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Protocol manuscript

The relationship between exclusive breastfeeding and motor development in children: a protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction:

The recommendations of most scientific societies encourage mothers to keep breastfeeding for at least 6 months, due to the numerous immunologic, cognitive developmental and motor skill benefits that breastfeeding confers. Although the influence of breastfeeding on motor development during childhood has been extensively studied, the findings are inconsistent, and some studies have even reported no effect. This manuscript presents a protocol for a systematic review and meta-analysis, with the aim of reviewing the relationship between breastfeeding and motor skill development in children; in terms of duration, exclusivity or non-exclusivity of breastfeeding, based on data from published observational studies.

Methods and analysis:

To identify relevant studies, the search will be conducted using MEDLINE (via PubMed), EMBASE, Web of Science and Cochrane Library. Observational studies (Cross-sectional and follow up studies) written in English or Spanish that investigate the association between breastfeeding and motor development in children will be included. This systematic review and meta-analysis protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). A Critical Appraisal Checklist for Analytical Cross-Sectional Studies and The Newcastle-Ottawa Quality Assessment Scale for longitudinal studies will be used to assess the quality of included studies. The effect of breastfeeding on motor skill development will be calculated as the primary outcome. Subgroup analyses will be carried out based on the characteristics of motor skill development and the population included.

Ethics and dissemination

Ethical approval is not required because the data used for will be obtained from published studies and there will be no concerns about privacy. The findings from this study will be relevant information regarding the association of breastfeeding and motor development in children, and could be used encourage to improve breastfeeding rates. The results will be published in a peer-reviewed journal.

Trial registration number: PROSPERO CRD42018093706. (24/04/2018)

Keywords: breastfeeding, motor development, motor skills, children.

Strengths and limitations of this study

- This review will present a comprehensive and standardised methodology, according to an established framework, to identify relevant studies that analyse the effect of breastfeeding on motor skills.
- Analysis of different sources of heterogeneity and the assessment of risk of bias of the included studies will be performed independently by two researchers.
- To identify studies that aim to determine the association between breastfeeding and motor development, an exhaustive literature search will be carried out.
- This study could be limited by the quality of available studies, insufficient methodological rigor and statistical heterogeneity.
- Different methods used for measuring breastfeeding and motor development from observational studies may be another limitation to the quality of evidence of this study.

INTRODUCTION

The first two years of a child's life is a critical period for health, growth and development; all of which are affected by nutritional status. It is well documented that breastfeeding provides many important health benefits to children and mothers, and this is considered the gold standard in infant feeding.[1,2]

The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life as an ideal feed, and continuation of breastfeeding for at least the first and second years to supplement the introduction of complementary feed. There is no evidence against this recommendation,[1,2,3,4] which is also supported by many scientific and practitioner associations.[5,6,7] The World Health Assembly, as part of its Global Strategy for the Feeding of Infants and Young Children, encouraged Member States to promote exclusive breastfeeding for 6 months as a global public health recommendation which provides many benefits to babies, reduces the risk of diseases and helps to promote good physical and cognitive growth.[8,9]

However, the rates of breastfeeding at 6 months of age remain low in Europe; and even in countries where initial rates are high, there is a marked decrease by the sixth month.[10,11,12] Early cessation of breastfeeding and the introduction of solids before 4 months can have considerable adverse effects on the health of women and children. [12,13,14,15] Therefore, it is important to consider what is causing the failure to comply with recommendations, and there is a need for greater efforts to disseminate the benefits of breastfeeding and create a social environment that favours it.

Although infant development is a process that is influenced by several factors, breastfeeding in the first months of life is a key determinant for optimal growth and adequate cognitive and motor development. Additionally, breastfeeding prevents gastrointestinal infection and decreases the risk of diseases later in life such as allergies, asthma, obesity and celiac disease.[2,3,7,9,12,16,17]

Thus, motor development and cognitive function represent indicators of overall development during the first years.[18,19] Although consistent evidence of the positive effects of extended breastfeeding on cognitive function has been reported,[20] few studies have focused on motor development. The relationship between motor development and breastfeeding is difficult to analyse because incomplete control for confounders is reported in the current literature, even when various assessments of motor milestones are

considered across studies. To date, no clear associations between the duration of breastfeeding and motor development have been reported.[21,22,23,24]

The purpose of this study protocol is to provide a clear methodology to review the effects of breastfeeding practices on motor development in children, in terms of duration and exclusive or not exclusive breastfeeding.

OBJECTIVE

The aim of this protocol study is to present an objective and transparent methodology with which to conduct a systematic review and meta-analysis aimed to increase knowledge and understanding of the associations between the duration and exclusivity of breastfeeding and motor development in early childhood.

METHODS AND ANALYSIS

The methodology of this protocol was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P)[25]. The Meta-analysis of observational studies in epidemiology: a proposal for reporting (MOOSE[26]), PRISMA and Cochrane Collaboration Handbook[27] will be used to guide the review methods. This protocol was registered with PROSPERO, (Registration number CRD42018093706) on 24 April 2018.

Inclusion/exclusion criteria for study selection

Studies will be retrieved from the literature by searching for studies which measure the effects of breastfeeding duration and exclusivity, and report any type of measure of motor development. To be considered inclusion, studies will be required to meet the following criteria: (i) participants, children who have not received supplementation in feeding; (ii) exposure, studies that measure the effect of breastfeeding in terms of duration and exclusivity and report any type of measure; (iii) outcome, studies in which motor development is an outcome measured using standardised tests; and (iv) study design, observational studies (cross-sectional or longitudinal design) that are written in English or Spanish.

Studies will be excluded when: (i) they include infants born in multiple pregnancies with congenital infections or special circumstances requiring intensive care or hospitalization during the neonatal period or children with mental disorders or any detected delay in communication, cognition or motor skills (ii) studies where breast milk has been supplemented and (iii) studies which have already been used in other similar reviews.

Search methods for the identification of studies

Search strategy

The literature search will be conducted in MEDLINE (via PubMed), EMBASE, Web of Science and Cochrane Library. The searches will be reviewed immediately prior to the final analysis in order to identify further potential studies. Study records will be managed using the Mendeley reference manager. The following search terms will be combined to conduct the search: breastfeeding, feeding, 'exclusive breastfeeding', breastfed, 'breast suckling', suckling, 'motor skill', 'psychomotor performance', 'motor development', 'psychomotor development', 'development milestones', children, child, infant, childhood, 'observational study', 'cohort study', 'population-based' and 'cross sectional' (Table 1). Previous reviews and meta-analyses will be screened, as well as the reference lists of the selected studies.

Table 1 Search strategy for MEDLINE database

Breastfeeding OR feeding OR 'exclusive breastfeeding' OR breastfed OR 'breast suckling' OR 'suckling'	AND	'motor skills' OR 'psychomotor performance' OR 'motor development' OR 'psychomotor development' OR 'motor development milestones'	AND	children OR child OR infant OR childhood	AND	'observational study' OR 'cohort study' OR 'population-based' OR 'cross sectional'

Selection of studies and data extraction

Two researchers will screen all relevant titles and abstracts of the retrieved publications to identify eligible studies. Inclusion and exclusion criteria will be applied to full texts to identify all potentially eligible articles. Inconsistencies in data collection will be solved by consensus. A third reviewer will be consulted when disagreements persist. The process of identifying, screening and including/excluding articles will be illustrated using the PRISMA[25] flow chart (Figure 1).

