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Breastfeeding practices and head circumference in young children: a systematic review

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ABSTRACT

OBJECTIVE: To review observational studies on the association between breastfeeding (BF) practices and head circumference (HC) of children < 2 years old.

METHODS: A systematic review was conducted using the following electronic databases of health sciences: PubMed, Latin American and Caribbean Literature in Health Sciences (Lilacs), Web of Science and Scopus. We selected observational studies published in any language from January 01, 2010 to November 19, 2021, from different populations that investigated the association between BF practice and HC among healthy children < 2 years old. Titles and abstracts were screened independently by two evaluators.

RESULTS: From the 4,229 articles identified, 24 were included in this review: 6 cross-sectional, 17 longitudinal, and 1 case-control. The studies varied in their definition of the variables for BF and in reporting its practice, frequency, duration, and feeding method. Regarding HC, the authors analyzed the mean differences, abnormal values (z-score above + 2SD or below -2SD according to the World Health Organization (WHO) growth standards, 2007), and longitudinal growth parameters. The findings of this review suggest that BF may have a positive relationship with HC at the beginning of life.

CONCLUSIONS: Our findings suggest that BF, especially exclusive BF, may play a protective role against abnormal HC values in young children. However, more robust evidence with standardized BF indicators and WHO growth standards (2007) are required.

DESCRIPTORS: Head Circumference. Cephalometry. Anthropometry. Breastfeeding. Exclusive Breastfeeding. Formula Feeding. Child Growth. Child Development. Systematic review.

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INTRODUCTION

After birth, the human skull and brain undergo intense connectivity and transformation. Such changes occur at a greater speed, mainly during the first years of life, and an accelerated increase in head circumference (HC) reflects this process. HC is an easy, valid, and low-cost anthropometric measure with a positive correlation with intracranial and cerebral volume in children up to six years of age[1].

The identification of maternal and child associated factors with HC in the first years of life can have significant short and long-term contributions for child health. A population-based study of 633 English babies born at term found a positive association between HC in the first year of life and the intelligence quotient of children aged 4 to 8 years[2], reinforcing the importance of studies on predictors of brain development early in life. In another Canadian longitudinal study with 756 children, HC was a predictor of better coordination, planning, and balance skills, possibly related to sensorimotor and cerebellar development[3].

Although there is a consensus in the scientific community regarding the accelerated growth of HC at the beginning of life, its multifactorial and complex determination pathways have yet to be discussed. Therefore, identifying possible predictors of HC can strongly contribute to strategies for child health and development. Literature suggests that HC has known associated factors, such as age[4], sex[5], maternal and paternal HC[6], weight gain[7], and gut microbiome profiles[8]. At a more proximal level, nutritional status indicators and diet quality have also been shown as potential predictors of cephalic growth in the early years[5].

Breastfeeding (BF) plays a pivotal role in early brain development owing to its nutritional composition and emotional mother-infant interaction and bonding, but its effects on HC remain uncertain. This systematic review aims to gather observational studies that investigated the association between BF practices and HC in children up to two years of age in different populations.

METHODS

Protocol and Registration

A search protocol was developed beforehand by two authors (I.G. and M.A.C.) and registered in the International Prospective Register of Systematic Reviews (Prospero) database (registration date: May 3rd, 2021, ID 252891). To report the results, we followed the recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Prisma)[9].

Eligibility and Exclusion Criteria

To formulate our eligibility criteria, we used the PECOS framework (P: population, E: exposure, C: comparison, O: outcome, S: study design) as follows: Population – healthy children up to 2 years old; Exposure – BF practices; Comparison – statistical analysis results; Outcome – HC value differences; Study design – observational studies in any language. We selected articles published from January 01, 2010, to November 19, 2021, so that the evidence gathered was published after the most recent WHO growth standards[4].

We excluded literature reviews and studies conducted exclusively with animal and in-vitro studies; premature, low birth weight or small for gestational age babies; children older than 24 months; twins; children with microcephaly, macrocephaly or hydrocephaly; clinical conditions affecting pregnancy or the child's growth; children from assisted reproductive technology pregnancies; and descriptive and interventional studies. In addition, we excluded studies in which BF practices were not the exposure; HC was not an outcome or studies with other head measurements (i.e. shape); and in which the association between

BF and HC was not investigated. Studies that analysed the effects of chemical composts or drugs (i.e. pollutants; smoke; alcohol; illicit drugs medicines); those that HC measured during pregnancy (fetal) or at birth; studies about genetic factors; and individual studies were also excluded.

