

BMJ Open Relationship between exclusive breast feeding and cardiorespiratory fitness in children and adolescents: a protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction Breast feeding has been considered important due to its short-term and long-term benefits on infant and maternal health. Regarding the long-term benefits, the influence of exclusive breastfeeding on cardiorespiratory fitness (CRF) during childhood and adolescence has been studied, although with controversial conclusions. This study protocol aims to provide a clear and standardised procedure for systematically reviewing the relationship between breast feeding, in terms of duration and exclusivity, and CRF in children and adolescents.

Methods and analysis This systematic review and meta-analysis protocol is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols. A literature search will be conducted in MEDLINE, EMBASE, Web of Science and Cochrane Library. Observational studies regarding the association between breast feeding and CRF in children and adolescents written in English or Spanish will be included. A Critical Appraisal Checklist for Analytical Cross Sectional Studies and The Newcastle-Ottawa Quality Assessment Scale for longitudinal studies will be used for quality assessment of included studies. Standardised mean differences of CRF by exclusive breastfeeding categories will be calculated as the primary outcome. Subgroup analyses and meta-regression will be performed based on the sources of heterogeneity.

Ethics and dissemination This evidence-based systematic review will summarise the relevant information on the association of exclusive breast feeding and CRF in children and adolescents. The results will be disseminated by publication in a peer-reviewed journal. Given that the data used for this systematic review will be exclusively extracted from published studies, ethical approval will not be required.

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INTRODUCTION

The WHO recommends exclusive breast feeding during the first 6 months of life, then combining with complementary solid foods up to 2 years of age or more.¹

Strengths and limitations of this study

- A systematic review and meta-analysis will be conducted derived from observational studies which limits our ability to establish causal relationships.
- Another limitation of this study is the differences in study design, sample characteristics, different methods used for measuring breast feeding or cardiorespiratory fitness (CRF), and poor quality statistical analyses which may limit comparability among included studies and decrease the quality of evidence of this systematic review and meta-analysis.
- One more limitation might be the restriction of the analysis to studies published in English and Spanish.
- An exhaustive literature search will be thoroughly carried out to identify studies aimed to assess the association between exclusive breast feeding and CRF in childhood and adolescence.
- The analysis of different sources of heterogeneity and the assessment of risk of bias of the included studies is a key point for extracting and synthesising evidence-based conclusions.

Nevertheless, in spite of these evidence-based guidelines, very low rates of compliance have been reported. Approximately, between 2007 and 2014, just 36% of babies (0–6 months) around the world were exclusively breast fed, and in most high-income countries the prevalence is less than 20% which shows the necessity of increasing the compliance rate with the WHO recommendations.^{1–3} Thus, more efforts are required to disseminate the importance of implementing this type of feeding during the first 2 years of life.²

Several studies have shown the short-term and long-term benefits of breast feeding on infant and maternal health. When breast feeding is primarily exclusive, it protects against common diseases during childhood, such as respiratory infections, otitis media or diarrhoea. Additionally, data

suggest that exclusive breast feeding might decrease the probability of infectious mortality and dental malocclusions, and reduces the risk of sudden infant death syndrome.^{3 4} Neuropsychological benefits for infants, better motor development in childhood and more intelligence during young adult life are a few examples of the long-term advantages related to breast feeding, notwithstanding that further investigations are necessary.⁵⁻⁷ Moreover, breast feeding acts as a protective factor against severe cardiovascular risk factors in children: overweight, obesity, hypertension, high fasting plasma glucose, high blood concentration of triglycerides or low blood concentrations of high-density lipoprotein cholesterol which all have deleterious effects in adulthood.⁸⁻¹¹ Regarding maternal health, breast feeding has been shown to accelerate postpartum weight loss, and it is involved in the risk reduction of breast and ovarian cancer, and type 2 diabetes, among others.^{9 12}

