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REVIEW ARTICLE

Long-term consequences of breastfeeding on cholesterol, obesity, systolic blood pressure and type 2 diabetes: a systematic review and meta-analysis

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Keywords
Blood lipids, blood pressure, breastfeeding, meta-analysis, obesity, systematic review, type 2 diabetes

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ABSTRACT

Aim: To systematically review the evidence on the associations between breastfeeding and overweight/obesity, blood pressure, total cholesterol and type 2 diabetes.

Methods: Two independent literature searches were carried out using the MEDLINE, LILACS, SCIELO and Web of Science databases. Studies restricted to infants and those without an internal comparison group were excluded. Fixed- and random-effects models were used to pool the estimates.

Results: Breastfed subjects were less likely to be considered obese/overweight [pooled odds ratio: 0.74 (95% confidence interval (CI): 0.70; 0.78)] (n = 113). Among the 11 high-quality studies, the association was smaller [pooled odds ratio: 0.87 (95%CI: 0.76; 0.99)]. Total cholesterol (n = 46) was independent of breastfeeding [pooled mean difference: −0.01 mmol/L (95%CI: −0.05; 0.02)]. Systolic blood pressure (n = 43) was lower among breastfed subjects [mean difference: −0.80 (95%CI: −1.17; −0.43)], but no association was observed among larger studies, and for diastolic blood pressure (n = 38) [mean difference: −0.24 (95%CI: −0.50; 0.02)]. For type 2 diabetes (n = 11), the odds ratio was lower among those subjects who had been breastfed [pooled odds ratio: 0.65 (95%CI: 0.49; 0.86)].

Conclusion: Breastfeeding decreased the odds of type 2 diabetes and based on high-quality studies, decreased by 13% the odds of overweight/obesity. No associations were found for total cholesterol or blood pressure.

INTRODUCTION

Breastfeeding has clear short-term benefits for child health, reducing mortality and morbidity from infectious diseases (1,2). Furthermore, infants who are exclusively breastfed in early life present lower morbidity from gastrointestinal and allergic diseases, whilst showing similar growth rates to nonbreastfed children (3).

With regard to the long-term consequences of breastfeeding, research suggests that infant feeding may influence the development of noncommunicable diseases in adulthood. Breastfeeding would decrease the risk of obesity (4–7) and diabetes (8), as well as blood pressure (9). Several mechanisms for a programming effect of breastfeeding have been proposed. Breast milk has long-chain polyunsaturated fatty acids (LCPUFAs) and supplementation with these fatty acids is associated with a reduction in blood pressure among subjects with hypertension (10). In addition, LCPUFAs would induce early changes in skeletal muscle that would protect against insulin resistance and type 2 diabetes (11). It has also been suggested that insulin-like growth factor 1 (IGF-1) could be another pathway for a programming effect on blood pressure (12), but a breastfeeding promotion trial failed to observe any association with IGF-1(13). Therefore, this is an unlikely pathway. Furthermore, the high levels of cholesterol in breast milk would downregulate the hepatic hydroxymethylglutaryl coenzyme A and decrease the synthesis of cholesterol (14). Breastfed infants present higher Bifidobacteria counts (15), and a lower counts of these bacteria has been observed in faecal samples of obese children (16,17). Differences in taste and diet are another possible biological mechanism, as some studies report that children who had been breastfed are more likely to have a higher intake of fruit and

Abbreviations
ALSPAC, Avon Longitudinal Study of Parents and Children; CI, Confidence interval; IGF-1, Insulin-like growth factor 1; LCPUFAs, Long-chain polyunsaturated fatty acids.

Key notes
- Breastfeeding may have long-term benefits.
- There is growing evidence that breastfeeding protects against overweight/obesity and type 2 diabetes.
- Blood pressure and total cholesterol are not associated with breastfeeding.

vegetables than those who were never breastfed (18). It has also been reported that formula-fed infants have higher concentrations of insulin, which would also lead to β-cell failure (19,20). The negative association between breastfeeding and obesity may also be another mechanism to explain the association between breastfeeding and type 2 diabetes.