Search Strategy

Search strategy was developed so that the process of identifying studies was highly sensitive and considered syntax using Boolean operators and controlled vocabulary for each one of the databases. Articles were initially identified using PubMed, Lilacs, Web of Science, and Scopus.

In the Pubmed database, we combined the Medical Subject Headings (MeSH) terms and their corresponding words in the Health Sciences Descriptors (DeCS): (Cephalometry[tiab] OR Craniometry[tiab] OR "head circumference"[tiab] OR "head growth"[tiab] OR Cephalometry[Mesh]) AND (predict*[tiab] OR associat*[tiab] "epidemiologic factors"[Mesh] OR "demography" [Mesh] OR "Nutritional Physiological Phenomena"[Mesh] OR "Child Development"[Mesh] OR health[Mesh]). The filters "humans" in the species field, "infant: birth-23 months" in the age field were applied.

Studies Selection and Data Extraction

Based on the exclusion criteria previously defined, titles and abstracts were read independently by two evaluators (I.G. and L.D.F.). Articles approved by the consensus of both authors were included in the review. In cases of disagreement, a third evaluator (M.A.C. or P.S.M.) assisted with the final decision. Studies approved by the screening process were read in full, excluding those that did not meet the eligibility criteria or did not fit the purpose of this review.

The data extraction process was carried out by the first author (I.G) and checked by the last author (M.A.C.) using electronic spreadsheets. The data extracted from each article were: participant's age at HC measurement, HC value expression/classification, BF practices investigated, and their association and statistical significance with the outcome (e.g. confidence intervals, p values). The overall quality of the eligible studies was analyzed according to the adherence to guidelines for reporting observational epidemiological study designs.

To allow for a comparison, we grouped the studies by data collection design (e.g., cross-sectional *versus* longitudinal) and the regional economy of the population according to the country's Gross National Income (GNI) per capita[10]. Low-income economies were defined as those with GNI per capita of $1,045 or less in 2020; lower middle-income economies with GNI per capita between $1,046 and $4,095; upper middle-income economies with GNI per capita between $4,096 and $12,695; and high-income economies with GNI per capita of $12,696 or more[10].

RESULTS

Study Characterization

As described in the flowchart, we initially identified 4,229 studies (Figure). Among them, 1,043 were identified in PubMed, 1197 in Scopus, 101 in Lilacs, and 1888 in the Web of Science. After removing duplicates and screening titles and abstracts, 487 full-text articles were assessed. A total of 24 articles, out of the 487, were included in this review and the nature of the studies were as follows: 6 cross-sectional (Table 1), 17 longitudinal (Table 2), and 1 case-control. However, this case-control study[11] was not included in the qualitative synthesis due to limitations in the study design as the cases were defined based on exposure.