Cardiorespiratory fitness (CRF) is a powerful and effective indicator of cardiovascular health in the early stages of life,¹³ besides being related to a lower risk of all-cause mortality in adulthood.¹⁴⁻¹⁶ In fact, CRF improves blood pressure and decreases abdominal adiposity, and is considered a protective factor for metabolic syndrome, cardiovascular illnesses and cancer occurrence in adult life.^{14 17 18} It is important to highlight that the last two are among the 10 leading causes of death in the world.¹⁹ Likewise, the death risk is twice higher in unfit people, those who do not meet the 2008 Physical Activity Guidelines, independently of body mass index (BMI), as was shown in a recent meta-analysis.^{20 21}

CRF is influenced by several genetic, biological, social, environmental and lifestyle factors,²² including breast feeding. Recently, many studies have analysed the importance of breast feeding in CRF and other fitness components in children and adolescents.²³⁻²⁷ However, their conclusions are controversial, in such a way that while some of them did not report a relationship between breast feeding and CRF,^{23 25 27} others found that duration of exclusive breast feeding is positively related to later CRF.^{24 26} Human milk components, such as polyunsaturated fatty acids, prostaglandin J2 and adipokines might explain the positive influence of breast feeding on CRF.²⁸ Therefore, further research is necessary to obtain stronger conclusions on the possible effects of breast feeding on CRF.

Thus, the aim of this novel methodological study protocol is to provide a clear procedure for systematically reviewing the relationship between breast feeding, in terms of duration and exclusivity, and CRF in children and adolescents.

OBJECTIVE

The purpose of this study protocol is to report a standardised and clear methodology to carry out a systematic review and meta-analysis aimed to assess the relationship between breast feeding, in terms of duration and

exclusivity, and CRF in children and adolescents aged 4–18 years.

METHODS AND ANALYSIS

This systematic review and meta-analysis protocol has been registered in PROSPERO. In addition, this protocol adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P).²⁹ The systematic review and meta-analysis will be guided by the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statement and Cochrane Collaboration Handbook recommendations.^{30 31}

Inclusion/exclusion criteria for study selection

Studies concerning the association between breast feeding, in terms of duration and exclusivity, and CRF in children and adolescents which meet all inclusion criteria will be included in the systematic review: (1) participants: children aged 4–12 years and adolescents aged 12–18 years; (2) exposure: exclusive breast feeding and duration (even if it is little or no exclusive breast feeding); (3) outcome: CRF determined by standardised tests whose scientific rationale, validity and reliability has been previously published, such as 20m shuttle run test, cardiorespiratory exercise test (by treadmill or ergometer bike) or heart rate; and (4) study design: observational studies (cross-sectional or follow-up studies).

Studies will be excluded when: (1) they are not written in English or Spanish; and (2) they include participants older than 18 years. Studies will also be excluded when the target population was specifically: (1) children with severe physical limitations that could impede CRF measurement; and (2) they refer to a particular population group, such as professional and high-performance athletes.

Search strategy

A literature search will be conducted, and studies will be identified through a combination of resources. First, a systematic search will be performed in MEDLINE (via PubMed), EMBASE, Web of Science and Cochrane Library from their inception. The search strategy will combine boolean operators from the following relevant concepts: breastfeeding, feeding, breast, 'breast suckling', suckling, 'exclusive breastfeeding', 'cardiorespiratory fitness', fitness, 'VO2 max', 'physical fitness', 'aerobic capacity', 'cardio fitness', children, adolescents, childhood, scholars and school-aged (table 1). Previous systematic reviews and meta-analyses, and relevant references of the selected studies will be reviewed to identify additional sources. Study records will be organised using the Mendeley Reference Manager.