On the other hand, it has been suggested that these associations could be due to residual confounding by socio-economic status. Most studies on the long-term consequences of breastfeeding were carried out in high-income countries and breastfeeding duration is positively associated with socio-economic status in this setting (21). Brion et al. (22) compared the association of breastfeeding with blood pressure and body mass index in two settings: Pelotas (breastfeeding is independent of socio-economic status) and the Avon Longitudinal Study of Parents and Children (ALSPAC) (breastfeeding is positively associated with socio-economic status). Breastfeeding was associated with lower blood pressure and body mass index in the ALSPAC cohort, whereas no association was observed in the Pelotas cohort. Furthermore, a collaborative analysis of cohort studies from low- and middle-income countries did not observe an association between breastfeeding and several metabolic cardiovascular risk factors (23). This suggests that residual confounding should be taken into consideration in assessing the evidence on the long-term consequences of infant feeding.

This systematic review and meta-analyses were aimed at reviewing the evidence on the long-term consequences of breastfeeding on overweight/obesity, and mean blood pressure, total cholesterol and type 2 diabetes.

METHODS

We updated systematic reviews and meta-analyses on the long-term consequences of breastfeeding that were carried out in 2006 (24) and 2011 (8), commissioned by the World Health Organization. Two independent literature searches were carried out at the Federal University of Pelotas (B.L.H., CLM), and any disagreement was solved by consensus. This strategy was aimed at identifying as many relevant articles as possible (25). MEDLINE, LILACS, SCIELO and Web of Science databases were searched for observational and randomized studies that evaluated the long-term consequences of breastfeeding. As the previous update of the systematic review covered manuscripts that had been published before September 2011 (8), we searched for papers that had been published from September 2011 to August 2014.

The literature search used the following terms for breastfeeding: breastfeeding; breast feeding; breastfed; breastfeed; bottle feeding; bottle fed; bottle feed; infant feeding; human milk; formula milk; formula feed; formula fed; weaning. The breastfeeding terms were combined with the following outcomes keywords:

- Cholesterol: cholesterol; LDL; HDL; triglycerides; blood lipids.
- Blood pressure: blood pressure; hypertension; systolic blood pressure; diastolic blood pressure.
- Overweight or obesity: overweight; obesity; body mass index; growth; weight; height; child growth.
- Type 2 diabetes: diabetes; glucose; or glycaemia.

In each manuscript, the following outcomes were searched for:

- Blood pressure: mean difference (in mmHg) in systolic and diastolic blood pressure;
- Cholesterol: mean difference (in mg/dL) in total cholesterol;
- Overweight and obesity: odds ratio comparing breastfed and nonbreastfed subjects.
- Type 2 diabetes: odds ratio comparing breastfed and nonbreastfed subjects.

After excluding the duplicates, titles and abstracts were perused to exclude those that were obviously irrelevant. The full texts of the remaining studies were retrieved, and relevant articles were identified. In addition to the electronic search, reference lists of the articles identified were searched and we perused the Web of Science Citation Index for manuscripts citing the identified articles. Attempts were made to contact the authors of all studies that did not provide sufficient data to estimate the pooled effect. Figure 1 shows the studies selection flow charts in the update of the systematic reviews.

Observational and randomised studies were eligible for inclusion. Studies restricted to infants were excluded, as well as those without an internal comparison group. However, the type of comparison group (e.g. never breastfed, breastfed for less than a given number of months) was not considered as exclusion criteria.

Using a standardised protocol, two reviewers evaluated the studies and disagreements were resolved by consensus. The following information was extracted from each study:

- Sample size.
- Follow-up rate: we collected the information on the proportion of subjects lost during the study.
- Type of study.
- Length of recall of breastfeeding duration: mean elapsed time between weaning and collect of the information on breastfeeding duration.
- Categorisation of breastfeeding: some studies compared ever-breastfed subjects to those who were never breastfed, while others compared subjects breastfed for more or less than a given number of months.
- Control for confounding we evaluated whether the estimates were adjusted for potential confounding variables. For the meta-analysis on the association between breastfeeding and risk of overweight/obesity, the studies were classified in one of the following categories: no adjustment; adjusted only for socio-economic variables; adjusted for socio-economic and birth conditions (birthweight, gestational age or intrauterine growth); or adjusted for socio-economic vari-

