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REVIEW

Breast-feeding and childhood obesity—a systematic review

S Arenz[1], R Rückerl[2], B Koletzko[3] and R von Kries[1]*

[1]*Institute for Social Paediatrics and Adolescent Medicine, Ludwig-Maximilians University, Munich, Germany;*
[2]*gsf—National Research Center for Environment and Health, Institute of Epidemiology, Neuherberg, Germany; and*
[3]*Dr von Haunersches Kinderspital, Ludwig-Maximilians-University, Munich, Germany*

OBJECTIVE: To investigate the relationship between breast-feeding and obesity in childhood.
DESIGN: Systematic review and meta-analysis of published epidemiological studies (cohort, case–control or cross-sectional studies) comparing early feeding-mode and adjusting for potential confounding factors. Electronic databases were searched and reference lists of relevant articles were checked. Calculations of pooled estimates were conducted in fixed- and random-effects models. Heterogeneity was tested by *Q*-test. Publication bias was assessed from funnel plots and by a linear regression method.
OUTCOME MEASURES: Odds ratio (OR) for obesity in childhood defined as body mass index (BMI) percentiles.
RESULTS: Nine studies with more than 69 000 participants met the inclusion criteria. The meta-analysis showed that breast-feeding reduced the risk of obesity in childhood significantly. The adjusted odds ratio was 0.78, 95% CI (0.71, 0.85) in the fixed model. The assumption of homogeneity of results of the included studies could not be refuted (*Q*-test for heterogeneity, $P>0.3$), stratified analyses showed no differences regarding different study types, age groups, definition of breast-feeding or obesity and number of confounding factors adjusted for. A dose-dependent effect of breast-feeding duration on the prevalence of obesity was reported in four studies. Funnel plot regression gave no indication of publication bias.
CONCLUSION: Breast-feeding seems to have a small but consistent protective effect against obesity in children.
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Introduction

While the first indication of a significant protective effect of breast-feeding against childhood obesity was published in 1981 by Kramer,[1] these findings were only confirmed recently when several large-scale epidemiological studies with an adequate study design and sufficient power were published.[2–11] Most of these studies were narratively reviewed in 2003,[12] however, without systematic identification of relevant studies. This is the first review on this issue applying a systematic identification of relevant studies and a prospective study protocol with a focus on careful adjustment of potential confounding factors. Publication bias and potential heterogeneity including its possible causes are assessed and a weighted odds ratio (OR) is calculated applying the established methods for meta-analyses.[13]

*Correspondence: Professor R von Kries, Institute for Social Paediatrics and Adolescent Medicine, Ludwig-Maximilians-University, Heiglhofstr. 63, D-81377 Munich, Germany.
E-mail: prof.von.kries@gmx.de
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Methods

Inclusion criteria

The systematic review and the subsequent meta-analysis were conducted using a prospective study protocol, defining the inclusion criteria to be met on *a priori* by a person initially not familiar with the study results. For the assessment of the association between breast-feeding and obesity in childhood we included population-based cohort, cross-sectional or case–control studies. In cross-sectional studies outcome and exposure are assessed at the same time. However, in cross-sectional studies on breast-feeding the exposure is ascertained retrospectively at the time of assessment of obesity, whereas in cohort studies the exposure is assessed in the first year of life and obesity is measured later on. In retrospective cohort studies, the information on the exposure is retrospectively abstracted from files documented at recruitment. The first step was a systematic review of all eligible studies on children older than 1 y at the last follow-up stage. Studies had to be published in English, French, Italian, Spanish or German. In the second step a meta-analysis was conducted. Only studies with adjustment for at least three of the following relevant confounding or interacting factors birth weight, parental overweight, parental smoking, dietary factors, physical activity and socioeconomic status were included in this meta-analysis. As suggested by Liberatos *et al,*[14] we accepted parental education as an appropriate indicator of socioeconomic status. Other inclusion criteria were: comparable risk estimates as OR or relative risk had to be reported and age at the last follow-up had to be between 5 and 18 y; feeding-mode had to be assessed and reported and obesity as outcome had to be defined by body mass index (BMI) percentiles ≥ 90, 95 or 97 kg/m^2, to allow for comparison of the studies. We did not require all studies to use identical reference values. If risk estimates were calculated for different percentile values in a particular study, the estimate for the highest percentile-value was included in the meta-analysis.

