Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we will categorise the method used to conceal the allocation sequence as:

- low risk (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth); or
- unclear risk

3. Blinding of participants and personnel (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study?

For each included study, we will categorise the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk, high risk or unclear risk for participants; and
- low risk, high risk or unclear risk for personnel.

4. Blinding of outcome assessment (checking for possible detection bias). Was knowledge of the allocated intervention adequately prevented at the time of outcome assessment?

For each included study, we will categorise the methods used to blind outcome assessment. Blinding will be assessed separately for different outcomes or class of outcomes. We will categorise the methods as:

- low risk for outcome assessors;
- high risk for outcome assessors; or
- unclear risk for outcome assessors.

5. Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we will describe the completeness of data including attrition and exclusions from the analysis. We will note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information is reported or supplied by the trial authors, we will re-include missing data in the analyses. We will categorise the methods as:

- low risk (< 20% missing data);
- high risk (\geq 20% missing data); or
- unclear risk.

6. Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we will describe how we investigated the possibility of selective outcome reporting bias and what we found. For studies in which study protocols were published in advance, we will compare prespecified outcomes versus outcomes eventually reported in the published results. If the study protocol was not published in advance, we will contact study authors to gain access to the study protocol. We will assess the methods as:

- low risk (where it is clear that all of the study's prespecified outcomes and all expected outcomes of interest to the review have been reported);
- high risk (where not all the study's prespecified outcomes have been reported; one or more reported primary outcomes were not prespecified outcomes of interest and are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported); or

- unclear risk.

7. Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we will describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We will assess whether each study was free of other problems that could put it at risk of bias as:

- low risk;
- high risk;
- unclear risk

If needed, we plan to explore the impact of the level of bias through undertaking sensitivity analyses.

CONTRIBUTIONS OF AUTHORS

Mariana Muelbert wrote the first draft of the protocol and subsequent drafts, with significant editorial assistance by JH. All review authors contributed to subsequent drafts and approved the final version.

DECLARATIONS OF INTEREST

Frank Bloomfield and Jane Harding have designed and are steering committee members of a randomised controlled trial of different nutritional approaches to feeding moderate-to late-preterm infants that includes provision of smell and taste as one intervention. Mariana Muelbert is one of the research team members on this trial (DIAMOND Trial, Australian New Zealand Clinical Trials Registry ACTRN12616001199404).

There is no other conflict and in particular no benefits of any kind have been received by the authors in relation to any element of the proposed review.

1. Mariana Muelbert: None known.
2. Jane Harding: None known.
3. Frank Bloomfield: None known.

SOURCES OF SUPPORT

Internal sources

- Liggins Institute, University of Auckland, Auckland, New Zealand.
Infrastructure and support for the preparation of the review
- University of Auckland, Auckland, New Zealand.
Doctoral Scholarship for Mariana Muelbert

External sources

- Health Research Council of New Zealand, New Zealand.

This review is supported in part by a programme grant from the Health Research Council of New Zealand (16/605)

- National Institute for Health Research, UK.

Editorial support for Cochrane Neonatal has been funded with funds from a UK National Institute of Health Research (NIHR) Cochrane Programme Grant (16/114/03). The views expressed in this publication are those of the authors and not necessarily those of the National Health Service, the NIHR or the UK Department of Health.