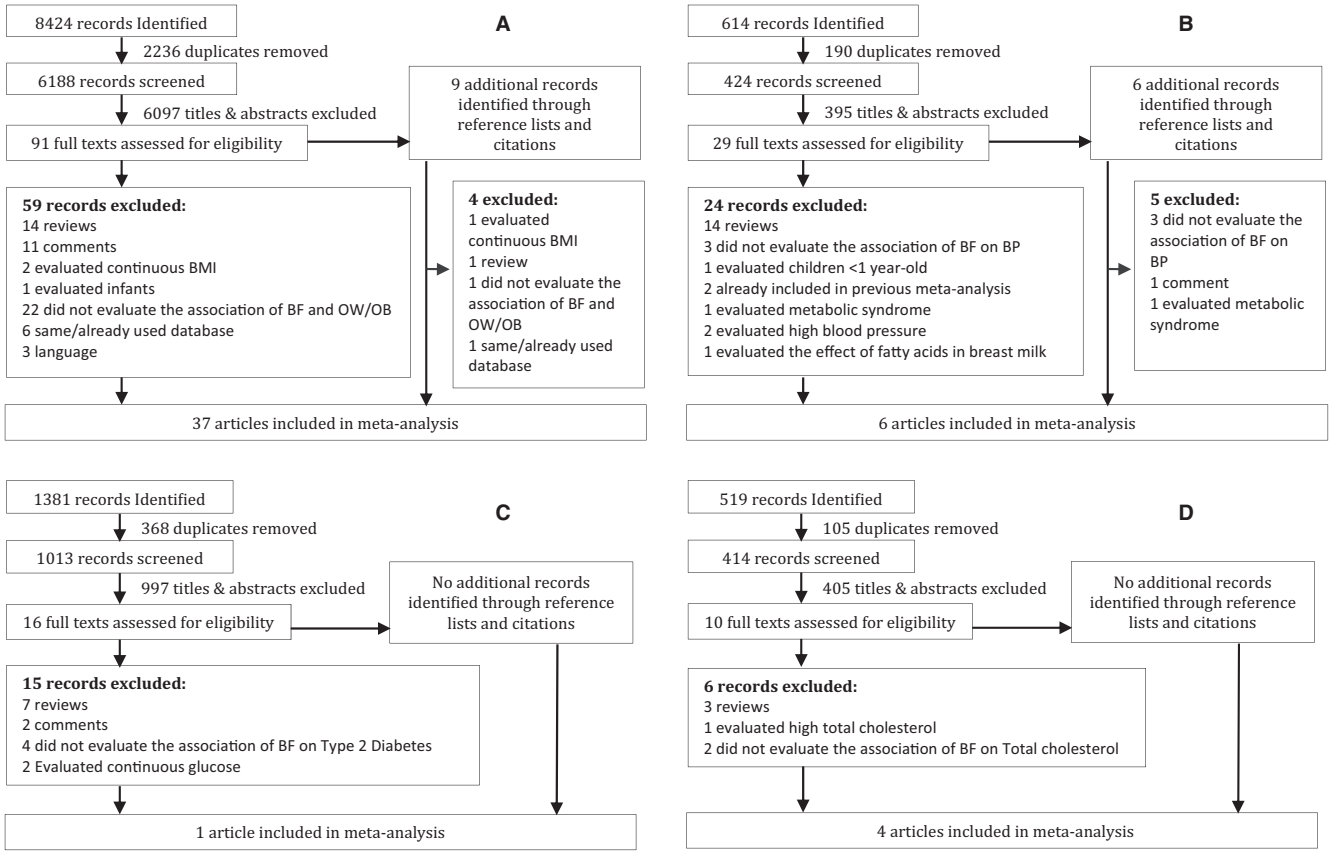

Figure 1 Flow diagram showing the different steps involved in the update searching for relevant publications. A: overweight/obesity. B: blood pressure. C: type 2 diabetes. D: total cholesterol. OW/OB = overweight/obesity. BF = breastfeeding. BP = blood pressure.

ables, birth condition and parental anthropometry. For the meta-analyses on total cholesterol the studies were evaluated whether the estimates had been adjusted for at least one confounder. For blood pressure, we assessed whether the estimates had been adjusted for socio-economic variables only, for socio-economic variables only, for both socio-economic and demographic variables, or for none. For type 2 diabetes, the studies were classified in one of the following categories: no adjustment; adjusted only for birthweight and gestational diabetes; adjusted for socio-economic status and birthweight; adjusted for socio-economic status, birthweight and body mass index.