Identification of studies

The systematic computerized literature search of published studies was carried out in January 2004. The search was conducted in Silver Platter Medline from 1966 to December 2003, in Embase from 1988 to December 2003, in the Cochrane Library 2/2003 and in Google (internet search engine) using the following search terms: 'breast-feeding or breast feeding or breastfeeding' and 'overweight or adiposity* or fat* or obesity' and 'child* or adolescent*'. No further limitations were made in order to be as sensitive as possible. Identification of further studies was made through hand-search in original articles and reviews on the subject found by electronic search.

Data extraction and statistical analysis

Data of each study were extracted using a standardized protocol to assess mode of feeding, outcome and potential confounders. The pooled crude and adjusted odds ratios (AOR) of the studies meeting the inclusion criteria were calculated in a fixed-effects model. The assumption of the fixed-effects model is that all studies measure the same effect. Heterogeneity was tested using a *Q*-test.[15] Additionally, random-effects pooled estimates using the DerSimonian and Laird method[16] were calculated, in which the study effects are treated as normally distributed around a population mean. Sensitivity analyses were carried out to detect potential sources of heterogeneity by testing the stability of the findings across different approaches in study design, exposure ascertainment and selection of study participants.[13] The studies were stratified by the definition of breast-feeding, definition of obesity, number of potential confounders considered for in the adjustment, type of the study or age of the children at follow-up. Additionally, we assessed the potential impact of inclusion of other studies—not matching the inclusion criteria for the meta-analysis—on the pooled estimates.

Publication bias was assessed by a funnel plot. The log of the ORs, representing estimates of the effects of breast-feeding on childhood obesity, were plotted against the inverse of the standard error of the log OR as a measure of precision reflecting the study size. The aim is to assess symmetry as an indicator of the absence of publication bias. A funnel plot regression was additionally computed.[17] In this approach, the degree of funnel plot asymmetry can be measured by the intercept from a linear regression of the standardized effect sizes against precision. In the absence of publication bias this intercept will be zero.

All analyses were performed with SAS software package, version 8.

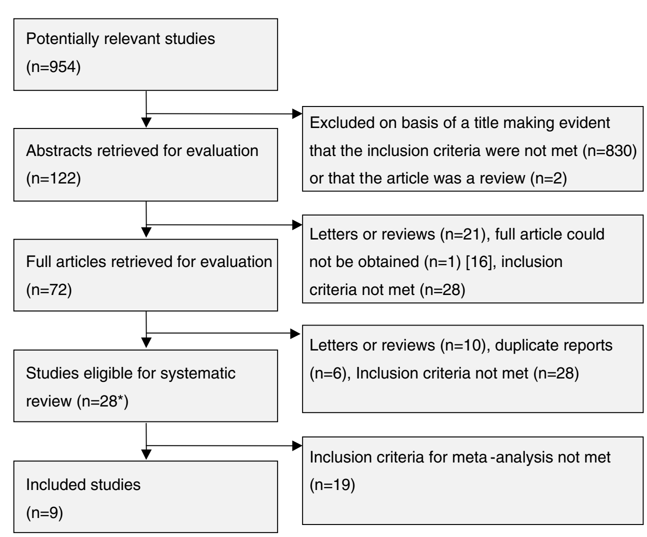
Results

Identification of studies

The applied search strategy yielded 953 potentially relevant publications in Medline and Embase. One additional article was found in the citations of the relevant studies by manual search.[18] No additional studies were found in the Cochrane Library and Google search. The evaluation of the 954 publications is shown in Figure 1.

Results of the systematic review

In total, 28 studies met the inclusion criteria for the systematic review, 19 of them were not eligible for the meta-analysis[1,2,11,19–34] because they did not meet the inclusion criteria of the meta-analysis (Table 1). Most of the studies excluded from the meta-analysis were small, only nine of them had a sample size of more than 100 per feeding group.[2,11,22,23,25,26,30,32,33] Six of these nine studies did not



* including two studies based on the same cohort

Figure 1 Breast-feeding and obesity. Identification and evaluation of the studies for the meta-analysis.