Finally, information about the main characteristics of the identified studies will be extracted, including the following data: i) first author´s name, ii) publication year, iii) country, iv) study design, v) characteristics of the study population (sample size, age of children at evaluation, gender and number of participants in each group), vi) breastfeeding category (as defined in Table 2) and vii) test used for assessment of motor development (Table 2). The authors of the included studies will be contacted to request any missing data.

Table 2 Characteristics of studies included in the systematic review and/or meta-analysis

Reference	Country	Study design	Population		Breastfeeding		Outcome MD	
			Sample size	Sample age	Categories	n	Tool	Measurement
First author´s name and year of publication	Country	Design of the study	Number of participants	Age of participants (years)	Duration periods of exclusive breastfeeding /any breastfeeding	Number participants in each breastfeeding category	Instrument used to measure MD	Measure used to express MD

Key: MD, Motor Development

Assessment of risk of bias

Two independent researchers will be blinded to the authors, titles and years of publication of the included studies to evaluate the risk of bias of each included study. The Critical Appraisal Checklist for Analytical Cross-Sectional Studies from The Joanna Briggs Institute will be used.[28] This tool evaluates the risk of bias according to eight items which are scored as "Yes", "No", "Unclear" or "Not applicable".

The Newcastle-Ottawa Quality Assessment Scale[29] will be used to assess the risk of bias of longitudinal studies, including case control and cohort studies. This tool evaluates the risk of bias according to eight items which are grouped in three categories: selection, comparability and exposure or outcome (for case control or cohort studies, respectively). Each study can be awarded one star for each item within the selection and exposure categories, and a maximum of two stars in the comparability category. Any disagreements over the assessment of quality will be solved by consensus. A third researcher will be consulted if a consensus is not reached.

Statistical analysis

After data extraction, the reviewers will determine whether meta-analysis is possible. At least four studies addressing the association between breastfeeding and motor development will be required in order to conduct a meta-analysis. If meta-analysis is possible, STATA V.15 software will be used to compute the pooled effect size (ES) estimates with 95% confidence intervals (CIs). The standardized mean difference will be

calculated for each breastfeeding category as an estimate of ES,[30] using Cohen´s d index as the ES statistic. We will compare the level of motor development in children who have never been breastfed, as a reference group, with children who have been exclusively breastfed or breastfed for any length of time. If possible, a comparison between children breastfed for at least 6 months and children breastfed for less than 6 months will also be carried out.

A fixed-effects model[31] will be used in the case of no heterogeneity; otherwise, a random-effects model[32] will be used. Heterogeneity will be assessed by computing the I^2 statistic to quantify inconsistencies and variability within the meta-analysis.[33] The values of I^2 will be considered as follows: 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity and 75%–100% represents considerable heterogeneity.

Linear meta-analysis regression models will be used to explore the impact of covariates, directed by the results of heterogeneity analysis. Finally, publication bias will be evaluated using a funnel plot according to the method proposed by Egger.[34] When a meta-analysis is not feasible, we will perform a narrative synthesis.

Subgroup analysis and meta-regression

If enough studies are available, subgroup analysis will be conducted. Subgroup and meta-regression analyses will be carried out on the main factors causing heterogeneity, such as the type of motor development assessment (i.e., gross or fine motor), gender, age of study participants, birth weight, breastfeeding classification (never, less than 6 months or more than 6 months) and aspects related to motor skills such as the type of measure used. Furthermore, the design and risk of bias scores of the studies will be considered for additional subgroup analysis. Additional potential moderating variables may be identified after reviewing the literature.

Sensitivity analysis

We will perform sensitivity analysis to assess whether the findings are robust over the assumptions made. These analyses will be conducted by removing studies one by one from the main analysis.

No patient and Public Involvement

Existing databases will be used for the purpose of this study. Patients and public will not be involved in the design of this study. This review will assess the effect of breastfeeding on motor developmental outcomes in infants. Insights provided by this study could be used in clinical practice to ameliorate outcomes; specifically, motor development; of children in the population.

DISCUSSION

The aim of this study is to present an objective and transparent methodology with which to conduct a systematic review and meta-analysis investigating whether the duration of breastfeeding is associated with motor development and the child's developmental status.

Many studies have examined whether breastfeeding in early life, a critical phase of development, could affect later cognitive function and motor development in children.[18,19,20] Infant development is a complex process, which encompasses several factors that allow the acquisition of skills that will contribute to a child´s full participation in activities and will help to establish a direct relationship with the environment.[18]

Motor function is an accepted indicator of development during the first years of life.[35,36,37] It directly contributes to and reflects the relationship that the child establishes with the physical and social environments. In addition, motor development plays an important role in other areas of development, such as physical growth and cardiorespiratory fitness, the latter being a powerful and effective indicator of cardiovascular health.[38,39,40] Poor motor development performance may incline children towards activity avoidance and sedentary behaviours, which are linked to increased risk of chronic disease in adulthood.[41]

There is considerable evidence about the long- and short-term benefits of breastfeeding for infant health.[16,17] However, no consensus has been reached about the effects of breastfeeding on motor development, and the results and conclusions of existing studies are controversial.[19,23,24] The complexity of child development makes it difficult to evaluate these effects, and certain aspects of infant development are influenced by psychosocial and socioeconomic factors, which could contribute to some of the observed differences. The scientific evidence regarding the benefits of breastfeeding in terms of

motor development outcomes is weak, and the strength of this association is controversial because most studies lack adequate control for potential confounders. Furthermore, previous studies have measured infant development using different standardised tests.

Potential limitations of this research could include publication bias, information bias, lack of consultation of grey literature, inclusion of articles in English and Spanish only, analysis of cross-sectional studies as this does not allow a causal association to be evaluated (breastfeeding always precedes motor development), poor statistical analysis and inadequate reporting of methods and findings of the primary studies. To overcome these limitations, the study will be conducted and reported by two independent reviewers, and inconsistencies in data collection will be solved by consensus. Furthermore; existing guidelines, the MOOSE statement, PRISMA, and Cochrane Collaboration Handbook recommendations will be followed.

To summarise, we will carry out a systematic review and meta-analysis with the objective of reviewing existing literature on the relationship between breastfeeding and motor development. Despite the fact that some aspects of motor development appear to be controversial, if this study confirms the positive effects of breastfeeding on motor skill development through analysis of the evidence, it could encourage greater interest in breastfeeding within the areas of public and child health.

This situation highlights the need for guidelines or recommendations that are based on rigorous and updated bibliographical review of the best available scientific evidence, for use in daily practice to improve the quality and effectiveness of interventions. This could lead to an improvement in the health status and development of children worldwide.

ETHICS AND DISSEMINATION

The data included in this project will be provide by the original studies; therefore, ethical approval and informed consent of patients will not be required.