- Year of birth of subjects.
- Age at outcome assessment.

Effect measures were reported as weighted mean differences and their 95% confidence interval for continuous outcomes (blood pressure and total cholesterol) and as pooled odds ratio and 95% confidence interval for dichotomous outcomes (overweight and obesity). Subjects were classified as either breastfed or nonbreastfed, according to the criteria used in each study. For continuous outcomes, a negative mean difference denoted a lower value among breastfed subjects, whereas for dichotomous outcomes an odds ratio <1 denoted that breastfed subjects showed a lower odds of the outcome.

Heterogeneity among studies was assessed using the *Q*-test and *I*-square; if either test suggested that the between-study variability was higher than expected a random-effects model was used (26). Funnel plot and Egger test were used to investigate publication bias (27). All analyses were stratified by study size to assess the impact of publication bias on the pooled estimate.

Meta-regression was used to evaluate the contribution of the above-described study characteristics to between-study variability (28). Study characteristics were included as covariates in the meta-regression one at a time, rather than using an overall score. This approach allows for identification of aspects of study design that may be responsible for heterogeneity between studies.

RESULTS

We carried out three separate meta-analyses and the main results are presented below.

Overweight/obesity

We identified 37 new publications that provided information on the association between breastfeeding and prevalence of overweight/obesity. In the meta-analysis, we included 105 studies that provided 113 estimates (Table S1). Breastfed subjects were less likely to be classified as obese/overweight [pooled odds ratio: 0.74 (95% confidence interval: 0.70; 0.78)]. There was no effect modification by study setting nor by categorization of breastfeeding. Nevertheless, the association was slightly stronger among studies that reported on exclusive breastfeeding, and weaker for studies that compared ever with never breastfed subjects. In addition, the associations were smaller among studies that evaluated the overweight/obesity in adults compared to studies of children. The negative association with breastfeeding was also smaller in cohort studies, in studies that adjusted the estimates for

Table 1 Breastfeeding and the risk of overweight and obesity in later life: random-effects meta-analyses of risk of overweight/obesity by subgroup

Subgroup analysis	Number of estimates	Pooled odds ratio and 95% confidence interval	p-value	% heterogeneity explained
Age group				
1–9 years	74	0.74 (0.68; 0.79)	<0.001	9.1
10–19 years	25	0.63 (0.54; 0.73)	<0.001	
≥20 years	14	0.88 (0.82; 0.94)	<0.001	
Study size				
<500 participants	28	0.53 (0.44; 0.63)	<0.001	
500–1499 participants	31	0.66 (0.58; 0.75)	<0.001	16.2
≥1500 participants	46	0.81 (0.76; 0.87)	<0.001	
Year at birth				
Before 1980	16	0.88 (0.82; 0.94)	<0.001	13.6
After 1980	65	0.73 (0.68; 0.79)	<0.001	
Study design				
Cohort	54	0.79 (0.73; 0.85)	<0.001	11.6
Case-control	10	0.68 (0.48; 0.94)	0.02	
Cross-sectional	41	0.67 (0.61; 0.74)	<0.001	
Length of recall of breastfeeding				
<3 years	44	0.78 (0.72; 0.85)	<0.001	4.7
≥3 years	61	0.70 (0.65; 0.76)	<0.001	
Control for confounding				
None	28	0.69 (0.60; 0.80)	<0.001	5.6
Adjusted for socio-economic status only	6	0.64 (0.53; 0.76)	<0.001	
Also adjusted for birth condition	22	0.73 (0.67; 0.79)	<0.001	
Also adjusted for parental anthropometry	49	0.79 (0.73; 0.85)	<0.001	
Setting				
High-income country	71	0.73 (0.68; 0.78)	<0.001	0.0
Middle-/low-income country	34	0.76 (0.67; 0.85)	<0.001	
Categorization of breastfeeding				
Ever breastfed	26	0.77 (0.69; 0.86)	<0.001	0.0
Breastfed for a given number of months	54	0.74 (0.68; 0.80)	<0.001	
Exclusively breastfed for a given number of months	24	0.69 (0.61; 0.79)	<0.001	
Total	113	0.74 (0.70; 0.78)		