Table 1 Characteristics of the studies that examined the association between breast-feeding and obesity in children, but did not meet the inclusion criteria for the meta-analysis

Author, publication-year	*Country, time period*	N[a]	*Age at last follow-up (y)*	*Effect of breast-feeding*	*Study type*	*Reasons for exclusion*
Agras, 1987[20]	USA not reported	79	2	No correlation of BF and adiposity	Prospective cohort study	Only $n=8$ were exclusively BF, log BMI as outcome measure, definition of adiposity not reported, OR not reported
Agras, 1990[19]	USA not reported	54	6	Association of BF >5 mo. and adiposity at age 3 and 6 y ($P=0.01$)	Same cohort as Agras, 1987	Dropouts $n=45$, definition of adiposity not reported, OR not reported
Armstrong, 2002[2]	Scotland 1995–1999	32 200	3	AOR 0.72 (0.65, 0.79) for BMI ≥95th perc. AOR 0.7 (0.61, 0.8) for BMI ≥98th perc.	Population-based cohort study, adjustment for sex, birth weight, socioeconomic status	Children under 4 y (39–42 months)
Elliott, 1997[21]	USA 1977–1996	136	Adolescence	Crude OR 0.42 (0.19, 0.93) for any BF >2 mo. ($P<0.03$), no correlation in multiple- and logistic regression	Cross-sectional study	Age at follow-up not reported, 85% of original cohort excluded, obesity defined as BMI ≥85th perc., AOR not reported
Frye, 2003[22]	Germany 1992–1999	6650	11–14	OR 0.9 (0.7, 1.1) for overweight OR 0.6 (0.4, 0.9) for obesity, overweight and obesity defined according to the IOTF[35]	Three consecutive cross-sectional studies, adjustment for age, sex, survey	No adjustment for birth weight, maternal smoking, parental overweight, socioeconomic status
Haschke, 2003[23]	Europe not reported	2245	5	Crude OR 0.84 ($P<0.01$) for BMI >90th perc. at age 12 mo., no association at age 3 and 5 y	Prospective cohort study	AOR not reported
Ivanovic, 1987[24]	Chile 1986	306	5–8	No correlation between duration of breastfeeding and overweight	Cross-sectional study	Overweight defined as 110–120% of weight/height NCHS Standard, obesity defined as >120% of weight/height NCHS Standard, AOR not reported
Kramer, 1981[1]	Canada 1980	(1) 466 (2) 389	12–18	(1) Hospital-based: crude OR 0.24 (0.09, 0.63), AOR 0.30, inverse correlation of duration of BF and relative weight ($P<0.025$); (2) school-based: crude OR 0.44 (0.21, 0.93)	Case–control study, examination of potential confounding factors: age, sex, race, ethnicity, birth order, socioeconomic status, family history of obesity	Obesity defined as weight/height >120% or skinfold thickness >95th perc. or both >90th perc.
Langnäse, 2003[25]	Germany 1996–1998	1326	5–7	Prevalence of overweight 17.8%, 10.2% and 8.8% for never BF, BF ≤6 mo. and BF >6 mo., $P<0.05$	Cross-sectional study	OR not reported
Parsons, 2003[26]	Great Britain 1958–1991	9287	33	AOR 0.93 (0.74, 1.17) for males AOR 0.84 (0.67, 1.05) for females	Cohort study (BF ascertained at the age of 7 y), adjustment for social class, mother's smoking, mother's BMI	AOR for age 7–16 y not reported
Ravelli, 2000[27]	Netherlands 1944–1996	625	48–53	No correlation	Retrospective cohort study, adjustment for sex, maternal age, length of hospital stay	Definition of obesity not reported, OR not reported
Richter, 1981[28]	GDR 1957–1977	2385	School entry	Prevalence of obesity 9.8% for never BF *vs* 5.3% for BF ≥7 mo., crude OR 0.51 (0.15, 1.71)	Prospective cohort study	Adiposity defined as weight (kg) ≥20% above the normal value, exclusivity of BF not reported

Table 1 (Continued)