Selection of studies and data extraction

All titles and abstracts of the retrieved articles will be independently screened by two researchers to identify eligible studies for this systematic review, according

Table 1 Search strategy for the MEDLINE database

Breastfeeding		'cardiorespiratory		children
OR		fitness'		OR
feeding		OR		adolescents
OR		fitness		OR
breast		OR		childhood
OR		'VO2 max'		OR
'breast	AND	OR	AND	Scholars
suckling'		'physical fitness'		OR
OR		OR		School-
suckling		'aerobic capacity'		aged
OR		OR		
'exclusive		'cardio fitness'		
breastfeeding'				

to the inclusion criteria. The studies that do not meet the eligibility criteria will be excluded. Abstracts not providing enough information regarding the inclusion/exclusion criteria will be selected for full-text evaluation. Two reviewers will examine the included and excluded studies to verify the reason for each decision. Inconsistencies in data collection will be solved by consensus. A third researcher will be asked when consensus is not reached. The process of identifying, screening and including/

excluding articles will be shown using the PRISMA²⁹ flow chart (figure 1).

Additionally, the full text of the identified studies will be examined to extract the following data: (1) first author's name, (2) publication year, (3) country, (4) study design, (5) number of children in each sample, (6) age of children at evaluation, (7) breast feeding (categories and number of participants in each group) and (8) CRF (tools and measurements used for the assessment of participants). The authors of the included studies will be contacted when a lack of information is detected.

Assessment of risk of bias

Before assessing the methodological quality of the included studies, two reviewers will be blinded to the authors, title and year of publication of the studies. Then, standardised checklists for observational studies will be used. To assess the quality of cross-sectional studies, a Critical Appraisal Checklist for Analytical Cross Sectional Studies from The Joanna Briggs Institute will be applied.³² It consists of eight items scoring as 'yes', 'no', 'unclear' and 'not applicable'. The results of this appraisal will be used to show the possibility of bias in the design, conduct and analysis of each study.