This protocol provides a clear and structured procedure to extract relevant information on the association of breastfeeding and motor milestones. This study will have clinical and public health implications, because it could provide support for recommendations of breastfeeding, which might help to prevent low rates of breastfeeding and early abandonment. Suggestions for future research will be made according to the findings of

this systematic review and meta-analysis, and evidence-based recommendations to improve breastfeeding rates will be offered, due to the involvement of this practice in children's development.

Contributors:

BN-P and MH-L designed the study. BN-P was the principal investigator and guarantor. BN-P and MH-L were the main coordinators of the study. DPP-C, CA-B, CB-C, VM-V and BN-P conducted the study. MH-L, DPP-C and VM-V gave statistical and epidemiological support. MH-L wrote the article with the support of CB-C, VM-V and BN-P. All authors reviewed and approved the final version of the manuscript.

Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing:

Extra data is available by emailing: celia.alvarezbueno@uclm.es

Transparency

The manuscripts guarantor (BN-P) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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TABLES LEGENDS

Table 1. Search strategy for the MEDILINE database.

Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

FIGURE LEGENDS

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram of identification, screening, eligibility and inclusion of studies

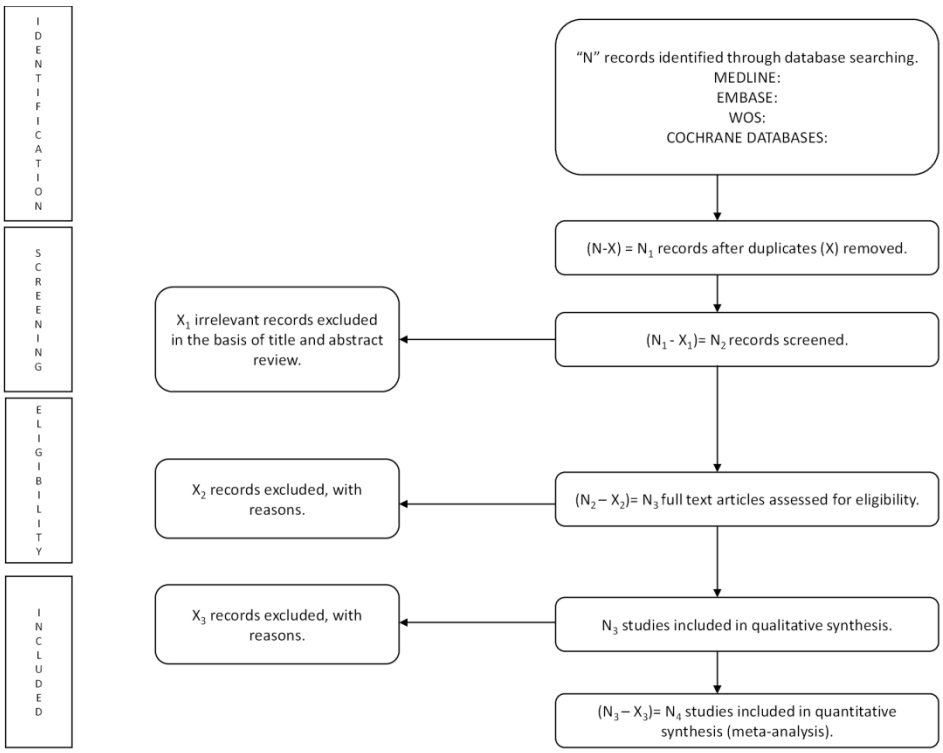

Figure 1 Literature search Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flow diagram of identification, screening, eligibility and inclusion of studies.

169x127mm (300 x 300 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification: p. 1	1a	Identify the report as a protocol of a systematic review
Update: NA	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration: p. 2	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors: pp. 1, 13		
Contact: p. 1	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions: p. 13	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments: NA	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: NA		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale: pp 4, 5	6	Describe the rationale for the review in the context of what is already known
Objectives p. 5	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria: pp. 5, 6	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources: p. 6	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy: pp. 6, 7	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records: pp. 7, 8		
Data management: p. 7	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process: p. 7	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process: p. 7	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items: pp 7, 10	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization: pp. 7, 8	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies: p. 8	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis: pp 9, 10	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es): NA	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence: NA	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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The relationship between breastfeeding and motor development in children: a protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction:

The recommendations of most health organizations encourage mothers to keep exclusive breastfeeding during the first 6 months and combining breastfeeding with the complementary feed at least the first and second years, due to the numerous immunologic, cognitive developmental and motor skill benefits that breastfeeding confers. Although the influence of breastfeeding on motor development during childhood has been studied, the findings are inconsistent, and some studies have even reported no effect. This manuscript presents a protocol for a systematic review and meta-analysis, with the aim of reviewing the relationship between breastfeeding and motor skill development in children; in terms of duration, exclusivity or non-exclusivity of breastfeeding.

Methods and analysis:

To identify relevant studies, the search will be conducted using MEDLINE (via PubMed), EMBASE, Web of Science and Cochrane Library from inception to December 2019. Observational studies (Cross-sectional and follow up studies) written in English or Spanish that investigate the association between breastfeeding and motor development in children will be included. This systematic review and meta-analysis protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). A Critical Appraisal Checklist for Analytical Cross-Sectional Studies and The Newcastle-Ottawa Quality Assessment Scale for longitudinal studies will be used to assess the quality of included studies. The effect of breastfeeding on motor skill development will be calculated as the primary outcome. Subgroup analyses will be carried out based on the characteristics of motor skill development and the population included.

Ethics and dissemination

Ethical approval is not required because the data used for will be obtained from published studies and there will be no concerns about privacy. The findings from this study will be relevant information regarding the association of breastfeeding and motor development in children and could be used encourage to improve breastfeeding rates. The results will be published in a peer-reviewed journal.

Trial registration number: PROSPERO CRD42018093706. (24/04/2018)

Keywords: breastfeeding, motor development, motor skills, children.

Strengths and limitations of this study

- This review will present a comprehensive and standardised methodology, according to an established framework, to identify relevant studies that analyse the effect of breastfeeding on motor skills.
- Analysis of different sources of heterogeneity and the assessment of risk of bias of the included studies will be performed independently by two researchers.
- To identify studies that aim to determine the association between breastfeeding and motor development, an exhaustive literature search will be carried out.
- This study could be limited by the quality of available studies, insufficient methodological rigor and statistical heterogeneity.
- Different methods used for measuring breastfeeding and motor development from observational studies may be another limitation to the quality of evidence of this study.