Author, publication-year	*Country, time period*	N[a]	*Age at last follow-up (y)*	*Effect of breast-feeding*	*Study type*	*Reasons for exclusion*
Scaglioni, 2000[29]	Italy 1991–1997	147	5	Crude OR 0,64 (0.24, 1.17) for BMI >90th perc., trend for longer Duration of full BF in children without overweight	Prospective cohort study	AOR not reported
Strbak, 1991[30]	CSFR not reported	1034	Median 5	Crude OR of BF>6mo. *vs* BF<2 weeks 0.28 (0.08, 1.04) for $n=334$	Prospective cohort study	Definition of obesity not reported
Tanasescu, 2000[31]	USA not reported	53	7–11	Trend: obese children are more often BF ($P=0.11$)	Case–control study of Puerto Rican children	Obesity defined as BMI ≥85th perc., OR not reported
Tulldahl, 1999[32]	Sweden 1994	781	15–16	Crude OR 0.66 (0.44, 0.98) for BMI ≥85th perc.	Cohort study	Obesity defined as BMI ≥85th perc., AOR not reported
Victora, 2003[11]	Brazil 1982–2000	2250	18	AOR 0.85 (0.57, 1.27) for overweight AOR 0.38 (0.2, 0.72) for obesity and BF 3–5 mo. *vs* ≥12 mo., no significant association for other duration of BF	Prospective cohort study	Overweight defined as BMI ≥85th perc., obesity defined as BMI ≥85th perc. and skinfold thickness ≥90th perc., BF ≥12 mo. as reference
Wadsworth, 1999[33]	Great Britain 1952	3550	6	Crude OR 0.95 for BMI >90th perc., n.s. crude OR 0.88 for BMI >97th perc., n.s. AOR's not significant	Cohort study, adjustment for social class, birth weight, number of people per room, fat intake at age 4 y	AOR not reported
Wolman, 1984[34]	USA not reported	164	Preschool children	No relation of BF or duration of BF to obesity	Cohort study of low social class children	Obesity defined as weight or weight/height or BMI or Eid-Index >95th perc., OR not reported

[a]Number of participants included at last follow-up.

report adequate assessment and adjustment for potential confounding factors so that inclusion criteria were not met.[22,23,25,30,32,33] The study of Wadsworth was published as a letter to the editor and adjusted for potential confounding factors, but did not report an AOR for breast-feeding.[33] In the case–control study of Kramer,[1] obesity was defined as weight/height >120% or skinfold thickness >95th percentile or both >90th percentile, which did not match our study criteria. The cohort study of Armstrong *et al*[2] included children at an age of 39–42 months at follow-up. The recently published study of Parsons *et al*[26] did not report AORs for the age group of 7–16 y, whereas in the study of Victora *et al*[11] the inclusion criteria of definition of overweight or obesity were not met. The studies of Kramer[1] and of Armstrong *et al*[2] showed a significant protective effect of breast-feeding, whereas the studies of Wadsworth *et al*,[33] Parsons *et al*[26] and Victora *et al*[11] failed to show such an association. Reasons for exclusion from the meta-analysis are shown in Table 1.

Results of the meta-analysis

Nine studies were eligible for the meta-analysis comprising more than 69 000 children included in the final analysis. Table 2 shows characteristics of these studies and potential confounders, for which adjustment was made.

Six studies used cutoff values for the respective BMI percentiles based on internal[8,9] or national[4–6,10] reference populations, whereas two studies used the reference populations according to the recommendations of the international obesity task force (IOTF)[35] or Rolland-Cachera *et al*.[36]

One of the studies included was a cohort study with longitudinal follow-up of the participants at several ages.[7] For this study, conducted by Poulton *et al*, we calculated a weighted estimate for the age-groups between 5 and 18 y. Children who had never been breastfed were compared to children breastfed for more than 6 months. This weighted AOR was used in the meta-analysis.