The total number of studies does not add to 113, due to exclusion of studies with repeated report on the effect of breastfeeding (8 studies), 24 studies with missing information on year of birth of subjects, and one study with missing information on categorization of breastfeeding.

Table 2 Breastfeeding and mean total cholesterol in later life: random-effects meta-analyses by subgroup

Subgroup analysis	Number of estimates	Mean difference in total cholesterol in mmol/L (95% confidence interval)	p-value	% heterogeneity explained
Age group				
1–9 years	18	0.01 (−0.06; 0.08)	0.74	
10–19 years	7	−0.01 (−0.08; 0.06)	0.73	92.0
≥20 years	21	−0.03 (−0.07; 0.01)	0.12	
Study size				
<500 participants	17	0.01 (−0.10; 0.13)	0.79	
500–1499 participants	16	−0.05 (−0.12; 0.03)	0.2	0.0
≥1500 participants	13	0.00 (−0.02; 0.02)	0.82	
Year at birth				
Before 1980	27	−0.02 (−0.07; 0.03)	0.5	0.0
After 1980	11	−0.02 (−0.09; 0.05)	0.55	
Birth cohort				
No	25	−0.02 (−0.06; 0.02)	0.37	0.0
Yes	21	−0.01 (−0.07; 0.05)	0.84	
Length of recall of breastfeeding				
<3 years	33	0.00 (−0.04; 0.04)	0.87	48.9
≥3 years	13	−0.05 (−0.11; 0.01)	0.1	
Control for confounding				
No	28	−0.02 (−0.09; 0.06)	0.61	0.0
Yes	18	−0.01 (−0.04; 0.02)	0.38	
Setting				
High-income country	39	−0.01 (−0.05; 0.02)	0.47	0.0
Middle-/low-income country	7	−0.09 (−0.25; 0.08)	0.29	
Categorization of breastfeeding				
Ever breastfed	26	−0.01 (−0.05; 0.02)	0.48	0.0
Breastfed for a given number of months	20	−0.02 (−0.08; 0.05)	0.64	
Total	46	−0.01 (−0.05; 0.02)		

The total number of studies does not add to 46, due to exclusion of 8 studies with missing information on year of birth of subjects.

confounding by socio-economic status, birth condition and parental anthropometry, and studies whose subjects were born before 1980. Furthermore, sample size was inversely related to the magnitude of the association, with smaller studies reporting a greater benefit of breastfeeding. Nevertheless, in spite of a decrease in the magnitude of the association, evidence of protection was still observed among the larger studies (≥1500 participants) [pooled odds ratio: 0.81 (95% confidence interval: 0.76; 0.87) (Table 1). The metaregression showed that these study characteristics explained only a small part of the heterogeneity among the studies.

Total cholesterol

Four new studies were identified in the update, and the meta-analysis included 46 studies (Table S2). Table 2 indicates that there was no association between breastfeeding and total cholesterol levels, the mean difference in total cholesterol between those who were breastfed and not breastfed was −0.01 mmol/L (95% confidence interval: −0.05; 0.02). Age at assessment of total cholesterol explained almost all heterogeneity among the studies.

Blood pressure

Six studies were identified in the updated systematic review on the association between breastfeeding and blood pressure. The meta-analysis included 43 estimates on the association of breastfeeding with systolic blood pressure and 38 with diastolic blood pressure (Table S3). Systolic blood pressure was lower among those subjects who had been breastfed [mean difference: −0.80 (95% confidence interval: −1.17; −0.43)], whereas no association was observed for diastolic blood pressure [mean difference: −0.24 (95% confidence interval: −0.50; 0.02)]. Table 3 shows that the mean difference was inversely related to study size, and among larger studies (≥1000 participants) the confidence interval included the reference [mean difference for systolic blood pressure: −0.29 (95% confidence interval: −0.70; 0.13)]. The benefit of breastfeeding was also smaller among those studies that controlled for confounding by socio-economic and demographic variables and that were carried out in low- and middle-income countries or that evaluated subjects older than 20 years. There was marked heterogeneity among the studies but none of the study characteristics evaluated explained this heterogeneity.