INTRODUCTION

The first two years of a child's life is a critical period for health, growth and development; all of which are affected by nutritional status. It is well documented that breastfeeding provides many important health benefits to children and mothers and is considered the gold standard in infant feeding.[1,2]

The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life as an ideal feed, and continuation of breastfeeding for at least the first and second years, which is also supported by many health organizations.[1-6] However, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) differs in the recommendation of the age when complementary feed should be included because of the risk of food allergies.[7] The World Health Assembly, as part of its Global Strategy for the Feeding of Infants and Young Children, encouraged Member States to promote exclusive breastfeeding for 6 months as a global public health recommendation which provides many benefits to babies, reduces the risk of diseases and helps to promote good physical and cognitive growth.[8,9]

However, the rates of breastfeeding at 6 months remain low in Europe; and even in countries where initial rates are high, there is a marked decrease by the sixth month.[10-11] Early cessation of breastfeeding and the introduction of solids before 4 months could have considerable adverse effects on the children and women's health.[12-15] Therefore, it is important to elucidate what are the reasons behind the failure to achieve the recommendations, and there is a need for greater efforts to disseminate the benefits of breastfeeding and create a social environment that could favour it.

Although infant development is a process that is influenced by several factors, breastfeeding in the first months of life is a key determinant for optimal growth and adequate cognitive and motor development. Additionally, breastfeeding provides quality nutrients improvement (higher proportion of unsaturated fatty acids), prevents gastrointestinal infection and decreases the risk of diseases later in life such as allergies, asthma, obesity and celiac disease.[2,3,7,9,12,16-19]

Thus, motor development and cognitive function represent indicators of overall development during the first years. Motor development allows the acquisition of skills that will contribute to a child´s full participation in activities, avoiding sedentary behaviours and will help to establish a direct and active relationship with the

environment.[20,21] Although consistent evidence of the positive effects of extended breastfeeding on cognitive function has been reported,[22] few studies have focused on motor development. The relationship between motor development and breastfeeding is difficult to analyse because incomplete control for confounders is reported in the current literature, even when various assessments of motor milestones are considered across studies. To date, no clear associations between the duration of breastfeeding and motor development have been reported.[23-26]

The purpose of this study protocol is to provide a clear methodology to review the effects of breastfeeding practices on motor development in children, in terms of duration and exclusive or not exclusive breastfeeding.

OBJECTIVE

The aim of this protocol study is to present an objective and transparent methodology to conduct a systematic review and meta-analysis aimed to increase knowledge and understanding of the associations between the duration and exclusivity of breastfeeding and motor development in children age 0 to 10 years old.

METHODS AND ANALYSIS

The methodology of this protocol was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P)[27]. The Meta-analysis of observational studies in epidemiology: a proposal for reporting (MOOSE[28]), the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Cochrane Collaboration Handbook[29] will be used to report and guide the review methods. This protocol was registered with PROSPERO, (Registration number CRD42018093706) on 24 April 2018.

Inclusion/exclusion criteria for study selection

Studies will be retrieved from the literature by searching for studies which measure the effects of breastfeeding duration and type (exclusivity, even if it is little, or no exclusive breastfeeding), and report any type of measure of motor development. To be considered

for inclusion, studies will be required to meet the following criteria: (i) children age 0 to 10 years old (ii) exposure, breastfeeding in terms of duration and type (exclusivity or non-exclusivity) and reported any type of measure; (iii) outcome, motor development measured using standardised tests; and (iv) studies written in English or Spanish.

Studies will be excluded when: (i) include infants born in multiple pregnancies, with congenital infections or special circumstances requiring intensive care or hospitalization during the neonatal period; (ii) include children with mental disorders or any detected delay in communication, cognition or motor skills; (ii) breast milk has been supplemented, (iii) multiple publication derived from a single study; and (iv) do not adjust for confounding variates such as socioeconomic status and home environment.

Search methods for the identification of studies

Search strategy

The literature search will be conducted in MEDLINE (via PubMed), EMBASE (via Scopus), Web of Science and Cochrane Library from inception to December 2019. Searches for unpublished studies will be conducted at: OPEN GRAY, ProQuest dissertations & Thesis Global, Theseo, Networked digital library of theses and dissertations (NDLTD), and Google Scholar. A search of ClinicalTrials.gov and EudraCT clinical trial records will also be conducted. The searches will be reviewed immediately prior to the final analysis in order to identify further potential studies. Study records will be managed using the Mendeley reference manager.

The following search terms will be combined: breastfeeding, feeding, 'exclusive breastfeeding', breastfed, 'breast suckling', suckling, 'motor skill', 'psychomotor performance', 'motor development', 'psychomotor development', 'development milestones', children, child, infant, childhood (Table 1). Previous reviews and meta-analyses will be screened, as well as the reference lists of the selected studies to complete the literature search.

Table 1 Search strategy for MEDLINE database

Breastfeeding OR feeding OR 'exclusive breastfeeding' OR breastfed OR 'breast suckling' OR 'suckling'	AND	'motor skills' OR 'psychomotor performance' OR 'motor development' OR 'psychomotor development' OR 'motor development milestones'	AND	children OR child OR infant OR childhood

Selection of studies and data extraction

Two researchers will screen all relevant titles and abstracts of the retrieved publications to identify eligible studies. Inclusion and exclusion criteria will be applied to full texts to identify all potentially eligible articles. Inconsistencies in data collection will be solved by consensus. A third reviewer will be consulted when disagreements persist. The process of identifying, screening and including/excluding articles will be illustrated using the PRISMA[27] flow chart (Figure 1).

Finally, information about the main characteristics of the identified studies will be extracted, including the following data: i) first author´s name, ii) publication year, iii) country, iv) study design, v) characteristics of the study population (sample size, age of children at evaluation, gender and number of participants in each group), vi) breastfeeding category (as defined in Table 2) and vii) test used for assessment of motor development, vii (Table 2). The authors of the included studies will be contacted to request any missing data.

Table 2 Characteristics of studies included in the systematic review and/or meta-analysis

Reference	Country	Study design	Population		Breastfeeding		Outcome MD	
			Sample size	Sample age	Categories	n	Tool	Measurement
First author´s name and year of publication	Country	Design of the study	Number of participants	Age of participants (years)	Duration periods of exclusive breastfeeding /any breastfeeding	Number participants in each breastfeeding category	Instrument used to measure MD	Mean value (SD)

Key: MD, Motor Development; SD: Standard Deviation

Assessment of risk of bias

Two independent researchers will be blinded to the authors, titles and years of publication of the included studies to evaluate the risk of bias of each included study. The Critical Appraisal Checklist for Analytical Cross-Sectional Studies from The Joanna Briggs Institute will be used.[30] This tool evaluates the risk of bias according to eight items that could be scored as "Yes", "No", "Unclear" or "Not applicable".

The Newcastle-Ottawa Quality Assessment Scale[31] will be used to assess the risk of bias of longitudinal studies, including case control and cohort studies. This tool evaluates the risk of bias according to eight items which could be grouped in three categories: selection, comparability and exposure or outcome (for case control or cohort studies, respectively). Each study can be awarded one star for each item within the selection and exposure categories, and a maximum of two stars in the comparability category.

Any disagreements over the assessment of quality will be solved by consensus. A third researcher will be consulted if a consensus is not reached.