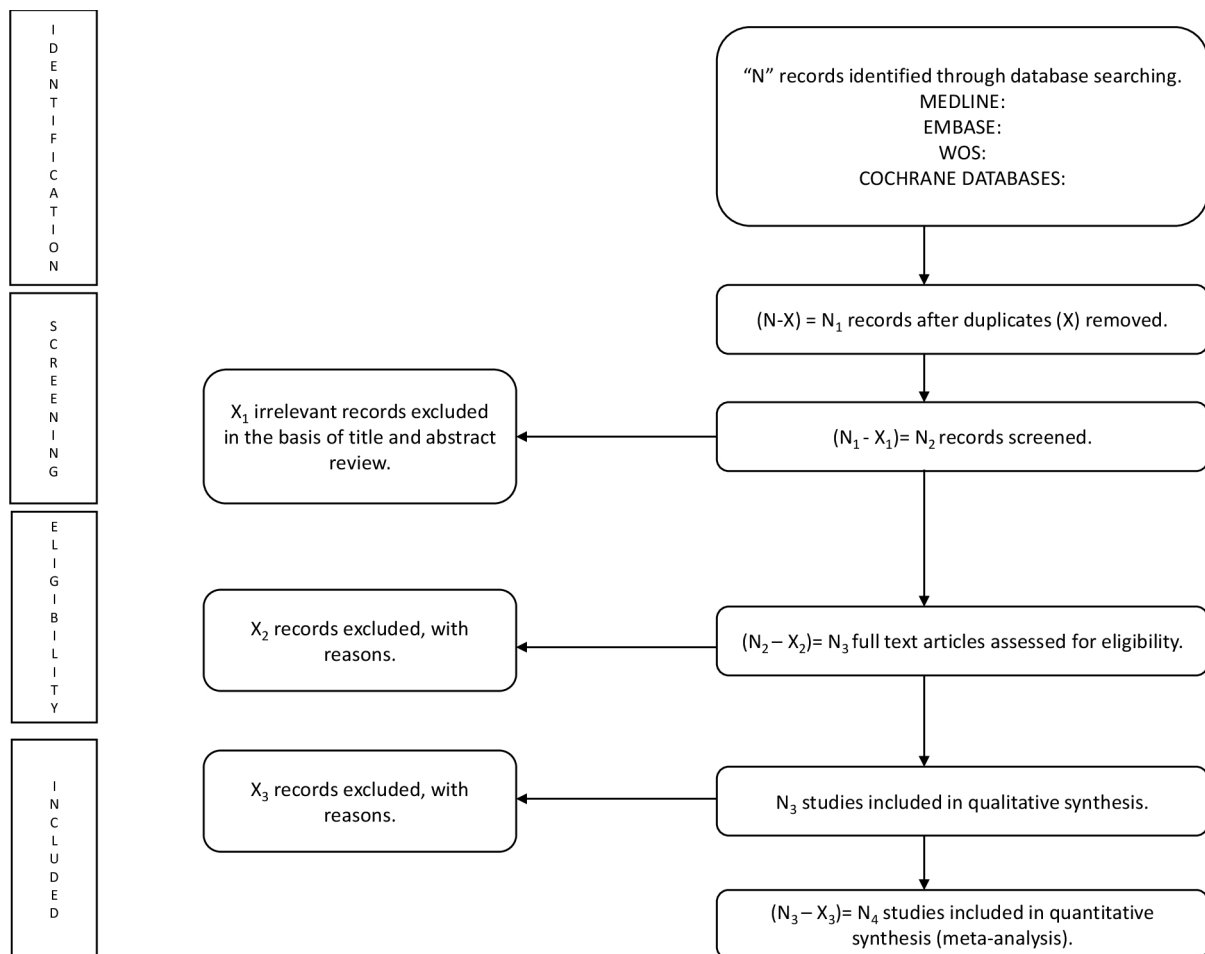


Figure 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of identification, screening, eligibility and inclusion of studies.

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

Reference	Country	Study design	Population		Breast feeding		CRF	
			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 breast feeding	Number of participants in each breastfeeding category	Instrument used to measure CRF	Measure used to express CRF

CRF, cardiorespiratory fitness.

The Newcastle-Ottawa Quality Assessment Scale³³ will be used to assess the quality of longitudinal studies in meta-analyses, including case-control and cohort studies. This scale includes eight items grouped in three categories: (1) selection, (2) comparability and (3) exposure or outcome (depending on whether it is case-control or cohort studies, respectively). In the evaluation process, each study can obtain one star for each item within the selection and exposure categories, and a maximum of two stars in the comparability category.

Any conflicts over the assessment of quality will be solved by consensus. A third researcher will be consulted if a consensus cannot be reached.

Statistical analysis

Authors will summarise the main characteristics of included studies and any relevant question according to the aim of this systematic review through table 2, in which the study's characteristics, methods, description of population and relevant issues related to outcomes will be included. After data extraction, it will be determined if a meta-analysis is possible. If possible, a meta-analysis will be carried out using STATA V.14 software to compute pooled effect size (ES) estimates with 95% CIs.

Adjusted or unadjusted models, depending on the data extracted, will be used to compare the level of CRF when children and adolescents have never been breast fed, as reference, with CRF when children and adolescents have been exclusively breast fed for any time. A fixed-effects model³⁴ will be used if there is no evidence of heterogeneity; otherwise, a random-effects model³⁵ will be used. The standardised mean difference will be calculated for each breastfeeding category as an estimate of ES,³⁶ using Cohen's index as the ES statistic, if possible, in which a positive ES value indicates an increase of CRF in favour of breastfeeding versus the never breastfed group.

The heterogeneity of results across studies will be evaluated using the I^2 statistic that is considered as: not important (0%–40%), moderate (30%–60%), substantial (50%–90%) and considerable (75%–100%); the corresponding p values will also be considered.³⁷ Additionally, publication bias will be assessed using a funnel plot, according to the method proposed by Egger *et al.*³⁸

Finally, if a meta-analysis is not possible, due to a lack of quantitative information or if there is considerable heterogeneity between studies, a systematic review with descriptive analysis will be conducted.