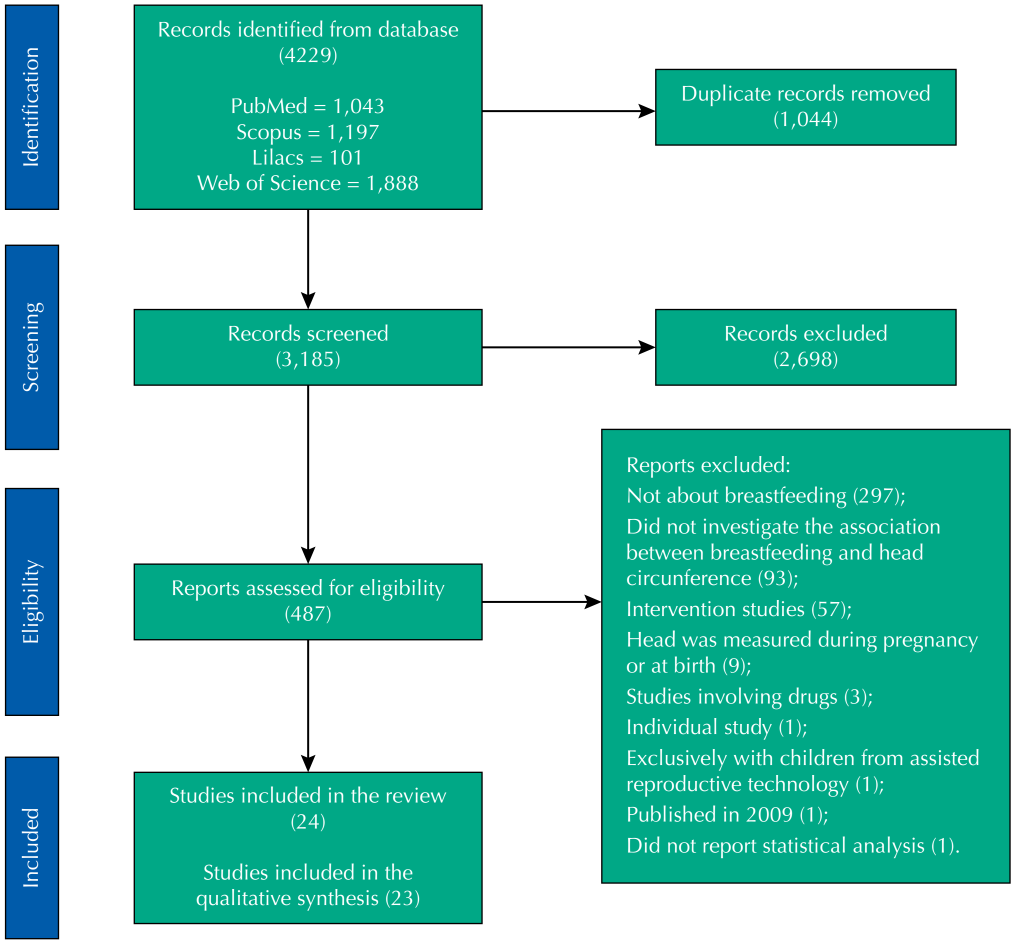

Figure. Flow chart of published studies for inclusion in the systematic review.

Main Outcome: Head Circumference

Most of the studies presented HC in z-score (HCZ) according to HC-for-age z-score values proposed by the WHO[4]. However, two studies used national reference growth curves[12,13], whereas the others used HC values in centimeters[14–21].

HCs were classified in different ways across studies. Six cross-sectional studies[6,12,22–25] observed abnormal HCZ values (z-score above +2SD or below -2SD according to the WHO growth standards[4] or a national reference growth curve). Additionally, two studies[17,21] observed the influence of BF practices on HC measures over time, and others analyzed the association between BF and the mean values found for HC (adjusted and/or not adjusted analyses by covariates).

Main exposure: Breastfeeding Practices Assessment

All 23 eligible studies considered BF as an independent variable in the analysis. Four studies included only breastfed children, investigating BF duration and age at weaning[26], BF offering route by breast or bottle with breast milk[27], BF in the first hour of life[23], and BF frequency[23,25]. The other studies included non-BF children, comparing different groups according to their feeding practices.

Ten studies mentioned EBF practices in their investigation. However, although some of them provided a detailed description of what was considered EBF[7,19,22–24,28], the majority did not account for the consumption of solid food and other liquids[6,14,16,17,21,29]. In addition to impairing comparability across studies, this aspect can represent a very important risk of bias.

Table 1. Characteristics of cross-sectional studies and the main results for the association between breastfeeding practices and head circumference.

Author (year)	Local	Sample	Age	Breastfeeding evaluation	HC outcome [95%CI]
Júlíusson et al. (2011)[29]	Norway	304	1–12 m	EBF for 6 m + BF for at least 12 m (*versus* EBF for 6 m)	No significant difference
	HIC	Flanders Growth Study			
		Population-Based			
Ferreira et al. (2013)[22]	Brazil	725	12–60 m	EBF ≥ 120 d (EBF 30–119 d *versus* EBF < 30 d)	Lower prevalence of HC deficits (5.8% *versus* 10.6% *versus* 13.3%)
	UMIC	*Quilombolas* communities			*Adjusted PR: 0.48 [0.24–0.97] (1.02 [0.63–1.67] *versus* EBF < 30 d as reference)
				EBF ≥ 120 d (EBF 30–119 d *versus* EBF < 30 d)	Higher HCZ means: 0.33 [0.14–0.52] (*versus* 0.13 [-0.05–0.31] *versus* EBF < 30 d as reference)
Wren et al. (2015)[23]	Guatemala	190 BF	< 46 d	BF in the 1st hour of life	Higher HCZ mean differences: -0.33 (*versus* -0.76; p = 0.03)
	UMIC	Mam-Mayan communities			No association with HC deficit: 14% (*versus* 22%)
				EBF (*versus* predominant BF)	No significant difference between HCZ means: -0.57 (*versus* -0.56)
					No association with HC deficit: 17% [10.5–25.2] (*versus* 20% [11.4–30.4])
				BF frequency (< 8 times/d; 8–12 times/d; >12 times/d)	No significant difference between HCZ means: -0.49 (*versus* -0.66 *versus* -0.59)
					No association with HC deficit: 29% [12.6–51.0] (*versus* 17% [9.6–26.9] *versus* 18% [9.2–29.5])
Wren-Atilola et al. (2018)[25]	Guatemala	105 BF	0–6 w or 4–6 m	BF frequency in the last 24h	Lower frequency/24h of BF was associated with HC deficits (p = 0.041)
	UMIC	Mam-Mayan communities			
					†Adjusted model: higher BF frequency/day associated with lower odds of HC deficits (OR = 0.74, p = 0.031)
Ananta et al. (2016)[24]	Indonesia	1,275	0–11 m	EBF until 6 m (*versus* FF)	Lower prevalence of abnormal HC values: 6% (*versus* 9%, p = 0.031)
	LMIC	Survey conducted by Indonesian Pediatric Society			
Delvarianzadeh et al. (2015)[12]	Iran	706	< 2 y	BF (*versus* no BF)	No association with HC deficit: 7% (*versus* 12.5%)
	LMIC	Convenience (cluster sampling)			