The pooled crude OR for breast-feeding and obesity defined as BMI ≥90th, 95th or 97th percentile could be

Table 2 Characteristics of the studies that met the inclusion criteria for the meta-analysis

Author, publication-year	*Country, time period*	N[a]	*Age at last follow-up (y)*	*Effect of breast-feeding*	*Definition of overweight (BMI-centile)*	*Definition of feeding mode*	*Study type*	*Potential confounding factors adjusted for*
Bergmann, 2003[3]	Germany	480	6	AOR 0.53 (0.31, 0.89), AOR 0.46 (0.23, 0.92)	90th–96th perc., ≥97th perc.	Never BF or partly BF <3 mo. *vs* BF ≥3 mo.	Population-based prospective cohort study	Maternal overweight, smoking during pregnancy, education, occupation, income[b]
Gillman, 2001[4]	USA	14 377	9–14	AOR 0.78 (0.66, 0.91)	>95th perc.	Mostly or only BF *vs* mostly or only FF in the first 6 mo.	Cross-sectional study of a cohort of the Growing Up Today Study	Maternal overweight, birth weight, maternal smoking, diet and weight concerns, income, Tanner stadium, birth order, weekly hours of TV, physical activity[b]
Hediger, 2001[5]	USA	2498	3–5	AOR 0.63 (0.41, 0.96), AOR 0.84 (0.62, 1.13)	85th–94th perc. ≥95th perc.	BF never *vs* ever	Cross-sectional study (NHANES III)	Race, maternal overweight, birth weight, introduction of solid foods
Li, 2003[10]	Great Britain	2631	4–18	AOR 0.25–1.01 for age 4–8, depending on duration of BF AOR 0.25–1.01 for age 9–18, depending on duration of BF	>95th perc	BF groups: <1 week, 1 week–1 mo., 2–3 mo., 4–6 mo., 7–9 mo., >9 mo., exclusivity of BF not reported	Population-based cross-sectional study	Parental BMI, smoking during pregnancy, birth weight, social class
Liese, 2001[6]	Germany	2108	9–10	AOR 0.66 (0.52, 0.87)	≥90th perc.	BF never *vs* ever	Community-based cross-sectional study (ISAAC)	Nationality, socio-economic status, parental smoking, number of siblings
O'Callaghan, 1997[18]	Australia	3909	4–6	AOR 0.83 (0.59, 1.25), AOR 0.71 (0.43, 1.25)	85th–94th perc. ≥95th perc.	BF never *vs* >6 mo.	Population-based prospective cohort study	Parental overweight, birth weight, feeding problems, income, education, sleeplessness[b]
Poulton, 2001[7]	New Zealand	591–698 depending on age	3–26	(1) AOR 0.71–1.18 depending on age for never BF *vs* BF ≤6 mo. (2) AOR 0.25–1.01 depending on age for never BF *vs* BF >6 mo.	Definition according to Cole *et al*[35]	BF never *vs* BF ≤6 mo. BF never *vs* BF >6 mo. (exclusivity not determined)	Consecutive population-based cross-sectional studies of a British birth cohort	Parental overweight, birth weight, maternal education
Toschke, 2002[8]	Czech Republic	33 768	6–14	AOR 0.8 (0.71, 0.9), AOR 0.8 (0.66, 0.96)	>90th perc., >97th perc.	BF never *vs* ever	Cross-sectional study (5th Nationwide Anthropometric Survey)	Parental overweight, birth weight, maternal smoking, education, no. of siblings, hours watching TV, physical activity[b]

Table 2 (Continued)

Author, publication-year	*Country, time period*	N[a]	*Age at last follow-up (y)*	*Effect of breast-feeding*	*Definition of overweight (BMI-centile)*	*Definition of feeding mode*	*Study type*	*Potential confounding factors adjusted for*
von Kries, 1999[9]	Germany	9206	5–6	AOR 0.79 (0.68, 0.93), AOR 0.75 (0.57, 0.98)	>90th perc., >97th perc.	BF never *vs* ever	Population-based cross-sectional study	Birth weight, smoking during pregnancy, butter intake, education, children's own sleeping room[b]

[a]Number of children included in final model of adjusted odds ratio. [b]Adjustment for ≥7 potential confounding factors (adjustment for age and sex not mentioned in the table).

calculated for six studies[3–5,8,9,18] (Figure 2). The three other studies lacked information to calculate crude OR with confidence intervals.[6,7,10] Under the fixed-effects assumption, the OR was 0.67, 95% CI (0.62, 0.73). In the random-effects model an almost identical OR was found (data not shown). There was no indication of significant heterogeneity of the studies: the null hypothesis of homogeneity could not be rejected ($Q=7.8$, df$=5$, $P>0.1$).