Statistical analysis

After data extraction, the reviewers will determine whether meta-analysis is possible. At least four studies addressing the association between breastfeeding and motor development will be required in order to conduct the meta-analysis. If meta-analysis is possible, STATA V.15 software will be used. The standardized mean difference will be

calculated for each study reporting the association between breastfeeding category and motor development using Cohen´s d index.[32] To compute the pooled effect size (ES) estimates with 95% confidence intervals (CIs) fixed-effects models[33] will be used in the case of no heterogeneity; otherwise, random-effects model[34,35] will be used We will compare the level of motor development in children who have been exclusively breastfed or breastfed for any length of time, as a reference group, with the motor development of those who have never been breastfed. If possible, a comparison between children breastfed for at least 6 months and children breastfed for less than 6 months will also be carried out.

Heterogeneity will be assessed by computing the I^2 statistic.[36] The values of I^2 will be considered as follows: 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity and 75%–100% represents considerable heterogeneity.

Linear meta-analysis regression models will be used to explore whether covariates could be associated with the magnitude of the effect and could explain the observed statistical heterogeneity.[36] Finally, publication bias will be evaluated using a funnel plot according to the method proposed by Egger.[37] When a meta-analysis is not feasible, we will perform a narrative synthesis.

Subgroup analysis and meta-regression

If enough studies are available, subgroup analysis will be conducted. Several meta-regressions will be performed on study and sample characteristics including the type of motor development assessment (i.e., gross or fine motor), gender, age of study participants, birth weight, breastfeeding classification (never, less than 6 months or more than 6 months) and aspects related to motor . Furthermore, the design and risk of bias scores of the studies will be considered for additional subgroup analysis. Additional potential moderating variables may be identified after reviewing the literature.

Sensitivity analysis

We will perform sensitivity analysis by removing studies one by one from the main analysis to assess the robustness of the findings.

No patient and Public Involvement

Existing databases will be used for the purpose of this study. Patients and public will not be involved in the design of this study. This review will assess the effect of breastfeeding on motor developmental outcomes in infants. Insights provided by this study could be used in clinical practice to ameliorate outcomes; specifically, motor development; of children in the population.

DISCUSSION

The aim of this study is to present an objective and transparent methodology to conduct a systematic review and meta-analysis investigating whether the duration of breastfeeding is associated with motor development.

Many studies have examined whether breastfeeding in early life, a critical phase of development, could affect later cognitive function and motor development in children.[20-22] Infant development is a complex process, which encompasses several factors allowing the acquisition of skills that will contribute to the child´s full participation in activities and help to establish a direct relationship with the environment.[20]

Motor function is an accepted indicator of development during the first years of life.[38-40] It directly contributes to and reflects the relationship that the child establishes with the physical and social environments. In addition, motor development plays an important role in other areas of development, such as physical growth and cardiorespiratory fitness, the latter being a powerful and effective indicator of cardiovascular health.[41-43] Poor motor development performance may incline children towards activity avoidance and sedentary behaviours, which are linked to increased risk of chronic disease in adulthood.[44]

There is considerable evidence about the long- and short-term benefits of breastfeeding for infant health.[16-19] However, no consensus has been reached about the effects of breastfeeding on motor development, and the results and conclusions of existing studies are controversial.[21,25,26] The complexity of child development makes it difficult to evaluate these effects, and certain aspects of infant development are influenced by psychosocial and socioeconomic factors, which could contribute to some of the observed differences. The scientific evidence regarding the benefits of breastfeeding in terms of

motor development outcomes is weak, and the strength of this association is controversial because most studies lack adequate control for potential confounders. Furthermore, previous studies have measured infant development using different standardised tests.

Potential limitations of this research could include publication bias, information bias, inclusion of articles in English and Spanish only, analysis of cross-sectional studies as this does not allow a causal association to be evaluated (breastfeeding always precedes motor development), poor statistical analysis and inadequate reporting of methods and findings of the primary studies. To overcome these limitations, the systematic review and meta-analysis will be conducted and reported by two independent reviewers and a third researcher will be consulted if inconsistencies exist in data collection or consensus is not reached. However, despite these strategies, is not possible to ensure the lack of risk of bias. Furthermore; existing guidelines, the MOOSE statement, PRISMA, and Cochrane Collaboration Handbook recommendations will be followed.

To summarise, we will carry out a systematic review and meta-analysis with the objective of reviewing existing literature on the relationship between breastfeeding and motor development. Despite the fact that some aspects of motor development appear to be controversial, if this study confirms the positive effects of breastfeeding on motor skills development, it could encourage greater interest in breastfeeding within the areas of public and child health.

The lack of evidence on the effect of breastfeeding and motor skills development highlights the need for guidelines or recommendations based on rigorous and updated reviews summarizing the available scientific evidence, to be used in daily practice in order to improve the quality and effectiveness of interventions. The findings of this review could lead to an improvement in the health status and development of children worldwide.

ETHICS AND DISSEMINATION

The data included in this project will be provide by the original studies; therefore, ethical approval and informed consent of patients will not be required.

This protocol provides a clear and structured procedure to extract relevant information on the association of breastfeeding and motor skills. This study will have clinical and public

health implications, because it could provide support for recommendations on breastfeeding, which might help to prevent low rates of breastfeeding and early abandonment. Suggestions for future research will be made according to the findings of this systematic review and meta-analysis, and evidence-based recommendations to improve breastfeeding rates will be offered. Moreover, longitudinal studies will be needed to confirm the duration effect of breastfeeding better associate with children's motor development.

Contributors:

BN-P and MH-L designed the study. BN-P was the principal investigator and guarantor. BN-P and MH-L were the main coordinators of the study. DPP-C, CA-B, CB-C, VM-V and BN-P conducted the study. MH-L, DPP-C and VM-V gave statistical and epidemiological support. MH-L wrote the article with the support of CB-C, VM-V and BN-P. All authors reviewed and approved the final version of the manuscript.

Competing interests:

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing:

Extra data is available by emailing: celia.alvarezbueno@uclm.es

Transparency

The manuscripts guarantor (BN-P) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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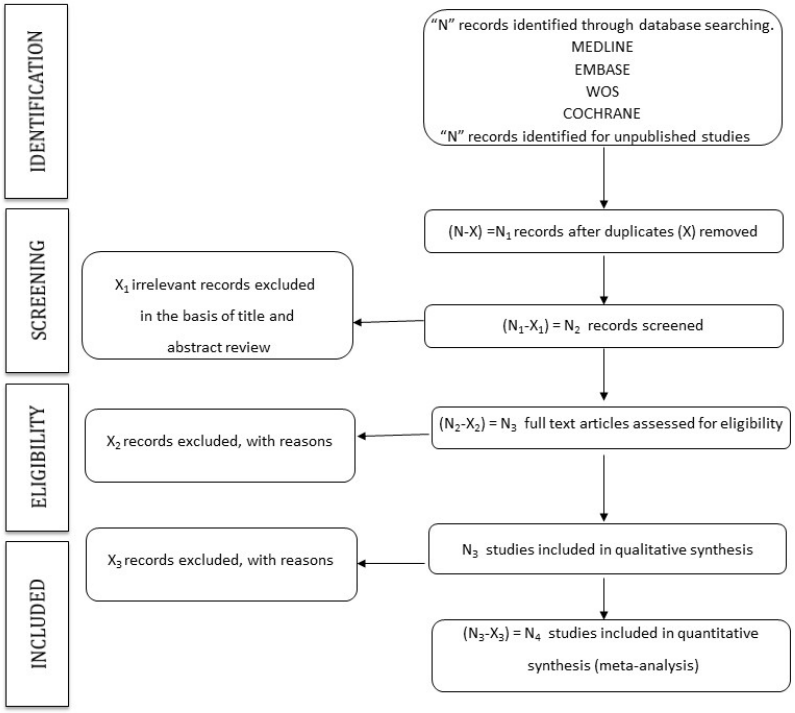
TABLES LEGENDS

Table 1. Search strategy for the MEDILINE database.

Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

FIGURE LEGENDS

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram of identification, screening, eligibility and inclusion of studies



254x190mm (96 x 96 DPI)

PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification: p. 1	1a	Identify the report as a protocol of a systematic review
Update: NA	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration: p. 2	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors: pp. 1, 13		
Contact: p. 1	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions: p. 13	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments: NA	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: NA		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale: pp 4, 5	6	Describe the rationale for the review in the context of what is already known
Objectives p. 5	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria: pp. 5, 6	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources: p. 6	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy: pp. 6, 7	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records: pp. 7, 8		
Data management: p. 7	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process: p. 7	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process: p. 7	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items: pp 7, 10	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization: pp. 7, 8	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies: p. 8	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis: pp 9, 10	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es): NA	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence: NA	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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The relationship between breastfeeding and motor development in children: a protocol for a systematic review and meta-analysis.

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Protocol manuscript

The relationship between breastfeeding and motor development in children: a protocol for a systematic review and meta-analysis.

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ABSTRACT

Introduction:

The recommendations of most health organizations encourage mothers to keep exclusive breastfeeding during the first 6 months and combining breastfeeding with the complementary feed at least the first and second years, due to the numerous immunologic, cognitive developmental and motor skill benefits that breastfeeding confers. Although the influence of breastfeeding on motor development during childhood has been studied, the findings are inconsistent, and some studies have even reported no effect. This manuscript presents a protocol for a systematic review and meta-analysis, with the aim of reviewing the relationship between breastfeeding and motor skill development in children; in terms of duration, exclusivity or non-exclusivity of breastfeeding.

Methods and analysis:

To identify relevant studies, the search will be conducted using MEDLINE (via PubMed), EMBASE, Web of Science and Cochrane Library from inception to December 2019. Observational studies (Cross-sectional and follow up studies) written in English or Spanish that investigate the association between breastfeeding and motor development in children will be included. This systematic review and meta-analysis protocol follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P). A Critical Appraisal Checklist for Analytical Cross-Sectional Studies and The Newcastle-Ottawa Quality Assessment Scale for longitudinal studies will be used to assess the quality of included studies. The effect of breastfeeding on motor skill development will be calculated as the primary outcome. Subgroup analyses will be carried out based on the characteristics of motor skill development and the population included.

Ethics and dissemination

Ethical approval is not required because the data used for will be obtained from published studies and there will be no concerns about privacy. The findings from this study will be relevant information regarding the association of breastfeeding and motor development in children and could be used encourage to improve breastfeeding rates. The results will be published in a peer-reviewed journal.

Trial registration number: PROSPERO CRD42018093706. (24/04/2018)

Keywords: breastfeeding, motor development, motor skills, children.

Strengths and limitations of this study

- This review will present a comprehensive and standardised methodology, according to an established framework, to identify relevant studies that analyse the effect of breastfeeding on motor skills.
- Analysis of different sources of heterogeneity and the assessment of risk of bias of the included studies will be performed independently by two researchers.
- To identify studies that aim to determine the association between breastfeeding and motor development, an exhaustive literature search will be carried out.
- This study could be limited by the quality of available studies, insufficient methodological rigor and statistical heterogeneity.
- Different methods used for measuring breastfeeding and motor development from observational studies may be another limitation to the quality of evidence of this study.

INTRODUCTION

The first two years of a child's life is a critical period for health, growth and development; all of which are affected by nutritional status. It is well documented that breastfeeding provides many important health benefits to children and mothers and is considered the gold standard in infant feeding.[1,2]

The World Health Organization (WHO) recommends exclusive breastfeeding for the first 6 months of life as an ideal feed, and continuation of breastfeeding for at least the first and second years, which is also supported by many health organizations.[1-6] However, the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) differs in the recommendation of the age when complementary feed should be included because of the risk of food allergies.[7] The World Health Assembly, as part of its Global Strategy for the Feeding of Infants and Young Children, encouraged Member States to promote exclusive breastfeeding for 6 months as a global public health recommendation which provides many benefits to babies, reduces the risk of diseases and helps to promote good physical and cognitive growth.[8,9]

However, the rates of breastfeeding at 6 months remain low in Europe; and even in countries where initial rates are high, there is a marked decrease by the sixth month.[10-11] Early cessation of breastfeeding and the introduction of solids before 4 months could have considerable adverse effects on the children and women's health.[12-15] Therefore, it is important to elucidate what are the reasons behind the failure to achieve the recommendations, and there is a need for greater efforts to disseminate the benefits of breastfeeding and create a social environment that could favour it.

Although infant development is a process that is influenced by several factors, breastfeeding in the first months of life is a key determinant for optimal growth and adequate cognitive and motor development. Additionally, breastfeeding provides quality nutrients improvement (higher proportion of unsaturated fatty acids), prevents gastrointestinal infection and decreases the risk of diseases later in life such as allergies, asthma, obesity and celiac disease.[2,3,7,9,12,16-19]

Thus, motor development and cognitive function represent indicators of overall development during the first years. Motor development allows the acquisition of skills that will contribute to a child´s full participation in activities, avoiding sedentary behaviours and will help to establish a direct and active relationship with the

environment.[20,21] Although consistent evidence of the positive effects of extended breastfeeding on cognitive function has been reported,[22] few studies have focused on motor development. The relationship between motor development and breastfeeding is difficult to analyse because incomplete control for confounders is reported in the current literature, even when various assessments of motor milestones are considered across studies. To date, no clear associations between the duration of breastfeeding and motor development have been reported.[23-26]

The purpose of this study protocol is to provide a clear methodology to review the effects of breastfeeding practices on motor development in children, in terms of duration and exclusive or not exclusive breastfeeding.

OBJECTIVE

The aim of this protocol study is to present an objective and transparent methodology to conduct a systematic review and meta-analysis aimed to increase knowledge and understanding of the associations between the duration and exclusivity of breastfeeding and motor development in children age 0 to 10 years old.

METHODS AND ANALYSIS

The methodology of this protocol was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols (PRISMA-P)[27]. The Meta-analysis of observational studies in epidemiology: a proposal for reporting (MOOSE[28]), the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) and Cochrane Collaboration Handbook[29] will be used to report and guide the review methods. This protocol was registered with PROSPERO, (Registration number CRD42018093706) on 24 April 2018.