HIC: high-income country; UMIC: upper-middle-income country; LMIC: low-middle-income country; d: day; w: week; m: month; EBF: exclusive breastfeeding; BF: breastfeeding; FF: cow's protein formula feeding; HCZ: head circumference in z-score; PR: prevalence ratio; abnormal HC values: HCZ < -2SD or HCZ > +2SD; HC deficit: HCZ < -2SD; no association: p > 0.05

*PR and 95%CI were adjusted for possible confounders (anthropometric, socioeconomic, demographic, and health-related variables)

†Adjusted for maternal intestinal protozoa – *Entamoeba coli* (p = 0.047), subclinical mastitis (p = 0.003), lactation stage, maternal age at first pregnancy, height, weight, and body mass index and maternal health (headache). $R^2 = 0.248$

Cross-sectional Studies Evidence

The only cross-sectional study conducted in a high-income-country considered a subgroup of 304 exclusively breastfed 'Norwegian children to analyze the possible additional effect of continuous BF up to at least 12 months of age[29]. No additional effects of continued BF on HC were observed in this study.

Among cross-sectional studies conducted in upper-middle-income countries, BF tended to have a positive effect on HC, but the results remain conflicting.

Table 2. Characteristics of longitudinal studies and the main results for the association between breastfeeding practices and head circumference.

Author (year)	Local	Sample	Age	Breastfeeding evaluation	HC outcome [95%CI]
Bartok (2011)[27]	USA	37	1, 2, 3, 4, 6 m	HM by bottle (*versus* breast)	No significant mean differences at any age
	HIC	Convenience			
Andres et al. (2012)[15]	USA	391	3, 6, 9 e 12 m	BF at 1–2m, 6 and 12 m (*versus* FF *versus* soy formula)	No significant mean differences at any age
	HIC	Beginnings Study			
		Convenience			
Bouthoorn et al. (2012)[13]	Netherlands	3,383	1, 2, 3, 4, 6, 11m	Maternal educational level:	Regression coefficients that reflect the differences in HC in offspring of mothers with low, mid-low, and mid high educational level relative to children of women with high educational level (reference group):
	HIC	Subsample of the Generation R		High: university degree	1 m: -0.38 [-0.50, -0.26], -0.15 [-0.25, -0.05], -0.07 [-0.16, 0.03], reference
		population-based cohort		Mid-high: higher vocational training, Bachelor's degree	3 m: -0.25 [-0.37, -0.13], -0.10 [-0.20, -0.003], -0.09 [-0.19, -0.003], reference
				Mid-low: > 3 years general secondary school, intermediate vocational training	4, 6, and 11 m: no association
				Low: no education, primary school, lower vocational training, intermediate general school, or 3 years or less general secondary school.	
				BF at 2, 6, and 12m as mediator between maternal educational levels and infant's HC	
					At 1 and 3 months of age, the differences in HC for the low and/or the mid-low education group were attenuated with more than 10% by individual adjustment for maternal and paternal height, pre-pregnancy BMI, birth weight, gestational age, child's weight and height and breastfeeding
Herba et al. (2013)[16]	Netherlands	680	Birth–2 m	Current BF practices	Main BF effect on HC at 12m- [a]Adjusted model: p = 0.09, R^2 = 0.470
	HIC	Subsample of the Generation R study		EBF (*versus* Bottle-fed)	No significant difference between means: 0.14 [-0.01, 0.29]
				EBF (*versus* Breast- and bottle-fed)	No significant difference between means: 0.07 [-0.11, 0.25]
		Population-Based		Breast- and bottle-fed (*versus* Bottle-fed)	No significant difference between means: 0.07 [-0.12, 0.26]
				Breastfeeding history in the first 2 months	Main BF effect - *Adjusted model: p = 0.04, R^2 = 0.471
				EBF (*versus* never BF)	Higher HC mean: 0.22 [0.00, 0.44], p = 0.05
				EBF (*versus* Breast- and bottle-fed)	No significant difference between means: 0.09 [-0.05, 0.23]
				breast- and bottle-fed (*versus* never BF)	No significant difference between means: 0.13 [-0.09, 0.34]
Shinn et al. (2018)[30]	USA	149	1m, 3m, 6m, 9m, 12m	BF (*versus* FF, FF+BF, complementary feedings) at 28 d to 6m	No association
	HIC	Convenience			
Pivik et al. (2019)[18]	USA	518	2, 3, 4, 5, and 6 m	BF up to 4m (*versus* FF *versus* soy formula)	No association at 3m, 4m, 5m, and 6m
	HIC	Beginnings Study			
		Convenience			Significant mean differences only at 2 m (p = 0.047) → boys p=0.016 and girls p = 0.405
Guzzardi et al. (2020)[19]	Italy	80	3, 6, 12, 18, 24m	EBF at 3 and 6 m (*versus* no EBF)	No significant differences
	HIC	PISAC			
		Convenience			