The AOR calculated for nine studies[3–10,18] (Figure 3) was 0.78, 95% CI (0.71, 0.85) for both fixed and random-effects model, suggesting that there was no heterogeneity between the studies (Figure 3). The homogeneity hypothesis could not be rejected by the *Q*-test ($Q=9.4$, df$=8$, $P>0.3$). Although the studies appeared to be homogeneous, sensitivity analyses were performed, comparing the studies according to the following criteria: cohort study or cross-sectional study, different definitions of breast-feeding, different definitions of obesity, different age-groups and number of potential confounders considered for adjustment. The protective effect of breast-feeding was more pronounced in studies with adjustment for less than seven potential confounding factors compared to adjustment for seven or more potential confounding factors (Table 3).

Eight of the studies provided data about a relationship between breast-feeding duration and risk of overweight or obesity in later childhood (Table 4). Four studies demonstrated an inverse association of breast-feeding duration and prevalence of obesity both in the crude and the adjusted analysis,[4,6,8,9] whereas one study found a dose–response contingency in the crude analysis that lost statistical significance after adjustment.[7] Three studies found no significant effect of duration of breast-feeding.[5,10,18]

The funnel plot showed an asymmetric pattern, which was due to a particular study (Figure 4). The funnel plot regression analysis did not reject the null hypothesis of symmetry (df$=8$, $P=0.71$), suggesting that there was no publication bias.

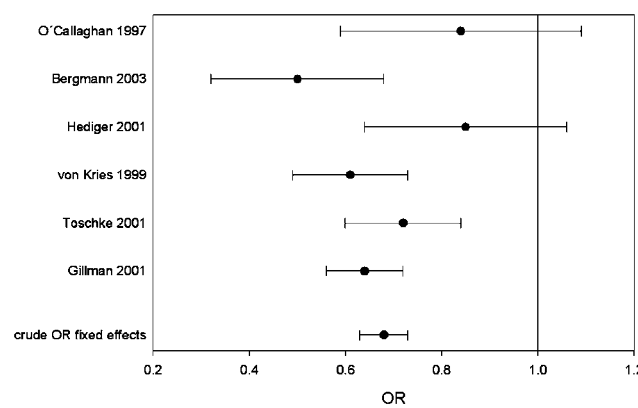


Figure 2 Effect of breast-feeding *vs* formula feeding on childhood obesity: crude odds ratios of six studies and pooled odds ratio.

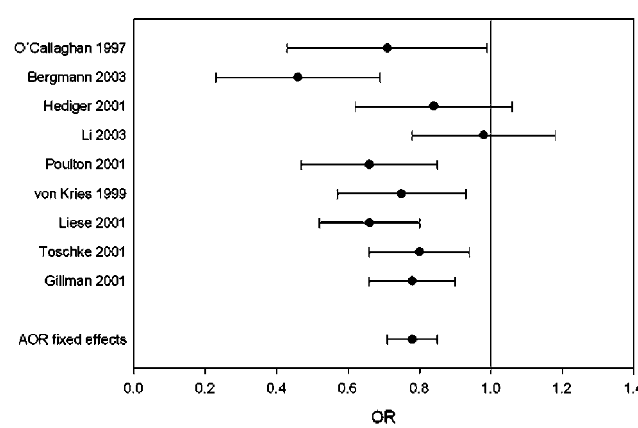


Figure 3 Effect of breast-feeding *vs* formula feeding on childhood obesity: covariate-adjusted odds ratios of nine studies and pooled odds ratio.

Discussion

A classical meta-analysis requires randomized controlled trials. Randomization of breast-feeding on an individual level is not ethical, however. Trials with randomized intervention on hospital level as recently published by Kramer *et al*[37] might provide data that will allow for better assessment of the effects of breast-feeding on obesity. Unfortunately, there are no cluster-randomized controlled trials on breast-feeding and obesity published yet. So far only cohort, cross-sectional and case–control studies have been performed on this issue.