Table 3 Breastfeeding and blood pressure in later life: random-effects meta-analyses subgroup

	Systolic blood pressure in mmHg			Diastolic blood pressure in mmHg		
Subgroup analysis	Number of estimates	Mean difference (95% confidence interval)	p-value	Number of estimates	Mean difference (95% confidence interval)	p-value
Age group						
1–9 years	19	−0.97 (−1.52; −0.43)	<0.001	16	−0.46 (−1.00; 0.09)	0.1
10–19 years	10	−1.03 (−2.07; 0.02)	0.06	8	−0.10 (−0.65; 0.45)	0.72
≥20 years	14	−0.30 (−0.75; 0.14)	0.18	14	−0.12 (−0.35; 0.12)	0.34
Study size						
<300 participants	13	−1.96 (−3.14; −0.78)	0.001	12	−0.57 (−1.32; 0.18)	0.14
300–999 participants	17	−1.20 (−2.03; −0.37)	0.005	15	−0.41 (−1.11; 0.28)	0.46
≥1000 participants	13	−0.29 (−0.70; 0.13)	0.18	11	−0.09 (−0.34; 0.15)	0.25
Year at birth						
Before 1980	16	−0.83 (−1.52; −0.15)	0.02	14	−0.14 (−0.36; 0.09)	0.24
After 1980	26	−0.76 (−1.22; −0.30)	0.001	23	−0.32 (−0.74; 0.10)	0.14
Length of recall of breastfeeding						
<3 years	27	−0.77 (−1.21; −0.33)	0.001	24	−0.23 (−0.51; 0.06)	0.12
≥3 years	16	−0.90 (−1.63; −0.17)	0.02	14	−0.22 (−0.76; 0.33)	0.44
Control for confounding						
None	16	−1.53 (−2.51; −0.56)	0.002	13	−0.46 (−1.19; 0.27)	0.22
Adjusted for socio-economic status	13	−1.05 (−1.85; −0.26)	0.009	13	−0.47 (−1.08; 0.14)	0.13
Adjusted for sociodemographic variables	13	−0.47 (−1.00; 0.07)	0.09	11	−0.05 (−0.38; 0.29)	0.79
Adjusted for demographic variables	1	−0.05 (−0.46; 0.36)	0.81	1	−0.07 (−0.38; 0.24)	0.66
Setting						
High-income country	34	−0.96 (−1.38; −0.53)	<0.001	30	−0.39 (−0.72; −0.07)	0.02
Middle-/low-income country	9	−0.30 (−1.02; 0.43)	0.43	8	0.17(−0.12; 0.45)	0.25
Categorization of breastfeeding						
Ever breastfed	19	−0.70 (−1.18; −0.21)	0.001	18	−0.34 (−0.76; 0.09)	0.13
Breastfed for a given number of months	24	−0.85 (−1.34; −0.35)	0.005	20	−0.19 (−0.52; 0.15)	0.28
Total	43	−0.80 (−1.17; −0.43)		38	−0.24 (−0.50; 0.02)	

The total number of studies does not add to 43 for systolic blood pressure and 38 to diastolic blood pressure, due to one study with missing information on year of birth of subjects.

Type 2 diabetes

In the update literature search, a new publication that evaluated the association between breastfeeding and prevalence of type 2 diabetes was identified,(29) and the meta-analysis included 11 studies (Table S4). Breastfeeding was associated with a lower odds of type 2 diabetes [pooled odds ratio: 0.65 (95% confidence interval: 0.49; 0.86)], using a random-effect model. Table 4 shows that the benefit of breastfeeding was higher among studies with adolescents [pooled odds ratio: 0.46 (95% confidence interval: 0.33; 0.66)]. Study size, study design and control for confounding did not modify the association between breastfeeding and type 2 diabetes.