Continue

Table 2. Characteristics of longitudinal studies and the main results for the association between breastfeeding practices and head circumference. Continuation

Jinno et al. (2020)[20]	Japan	167	1, 4, and 7m	Formula with a protein content of 2.2 g/100 kcal (*versus*BF babies with no formula intake at baseline)	No group-dependent effect on HC growth and no difference between means
	HIC	Prospective			
		Convenience			
Rodd et al. (2020)[28]	Canada	2,795	birth, 3m, 1y	EBF up to 6 m (*versus* BF+FF *versus* FF)	At 3m: lower HCZ mean (p = 0.002)
	HIC	Population based birth cohort			At 1 y: no significant difference between means
Wu et al. (2011)[14]	Taiwan	60	Birth, 4 w, and 8 w	EBF up to 8 w (*versus* FF)	No significant differences of mean changes
	UMIC	Convenience			
Huang et al. (2018)[26]	China	213 (EBF ≥ 4 m)	5–8 m, 12 m	BF duration	†Multivariate analysis:
	UMIC	Ewha Birth & Growth Cohort			At 5-8 m: no association (β = 0.02)
		Convenience			At 12 m: no association (β = -0.08)
				Age of weaning	At 5-8 m: negative association (β = -0.12)
					At 12 m: no association (β = -0.42)
Giacomini et al. (2020)[7]	Brazil	774	Birth, 10–15 m	EBF ≥ 90 d (*versus* EBF < 90 d)	‡Final model:
	UMIC	MINA-Brazil birth cohort			Higher HCZ means at 12m: β = 0.11 [0.00–0.23]
		Population-Based			
Dwipoerwantoro et al. (2015)[31]	Indonesia	160	2–6 w, 6w, 2, 3, 4, 6, 8, 10 and 12m	EBF at baseline (*versus* FF)	Significant mean differences only at 3 m (p < 0.05) and 4 m (p < 0.01)
	LMIC	Convenience			
Borazjani et al. (2019)[17]	Iran	195	birth, 2, 4 and 6 m	EBF (*versus* FF *versus* FF+BF)	Higher cumulative HC growth
	LMIC	Convenience			
Sindhu et al. (2019)[6]	India	226	Birth - 12m	EBF for < 4m (*versus* ≥ 4 m)	No association with HC deficit at 12m:
	LMIC	Indian sample of the birth cohort of MAL-ED			Crude analysis: OR = 1.68 [0.66–4.29]
		Convenience			§Final model: Adjusted OR = 3.279 [0.898–11.977]
Nicolaou et al. (2020)[32]	Multicenter:	1210	1, 12 e 24 m	Cumulative proportion of BF days	Weak association with higher HCZ values (p < 0.25)
	Bangladesh, India, Nepal,	MAL-ED			
	Tanzania (LMICs); Peru and South Africa (UMICs)	Convenience			
Fallah et al. (2021)[21]	Iran	274	Birth, 1–2, 2–4, 4–6, 6–9, 9–12, and 12–18 m	EBF < 6 m (*versus* ≥ 6 m)	‖No association with HC over time: β = -0.02 [-0.23–0.19]
	LMIC	Retrospective cohort			
		Convenience			

HIC: high-income country; UMIC: upper-middle-income country; LMIC: low-middle-income country; d: day; w: week; m: month; HM: human milk; EBF: exclusive breastfeeding; BF: breastfeeding; FF: cow's protein formula feeding; HCZ: head circumference in z-score; abnormal HC values: HCZ < -2SD or HCZ > +2SD; HC deficit: HCZ < -2SD; no association: p > 0.05.