Subgroup analyses and meta-regression

Subgroup analyses and meta-regression will be conducted on the main factors that could cause heterogeneity: (1) type of study design (longitudinal or cross-sectional); (2) country; (3) characteristics of population, such as age (children aged 4–12 years and adolescents aged 12–18 years); (4) breastfeeding classification (never, less than 6 months and more than 6 months)¹; (5) aspects related to CRF, such as type of tool used (20 m shuttle run test (20 m SRT), cycle-ergometer, treadmill test) and measurement reported (VO₂ max, stage from 20m SRT, watts); and (6) covariates included in the original studies (birth weight, BMI, physical activity, among others). Additionally, the methodological quality of included studies, as reported previously, will be taken into account for additional subgroup analyses.

Sensitive analyses

Sensitivity analyses will be carry out, removing the included studies one by one from the pooled analyses, to assess the robustness of summary estimates and to detect if any singular study accounts for a large proportion of heterogeneity.

Patient and public involvement

Patients and/or public will not be involved in the conducting of this study. However, once our results are disseminated by scientific publications, it will be shared through social networks and infant feeding-related population groups, in such a way that our conclusions would influence breastfeeding-related mother's behaviour.

DISCUSSION

Complying with WHO recommendations on breast feeding has important benefits for infant and maternal health. With long-term benefits, several studies have evaluated the influence of exclusive breast feeding over CRF in childhood and adolescence. However, there is no consensus on the real effects, since results and conclusions were controversial.^{23–27} Therefore, we will conduct a systematic review and meta-analysis, if possible, to show a general view of the current literature, as well as further improve research regarding exclusive breast feeding and CRF. For that purpose, the protocol of this systematic review provides a clear structure for extraction and synthesis of relevant information.

Another aspect to consider with the implementation of the systematic review is to know if strictly complying with WHO recommendations increases CRF during childhood and adolescence which is a powerful health marker at these ages. Likewise, we will report if breast feeding could mitigate the deleterious effect, over CRF, of several factors regarding intrauterine growth, such as low birth weight.³⁹ If this association is demonstrated through synthesis of evidence, breast feeding could acquire a greater interest in the public health of children and adolescents.

Additionally, since different types of observational studies will be considered for inclusion (cross-sectional and follow-up studies), we will use two tools for quality assessment: (1) a Critical Appraisal Checklist for Analytical Cross Sectional Studies³² and (2) The Newcastle-Ottawa Quality Assessment Scale for longitudinal studies.³³

Furthermore, any sources of heterogeneity of studies included, such as study design, country, sample characteristics (size and age range), confounding factors and tool used for measurement of breast feeding and CRF, will be considered in this review using random-effects meta-regression.⁴⁰ Subgroup analyses and sensitivity analyses will be conducted to control and determine if some included studies account for a proportion of heterogeneity.

Potential limitations are inherent in conducting systematic reviews and meta-analyses: publication bias, information bias, poor statistical analyses, poor methodological quality and inadequate reporting of methods and findings of the included studies. Another limitation might be the restriction of the analysis to studies published in English and Spanish, since it could introduce a language bias and overestimate the magnitude of the possible associations. Therefore, it is important to properly synthesise the information available in the manuscripts included. This task will be conducted independently by two reviewers, and disagreements will be resolved by consensus. Likewise, the MOOSE statement and Cochrane Collaboration Handbook recommendations will be followed.^{30 31}

In summary, due to a lack of agreement and robust conclusions about the relationship between exclusive breast feeding and CRF in children and adolescents, it seems logical and important to carry out a systematic review and meta-analysis.

ETHICS AND DISSEMINATION

Because the data used for this systematic review will be exclusively extracted from published studies, ethical approval and informed consent of patients will not be required. The resulting findings of this study could help us develop high-quality recommendations about the long-term role of breast feeding, such as: (1) breast feeding as an enabling factor for the enhancement of CRF in children and adolescents and (2) breast feeding as a resource for mitigating the negative effect of different covariates on CRF. Additionally, it could provide updated epidemiological data about the prevalence of exclusive breast feeding. This study could also have important

public health implications, as health professionals are key actors to promote and transfer knowledge about breast feeding in the general population. Finally, this protocol is considered as a necessary step for solidifying the methodological structure to conduct an evidence-based systematic review and meta-analysis regarding the association between exclusive breast feeding and CRF in young populations.

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

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