Table 5 shows the pooled effects among all studies, as well as among those that were less susceptible to publication bias, residual confounding and misclassification. For systolic blood pressure, the pooled effect dropped from −0.80 mmHg (95% confidence interval: −1.17; −0.43) to −0.48 (95% confidence interval: −1.21; 0.26) among those studies with a large sample size (>1000 participants), which controlled for confounding by sociodemographic variables and where the length of recall of breastfeeding was <3 years. With regard to obesity, the pooled effect among the 11 studies that met the three criteria for designation as high-quality evidence was smaller than that observed among all studies. Nevertheless, breastfed subjects showed a 13% reduction in the odds of overweight/obesity [pooled odds ratio: 0.87 (95% confidence interval: 0.76; 0.99)]. For type 2 diabetes, the pooled effect slightly changed from 0.65 to 0.76 among those three studies that provided an adequate control for confounding and had a large sample size (≥500 participants), but given the small number of studies the confidence interval included the reference.

Table 4 Breastfeeding and the risk of type-2 diabetes in later life: random-effects meta-analyses of risk of type-2 diabetes by subgroup

Subgroup analysis	Number of estimates	Pooled odds ratio (95% confidence interval)	p-value
Age group			
10–19 years	4	0.46 (0.33; 0.66)	<0.001
≥20 years	7	0.76 (0.55; 1.04)	0.07
Study size			
<500 participants	3	0.54 (0.29; 0.99)	0.04
≥500 participants	7	0.68 (0.48; 0.96)	0.03
Study design			
Cohort	6	0.73 (0.55; 0.96)	0.02
Cross-sectional or case-control	5	0.59 (0.34; 1.00)	0.05
Control for confounding			
None	2	0.69 (0.47; 1.03)	0.07
Birthweight and gestational diabetes	4	0.51 (0.27; 0.96)	0.04
Socio-economic status and birthweight	2	0.86 (0.40; 1.24)	0.14
Socio-economic status, body mass index, and birthweight	3	0.79 (0.43;1.44)	0.59
Total	11	0.65 (0.49. 0.86)	

The total number of studies does not add to 11, due to one study with missing information on study size.

DISCUSSION

In this paper, we updated the findings of two earlier reviews on the long-term consequences of breastfeeding (8,24). We were able to add 48 recently published studies on overweight/obesity, total cholesterol or blood pressure. In the 2013 review that included articles published until 2011 (8), we found that breastfeeding reduced the odds of obesity [pooled odds ratio: 0.76 (95% confidence interval: 0.71; 0.81)] compared to 0.74 (95% confidence interval: 0.70; 0.78)] in the present meta-analysis. We also observed that breastfeeding reduced the odds of type 2 diabetes, [pooled odds ratio (95% confidence interval: 0.65 (95% confidence interval: 0.49; 0.86)]. In contrast, there was no association with total cholesterol; our first review in 2006 suggested a possible association with cholesterol levels measured in adults (24). Likewise, the magnitude of the associations between breastfeeding and systolic and diastolic blood pressure decreased relative to the earlier estimates, and among the larger studies the confidence interval included the reference. This suggests that the earlier estimates had been affected by publication bias. Among the four outcomes studied in the present review overweight/obesity and type 2 diabetes remained consistently associated with breastfeeding.

The magnitude of protection against overweight/obesity was larger when the outcome was measured in children and adolescents, suggesting that the association may be diluted over time. Nevertheless, a significant reduction in prevalence of 12% (95% confidence interval: 6%; 18%) was still observed among adults. In particular, studies that compared subjects who had been exclusively breastfed suggested a slightly greater benefit of breastfeeding than studies reporting on other types of comparisons. Our investigation of publication bias showed that sample size was inversely related to the magnitude of protection. However, even in studies with ≥1500 participants, an association was present, with a 19% reduction. Therefore, the present results suggest that publication bias overestimated the magnitude of the association, but did not introduce a spurious one.