*Adjusted for: sex, age at the time of ultrasound, gestational age at birth, birthweight, mode of delivery, maternal education, family income, maternal age at enrolment, maternal depression and anxiety (mean score) at 2 months of post-natal age, maternal smoking during pregnancy, maternal drinking during pregnancy, maternal Mediterranean diet during pregnancy, pre-eclampsia.

†Adjusted for: Chinese ethnicity; maternal age; maternal pre pregnancy weight, maternal maximum weight in pregnancy, maternal post pregnancy weight, maternal height, maternal BMI, maternal smoker status, multiple pregnancy, maternal hypertension/ pre-eclampsia, maternal gestational diabetes mellitus, birth order, paternal weight, paternal height, paternal BMI, paternal smoker status, paternal age, midparental height, birthweight, birth length, birth head circumference, duration of breastfeeding, and age of weaning to solid foods.

‡Final model adjusted for conditional weight change (β = 0.41 [0.35–0.46]), maternal education (β = 0.10 [0.02–0.18]), mother living with a partner (β = 0.14 [0.00–0.28], primiparity (β = 0.09 [0.03–0.21]), birthweight (β = 0.24 [0.18–0.30], type of delivery). R^2 = 0.299

§Adjusted for low paternal HC (Adjusted OR = 0.734 [0.581 to 0.930]), low maternal HC (Adjusted OR = 0.759 [0.604 to 0.954]), birth weight, paternal and maternal body mass index, maternal intelligence quotient, serum zinc level and WAMI index (access to improved water and sanitation, eight selected assets, maternal education and household Income).

‖Final model adjusted for child's sex, mother's education, admission to critical care unit, mother's job, gestational age (weeks), newborn height and weight, and body mass index.

In a study carried out in Guatemala with Mayan breastfed children up to 46 days of life, mothers who breastfed in the first hour of life had babies with higher HCZ mean than those who started BF after the first hour of the child's life (p = 0.03)[23]. However, no association was found between EBF (*versus* predominant BF) or BF frequency (referring to the last 24 hours) and HCZ mean or deficit prevalence. Conversely, another study also carried out with BF Mayan children, between 0–6 weeks or 4–6 months, found that a lower frequency of BF on the previous day was associated with a higher prevalence of HCZ deficits, using an adjusted model for confounding variables ($p = 0.031$; $R^2 = 0.248$)[25].

In Brazil, findings from *quilombola* communities showed that the HCZ mean was 0.33 higher among babies exclusively breastfed for at least 120 days (95%CI, 0.14–0.52) than in the group that received EBF for less than 30 days[22]. After adjusting for confounding variables, this difference between the two groups decreased but remained statistically significant. Furthermore, EBF in the first four months was associated with a lower prevalence of HC deficits (prevalence ratio, 0.48; 95%CI 0.24–0.97) in adjusted analyses. It is important to emphasize that, in this study, children over 2 years of age (between 12 and 60 months) were included, meaning that the results did not specifically refer to the critical period for HC growth.

Similar results were observed in low-middle-income countries. Using an Iranian growth curve as a reference, one study did not show a statistically significant relationship between HCZ deficits and current BF in children up to 2 years of age[12]. However, results from Indonesia showed a lower prevalence of abnormal HCZ values for infants (0–11 months) who were exclusively breastfed compared to those who were formula-fed (6% *versus* 9%, p = 0.031) for the first six months of life or at the time of study for infants < 6 months of age[24].

Longitudinal Studies Evidence

A longitudinal study conducted in the United States analyzed 37 infants up to 6 months of age receiving breast milk, differentiating them according to the method of feeding[27]. Receiving similar amounts of human milk, the use of a bottle with breast milk *versus* breast milk directly from the breast showed no significant difference in HCZ values, suggesting that the method of feeding does not play a significant role in this relationship. Other longitudinal studies across different continents have compared HCs from different groups of children according to BF practices. The results are conflicting regardless of the local economic situation.

High-income countries

A study conducted with Italian children from 3 to 24 months found no significant difference in HC between children with EBF at 3 and 6 months *versus* those without EBF[19]. Similarly, another study did not find significant differences in HC between North American children with EBF using milk formula or soy formula until the first year of life[15]. In these two previous studies[15,19], HC values were not considered in the z-score, and no adjustment by age and sex was performed.

In a study conducted in the United States, participants were followed monthly in the first year of life and were categorized according to the following groups: BF, formula feeding (FF), FF+BF, and receiving complementary feeding[30]. No association was observed between BF and HCZ. A study conducted with Japanese children (at 1, 4, and 7 months) found no group-dependent effect on HC growth between breastfed children (with no formula intake) and those receiving a specific formula with a protein content of 2.2 g/100 kcal[20]. In this study[20] HC values were not considered in the z-score, but analyses were performed separately for age and sex.