Inclusion/exclusion criteria for study selection

Studies will be retrieved from the literature by searching for studies which measure the effects of breastfeeding duration and type (exclusivity, even if it is little, or no exclusive breastfeeding), and report any type of measure of motor development. To be considered

for inclusion, studies will be required to meet the following criteria: (i) children age 0 to 10 years old (ii) exposure, breastfeeding in terms of duration and type (exclusivity or non-exclusivity) and reported any type of measure; (iii) outcome, motor development measured using standardised tests; and (iv) studies written in English or Spanish.

Studies will be excluded when: (i) include infants born in multiple pregnancies, with congenital infections or special circumstances requiring intensive care or hospitalization during the neonatal period; (ii) include children with mental disorders or any detected delay in communication, cognition or motor skills; (ii) breast milk has been supplemented, (iii) multiple publication derived from a single study; and (iv) do not adjust for confounding variates such as socioeconomic status and home environment.

Search methods for the identification of studies

Search strategy

The literature search will be conducted in MEDLINE (via PubMed), EMBASE (via Scopus), Web of Science and Cochrane Library from inception to December 2019. Searches for unpublished studies will be conducted at: OPEN GRAY, ProQuest dissertations & Thesis Global, Theseo, Networked digital library of theses and dissertations (NDLTD), and Google Scholar. A search of ClinicalTrials.gov and EudraCT clinical trial records will also be conducted. The searches will be reviewed immediately prior to the final analysis in order to identify further potential studies. Study records will be managed using the Mendeley reference manager.

The following search terms will be combined: breastfeeding, feeding, 'exclusive breastfeeding', breastfed, 'breast suckling', suckling, 'motor skill', 'psychomotor performance', 'motor development', 'psychomotor development', 'development milestones', children, child, infant, childhood (Table 1). Previous reviews and meta-analyses will be screened, as well as the reference lists of the selected studies to complete the literature search.

Table 1 Search strategy for MEDLINE database

Breastfeeding OR feeding OR 'exclusive breastfeeding' OR breastfed OR 'breast suckling' OR 'suckling'	AND	'motor skills' OR 'psychomotor performance' OR 'motor development' OR 'psychomotor development' OR 'motor development milestones'	AND	children OR child OR infant OR childhood

Selection of studies and data extraction

Two researchers will screen all relevant titles and abstracts of the retrieved publications to identify eligible studies. Inclusion and exclusion criteria will be applied to full texts to identify all potentially eligible articles. Inconsistencies in data collection will be solved by consensus. A third reviewer will be consulted when disagreements persist. The process of identifying, screening and including/excluding articles will be illustrated using the PRISMA[27] flow chart (Figure 1).

Finally, information about the main characteristics of the identified studies will be extracted, including the following data: i) first author´s name, ii) publication year, iii) country, iv) study design, v) characteristics of the study population (sample size, age of children at evaluation, gender and number of participants in each group), vi) breastfeeding category (as defined in Table 2) and vii) test used for assessment of motor development, vii (Table 2). The authors of the included studies will be contacted to request any missing data.

Table 2 Characteristics of studies included in the systematic review and/or meta-analysis

Reference	Country	Study design	Population		Breastfeeding		Outcome MD	
			Sample size	Sample age	Categories	n	Tool	Measurement
First author´s name and year of publication	Country	Design of the study	Number of participants	Age of participants (years)	Duration periods of exclusive breastfeeding /any breastfeeding	Number participants in each breastfeeding category	Instrument used to measure MD	Mean value (SD)

Key: MD, Motor Development; SD: Standard Deviation

Assessment of risk of bias

Two independent researchers will be blinded to the authors, titles and years of publication of the included studies to evaluate the risk of bias of each included study. The Critical Appraisal Checklist for Analytical Cross-Sectional Studies from The Joanna Briggs Institute will be used.[30] This tool evaluates the risk of bias according to eight items that could be scored as "Yes", "No", "Unclear" or "Not applicable".

The Newcastle-Ottawa Quality Assessment Scale[31] will be used to assess the risk of bias of longitudinal studies, including case control and cohort studies. This tool evaluates the risk of bias according to eight items which could be grouped in three categories: selection, comparability and exposure or outcome (for case control or cohort studies, respectively). Each study can be awarded one star for each item within the selection and exposure categories, and a maximum of two stars in the comparability category.

Any disagreements over the assessment of quality will be solved by consensus. A third researcher will be consulted if a consensus is not reached.

Statistical analysis

After data extraction, the reviewers will determine whether meta-analysis is possible. At least four studies addressing the association between breastfeeding and motor development will be required in order to conduct the meta-analysis. If meta-analysis is possible, STATA V.15 software will be used. The standardized mean difference will be

calculated for each study reporting the association between breastfeeding category and motor development using Cohen´s d index.[32] To compute the pooled effect size (ES) estimates with 95% confidence intervals (CIs) fixed-effects models[33] will be used in the case of no heterogeneity; otherwise, random-effects model[34,35] will be used. We will compare the level of motor development in children who have been exclusively breastfed or breastfed for any length of time, as a reference group, with the motor development of those who have never been breastfed. If possible, a comparison between children breastfed for at least 6 months and children breastfed for less than 6 months will also be carried out.

We also will provide further information on the main confounders for our research. Some confounders we will require in order to get full points of the quality assessment of the published studies, are social class, mother´s and father´s education level, maternal age, home stimulation and maternal smoking during pregnancy.

Heterogeneity will be assessed by computing the I^2 statistic.[36] The values of I^2 will be considered as follows: 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity and 75%–100% represents considerable heterogeneity.

Linear meta-analysis regression models will be used to explore whether covariates could be associated with the magnitude of the effect and could explain the observed statistical heterogeneity.[36] Finally, publication bias will be evaluated using a funnel plot according to the method proposed by Egger.[37] When a meta-analysis is not feasible, we will perform a narrative synthesis.

Subgroup analysis and meta-regression

If enough studies are available, subgroup analysis will be conducted. Several meta-regressions will be performed on study and sample characteristics including the type of motor development assessment (i.e., gross or fine motor), gender, age of study participants, birth weight, breastfeeding classification (never, less than 6 months or more than 6 months) and aspects related to motor. If possible, the method of breast milk feeding will be investigated by subgroup analysis. Furthermore, the design and risk of bias scores of the studies will be considered for additional subgroup analysis. Additional potential moderating variables may be identified after reviewing the literature.

Sensitivity analysis

We will perform sensitivity analysis by removing studies one by one from the main analysis to assess the robustness of the findings.

Patient and Public Involvement

Existing databases will be used for the purpose of this study. Patients and public will not be involved in the design of this study. This review will assess the effect of breastfeeding on motor developmental outcomes in infants. Insights provided by this study could be used in clinical practice to ameliorate outcomes; specifically, motor development; of children in the population.

DISCUSSION

The aim of this study is to present an objective and transparent methodology to conduct a systematic review and meta-analysis investigating whether the duration of breastfeeding is associated with motor development.