Residual confounding by socio-economic status is another possible explanation for the findings. This is a methodological issue that should be taken into consideration in assessing the evidence on the long-term consequences of breastfeeding. In high-income countries breastfeeding is more common among mothers who are more educated and have a higher socio-economic position, in contrast to low- and middle-income countries where the gradient is in the opposite direction (30). Some earlier studies examined the association between breastfeeding and adult outcomes in different settings. Brion et al. (22) observed that breastfeeding was inversely associated with body mass index and blood pressure in a high-income country setting, but not in a middle-income-country sample.

Table 5 Pooled effects of each outcome, from all studies and from those deemed to be of higher scientific quality

	All studies		Large sample size and control for confounding *		Large sample size, control for confounding* and recall <3 years	
Outcome	N	Pooled effect (95% confidence interval)	N	Pooled effect (95% confidence interval)	N	Pooled effect (95% confidence interval)
Mean total blood cholesterol (mmol/L)	46	−0.01 (−0.05; 0.02)	9	0.00 (−0.02; 0.02)	5	0.01 (−0.02; 0.04)
Mean systolic blood pressure (mmHg)	43	−0.80 (−1.17; −0.43)	9	−0.35 (−0.96; 0.27)	7	−0.48 (−1.21; 0.26)
Mean diastolic blood pressure (mmHg)	38	−0.24 (−0.50; 0.02)	7	0.01 (−0.41; 0.42)	5	−0.03 (−0.61; 0.56)
Odds ratio for overweight/obesity	113	0.74 (0.70; 0.78)	23	0.87 (0.81; 0.94)	11	0.87 (0.76; 0.99)
Odds ratio for type-2 diabetes	11	0.65 (0.49; 0.86)	3	0.76 (0.40; 1.47)		**

*Variables relevant for each outcome blood pressure: at least controlled for socio-economic and demographic variables; total cholesterol: controlled for at least one confounding variable; overweight/obesity: controlled for socio-economic status, birth condition and parental anthropometry; type-2 diabetes: at least controlled for socio-economic status and birthweight.
**Only one study met the criteria, pooled result was not provided.

A collaborative analysis of five cohorts from low- and middle-income did not detect an association with overweight/obesity, although early introduction of weaning foods was associated with the outcome (23). The only randomised trial on breastfeeding promotion with overweight-related outcomes, carried out in Belarus, did not find any significant associations (13). On the other hand, sibling studies in within-family analyses reported that breastfeeding is associated with smaller body mass index and the odds of overweight (31,32). In the present review, the pooled effect from 71 studies carried out in high-income countries, with an odds ratio of 0.73, was similar to that derived from the 34 studies in low- or middle-income countries (odds ratio of 0.76).

The availability of over 100 studies allowed further stratification of the analyses according to study characteristics. High-quality studies – that are less susceptible to publication bias, confounding and information bias – show an odds ratio of 0.87(95% confidence interval: 0.76; 0.99) for overweight/obesity associated with breastfeeding. In contrast, high-quality studies did not find any association with total cholesterol or blood pressure, suggesting that there may be specific protection against overweight/obesity.

Based on the results from high-quality studies in both high-income and low- or middle-income settings, breastfeeding was associated with a 13% reduction in overweight/obesity. The evidence also suggests that breastfeeding may reduce the odds of type 2 diabetes. But given the small number of studies, further studies, that adjusted the estimates for confounding by socio-economic variables and birthweight, are needed. On the other hand, breastfeeding would not be related with blood pressure or total cholesterol.

CONFLICT OF INTEREST AND FUNDING STATEMENT

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AUTHOR STATEMENT

BLH designed the review protocol, carried out the literature search, extracted the data, conceived the analysis and participated in the preparation of the manuscript. CLM carried out the literature search, extracted the data and collaborated in the preparation of the manuscript. CGV designed the review protocol and participated in the preparation of the manuscript.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Breastfeeding and overweight/obesity in later life: studies included in the meta-analysis in ascending order of subjects age at which outcome was measured.
Table S2. Breastfeeding and blood pressure in later life: studies included in the meta-analysis in ascending order of subjects' age at which outcome was measured.
Table S3. Breastfeeding and total cholesterol in later life: studies included in the meta-analysis in ascending order of subjects' age at which outcome was measured.
Table S4. Breastfeeding and type-2 diabetes in later life: studies included in the meta-analysis in ascending order of subjects' age at which outcome was measured.