A study in Canada was the only one that found inferior HC values for children who were exclusively breastfed when compared to those who were not (p = 0.002)[28]; however, this was only true at 3 months of life and no differences were observed at the end of the first year of life.

However, in a study with Dutch children, a trend towards significance for the main effect of current BF practices on HC at 2 months of life was observed (p = 0.09, adjusted R^2 = 0.470)[16]. When examining feeding history, the main effect of BF on HC was even more pronounced (p = 0.04, adjusted R^2 = 0.471). Moreover, when compared with babies who were never breastfed, exclusively breastfed babies had a larger HC (95%CI 0.00–0.44). However, among the other groups (EBF *versus* BF and bottle; BF and bottle *versus* never BF), there were no significant differences in the HC mean. Notably, for this study, the sex of the baby was included in the adjusted analysis, but HC was not considered in the z-score.

Moreover, a study conducted in the United States found that HC values for children undergoing BF were significantly higher than those for children using soy formula at 2 months of age (p = 0.047), with a main effect for sex (boys, p = 0.016; girls p = 0.405). However, no significant differences were observed from the 3rd to the 6th month[18]. Even though the authors performed the analysis separately by sex, HC values were not considered in the z-score.

These results revealed that the relationship between HC and BF may be the result of different elements which interact in complex pathways for cranial growth. In a study conducted with children from the Netherlands (at 1, 2, 3, 4, 6, and 11 months), the association between maternal educational level and HC was investigated, including BF as a mediator[13]. Using a Dutch growth curve as a reference, the differences in HC at 1 and 3 months of age for the low and/or mid-low education groups were attenuated by more than 10% by individual adjustment for BF and covariables, including maternal and paternal height, pre-pregnancy body-mass index (BMI), birth weight, gestational age, child's weight, and height.

Upper-middle-income countries

In upper-middle-income countries, we found few studies on the relationship between BF and HC, and the results are even more conflicting.

In Taiwan, a study conducted with children from birth to 8 weeks of life found no significant differences in the HC mean between exclusively breastfed babies and those using only infant formula[14]. In that study, the authors did not report HC in the z-score and adjusted for age and sex. Another study conducted only with Chinese children with BF found a borderline significant negative influence of a later age of weaning on HCZ at 5–8 months (beta coefficient -0.12, p = 0.047)[26]. However, this was not true at the age of 12 months or when studying the duration of BF instead of weaning.

In a Brazilian study conducted in children aged 10–15 months[7], EBF of up to 90 days was associated with higher HCZ means (95%CI 0.00–0.23). The model adjusted for EBF practice, weight gain, and other covariates explained 30% of HCZ variation.

Low-middle-income countries

In low-middle-income countries, EBF practice has been explored, and studies have shown interesting results. In an Indian study, no association was observed between EBF in the first 4 months and HC at 12 months in an adjusted analysis for low parental HC and covariables[6]. Moreover, a study of Iranian children from birth to 12–18 months did not find a significant association between EBF in the first six months of life and HC over time[21]. Although HC values were not considered in the z-score in this study[21], the marginal model included the baby's sex.

In contrast, when observing the cumulative growth of HC, also in Iranian children, one study found a significantly higher trend for HC during the six months of follow-up in the

EBF group when compared to the groups using only formula or using both formula and BF[17]. Moreover, in this study, HC values were not considered in z-score and no adjustment by age and sex was performed.

In Indonesia, a study observed that BF babies at baseline (2–6 weeks of age), when compared to those using formula, had higher HCZ values over the 12 months of follow-up, but the differences were statistically significant only in the 3rd ($p < 0.05$) and 4th ($p < 0.01$) months, respectively[31].

Results from a study with children (1, 12, and 24 months) from low- and upper-middle-income countries showed a weak association between the cumulative proportion of BF and higher HCZ values ($p < 0.25$)[32].

DISCUSSION

The findings of this review suggest that BF may have a positive relationship with HC at the beginning of life. Cross-sectional studies provide some support that EBF may play a protective role against abnormal HC values in vulnerable contexts. However, when HC is considered as a continuous variable, the positive association with BF is not clear, regardless of the regional economy of the population under study.

This review gathered different studies conducted with populations in vulnerable contexts (Mayan or *quilombolas*) or in low-middle-income countries, suggesting that BF, especially EBF, may play a protective role against abnormal HC values in young children. Considering the very specific and complex process of nervous system development, and consequently cranial growth, it is no surprise that human milk may prompt this response.