Many studies have examined whether breastfeeding in early life, a critical phase of development, could affect later cognitive function and motor development in children.[20-22] Infant development is a complex process, which encompasses several factors allowing the acquisition of skills that will contribute to the child´s full participation in activities and help to establish a direct relationship with the environment.[20]

Motor function is an accepted indicator of development during the first years of life.[38-40] It directly contributes to and reflects the relationship that the child establishes with the physical and social environments. In addition, motor development plays an important role in other areas of development, such as physical growth and cardiorespiratory fitness, the latter being a powerful and effective indicator of cardiovascular health.[41-43] Poor motor development performance may incline children towards activity avoidance and sedentary behaviours, which are linked to increased risk of chronic disease in adulthood.[44]

There is considerable evidence about the long- and short-term benefits of breastfeeding for infant health.[16-19] However, no consensus has been reached about the effects of

breastfeeding on motor development, and the results and conclusions of existing studies are controversial.[21,25,26] The complexity of child development makes it difficult to evaluate these effects, and certain aspects of infant development are influenced by psychosocial and socioeconomic factors, which could contribute to some of the observed differences. The scientific evidence regarding the benefits of breastfeeding in terms of motor development outcomes is weak, and the strength of this association is controversial because most studies lack adequate control for potential confounders. Furthermore, previous studies have measured infant development using different standardised tests.

Potential limitations of this research could include publication bias, information bias, inclusion of articles in English and Spanish only, analysis of cross-sectional studies as this does not allow a causal association to be evaluated (breastfeeding always precedes motor development), poor statistical analysis and inadequate reporting of methods and findings of the primary studies. To overcome these limitations, the systematic review and meta-analysis will be conducted and reported by two independent reviewers and a third researcher will be consulted if inconsistencies exist in data collection or consensus is not reached. However, despite these strategies, is not possible to ensure the lack of risk of bias. Furthermore; existing guidelines, the MOOSE statement, PRISMA, and Cochrane Collaboration Handbook recommendations will be followed.

To summarise, we will carry out a systematic review and meta-analysis with the objective of reviewing existing literature on the relationship between breastfeeding and motor development. Despite the fact that some aspects of motor development appear to be controversial, if this study confirms the positive effects of breastfeeding on motor skills development, it could encourage greater interest in breastfeeding within the areas of public and child health.

The lack of evidence on the effect of breastfeeding and motor skills development highlights the need for guidelines or recommendations based on rigorous and updated reviews summarizing the available scientific evidence, to be used in daily practice in order to improve the quality and effectiveness of interventions. The findings of this review could lead to an improvement in the health status and development of children worldwide.

ETHICS AND DISSEMINATION

The data included in this project will be provide by the original studies; therefore, ethical approval and informed consent of patients will not be required.

This protocol provides a clear and structured procedure to extract relevant information on the association of breastfeeding and motor skills. This study will have clinical and public health implications, because it could provide support for recommendations on breastfeeding, which might help to prevent low rates of breastfeeding and early abandonment. Suggestions for future research will be made according to the findings of this systematic review and meta-analysis, and evidence-based recommendations to improve breastfeeding rates will be offered. Moreover, longitudinal studies will be needed to confirm the duration effect of breastfeeding better associate with children's motor development.

Contributors:

BN-P and MH-L designed the study. BN-P was the principal investigator and guarantor. BN-P and MH-L were the main coordinators of the study. DPP-C, CA-B, CB-M, VM-V and BN-P conducted the study. MH-L, DPP-C and VM-V gave statistical and epidemiological support. MH-L wrote the article with the support of CB-M, VM-V and BN-P. All authors reviewed and approved the final version of the manuscript.

Competing interests:

None declared. All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing:

Extra data is available by emailing: celia.alvarezbueno@uclm.es

Transparency

The manuscripts guarantor (BN-P) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

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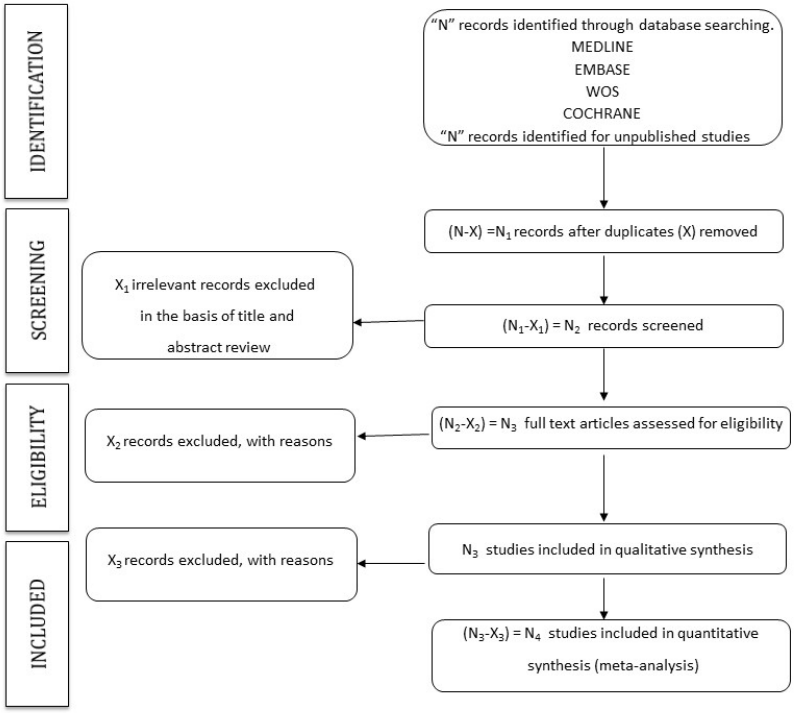
TABLES LEGENDS

Table 1. Search strategy for the MEDILINE database.

Table 2. Characteristics of studies included in the systematic review and/or meta-analysis.

FIGURE LEGENDS

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram of identification, screening, eligibility and inclusion of studies



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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item
ADMINISTRATIVE INFORMATION		
Title:		
Identification: p. 1	1a	Identify the report as a protocol of a systematic review
Update: NA	1b	If the protocol is for an update of a previous systematic review, identify as such
Registration: p. 2	2	If registered, provide the name of the registry (such as PROSPERO) and registration number
Authors: pp. 1, 13		
Contact: p. 1	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author
Contributions: p. 13	3b	Describe contributions of protocol authors and identify the guarantor of the review
Amendments: NA	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments
Support: NA		
Sources	5a	Indicate sources of financial or other support for the review
Sponsor	5b	Provide name for the review funder and/or sponsor
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol
INTRODUCTION		
Rationale: pp 4, 5	6	Describe the rationale for the review in the context of what is already known
Objectives p. 5	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)
METHODS		
Eligibility criteria: pp. 5, 6	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review
Information sources: p. 6	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage
Search strategy: pp. 6, 7	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated
Study records: pp. 7, 8		
Data management: p. 7	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review

Selection process: p. 7	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)
Data collection process: p. 7	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators
Data items: pp 7, 10	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications
Outcomes and prioritization: pp. 7, 8	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale
Risk of bias in individual studies: p. 8	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis
Data synthesis: pp 9, 10	15a	Describe criteria under which study data will be quantitatively synthesised
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned
Meta-bias(es): NA	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)
Confidence in cumulative evidence: NA	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

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