The brain has a very high concentration of lipids, especially long-chain polyunsaturated fatty acids. This nutrient is crucial for essential life aspects such as the structural integrity of cellular membranes. For early brain development, two types of long-chain polyunsaturated fatty acids are particularly important: docosahexaenoic acid and arachidonic acid, both present in adequate amounts in human milk for infants, as well as human milk oligosaccharides[33]. In addition, it is known that BF may prevent health problems, being associated with lower infectious morbidity and mortality[34,35] and, consequently, contributing to a proper physical growth.

Another possible explanation for the relationship between BF practice and HC is the impact of breast milk on the microbiota composition. Diet is known to play an important role in gut microbiota modulation, especially during the first 1000 days of life. Compared to those receiving infant formula, evidence shows that children with BF tend to have a microbiome profile that is more beneficial for child health[36]. Moreover, increasing evidence has shown that the gut and brain are intimately connected. A recent cross-sectional study conducted in children aged 10–18 months living in urban slums of Mumbai found that increased gut microbiome in Faith's phylogenetic diversity[37] was associated, in multivariate analysis, with current breastfeeding and greater HC[8].

In this review, there was no robust evidence of a superior effect of formula feeding instead of BF on HC. However, the positive association between BF and HC, as a continuous variable, was not unanimous among the reviewed studies. This could be due to the large number of differences between the study designs and because HCs have multiple determinants. Another reason that may explain this fact, is that human milk nutritional or hormonal composition can vary among women and interfere in HC of young children.

A study conducted with Swedish children found that the arachidonic acid/docosahexaenoic acid ratio in the mothers' milk was positively correlated not only with brain weight, but also with HC increase rate at 1 and 3 months of age[38]. In a more recent study with North American children, omega-3 PUFAs in breastmilk was positively associated with HC at 4–8 weeks of age. However, omega-6 PUFAs and omega-6/omega-3 PUFA ratio were negatively correlated with HC[39].

Studies suggest that cytokines and hormones contained in human milk can have an effect on HC in the beginning of life. In a study conducted with *Mam-Mayan* Guatemalan mothers found a positive association of Interleukin-8 in human milk during established lactation and daily cranial growth velocity[40]. In addition, a study conducted with Australian children found that human milk cortisol and cortisone levels were correlated with HC at 12 months of age[41]. Moreover, mineral and trace elements present in human milk, which are essential to child growth, seem to have an effect on HC. A study examined the association between the composition of breast milk from *Mam-Mayan* Guatemalan mothers at different stages of lactation and their child growth. Using principal component analysis, the study observed a positive association between clusters of minerals concentration in breast milk (composed by calcium, magnesium, potassium, rubidium, and strontium intakes) and HC during early and established lactation at 18–46 days and 4–6 months postpartum, respectively[42].

The quality of the mother's diet and complementary feeding after six months and up to two years of age are important aspects to be considered. In a study conducted in Bangladesh, children under 6 months of age who were living with household food insecurity presented smaller HC[43]. In another study conducted in Nepalese children under 3 years of age, higher HC means were observed among those who had consumed two or more animal-source foods within the previous 24 hours. In the final model, weight, and animal-source food consumption accounted for 43% of the variance in HCZ[5].

LIMITATIONS AND FUTURE RESEARCH

Comparability among the studies was impaired mostly because of the lack of reported data and lack of a standardized method for BF information assessment. A considerable number of studies did not report the criteria considered for classifying BF practices and/or whether the groups were homogeneous in this aspect. Therefore, for future research it is important to follow the indicators for assessing infant and young child feeding practices defined for household surveys[44]. This guidance brings standard indicators to assess feeding practices, including BF, among children under 2 years of age and provides the necessary tools for collecting, analysing, and reporting data. Moreover, even in longitudinal studies, BF information is often assessed at a one-time point and does not account for changes in participants' feeding practices over time.

The HC classification was an additional barrier for this review, as many of the studies expressed this outcome without using international reference standards. Therefore, it is essential for future research to present HC in z-scores according to HC-for-age z-score values proposed by the WHO[4]. Moreover, the wide range of analyses applied to investigate the relationship between BF and HC among the reviewed studies as well as the inclusion of different confounding variables may interfere the findings and did not allow for meta-analysis.

Our review also revealed an absence of studies on subjects conducted in low-income countries. This fact reinforces the gap already known in the field of epidemiology regarding places with greater social and economic vulnerability, warning about the urgent need for studies in such countries.

In conclusion, this review suggests that BF practices may be important for HC growth, especially when considering socially vulnerable contexts. However, more robust and standardized evidence is needed to investigate the effects of BF in HC in the first two years of life and to support public policies focused on the promotion of child health.

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