Definition of obesity

It has been reported that breast-feeding does not shift the whole distribution of BMI to the left, but only the upper tail as clearly shown in the publication of Koletzko *et al*.[38] We are not aware of other studies on the interdependencies of breast-feeding and childhood obesity taking into account both an effect on the median and the upper tail of the distribution. Therefore, we can only hypothesize that the impact on the upper tail of the distribution is the genuine effect of breast-feeding. Interestingly, the obesity epidemic in children as opposed to adults is predominantly caused by an increase of the BMI distribution in the upper percentiles.[39,40] Therefore, it appears reasonable to consider exposures, which affect the upper tail mainly. We confined our analyses to studies with overweight and obesity as end points. Although the studies used different percentiles for the definition of obesity, the results were comparable and the sensitivity analysis showed no difference between a cutoff at the 90th, 95th and 97th percentile.

Table 3 Sensitivity analyses of studies that met the inclusion criteria for the meta-analysis

Component	*Pooled odds ratio and 95%CI (fixed effects)*
Study type	
Cohort study	0.73 (0.64, 0.85)
Cross-sectional study	0.76 (0.67, 0.86)
Age group[a]	
Up to 6 y	0.75 (0.63, 0.90)
Older than 6 y	0.76 (0.68, 0.85)
Definition of breast-feeding	
Never-ever	0.76 (0.67, 0.86)
Other definition	0.74 (0.64, 0.85)
No. of confounding factors adjusted for	
<7	0.69 (0.59, 0.81)
≥7	0.78 (0.70, 0.87)
Definition of obesity	
≥95th perc.	0.79 (0.68, 0.91)
≥97th perc.	0.76 (0.65, 0.89)

[a]Study from Poulton was excluded because of longitudinal follow-up.

Definition of breast-feeding

The assessment of exposure to breast-feeding differed from study to study: Gillman *et al*[4] compared children who were mostly or only breastfed in the first 6 months with children

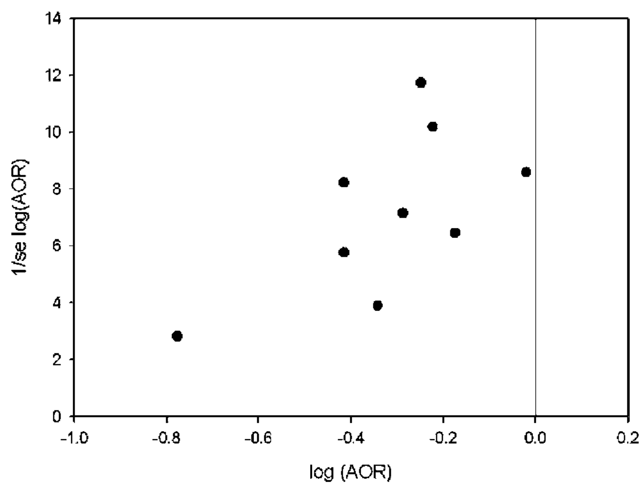


Figure 4 Funnel plot. Log (AOR) of the individual studies (horizontal axis) plotted against 1/se log (AOR) (vertical axis).

Table 4 Characteristics of the studies that met the inclusion criteria for the meta-analysis and examined the association of breast-feeding duration with childhood obesity

Author, publication-year	*Assessment of breast-feeding duration*	*Effect of breast-feeding duration*
Gillman, 2001[4]	Duration of BF (mostly or only): ≥7 mo. *vs* ≤3 mo.	AOR 0.92 (0.87, 0.98) for overweight for every increment of 3 mo. of BF
Hediger, 2001[5]	Duration of full BF	No effect
Li, 2003[10]	Duration of BF (exclusivity not reported)	No effect
Liese, 2001[6]	Duration of BF (any and full)	Decreasing prevalence of overweight with increasing duration of BF
O'Callaghan, 1997[18]	Duration of BF (exclusivity not reported)	No significant association
Poulton, 2001[7]	BF never *vs* BF ≤6 mo. and BF never *vs* BF >6 mo. (exclusivity not determined)	No significant association after adjustment
Toschke, 2002[8]	Duration of BF (exclusivity not determined)	Effect of duration of BF on decreased prevalence of overweight but not on prevalence of obesity
von Kries, 1999[9]	Duration of exclusive BF	Dose-dependent effect of duration of BF on decreased prevalence of overweight or obesity

mostly or only formula fed, while most of the studies compared children who were never breastfed with children ever breastfed (Table 2). However, in a sensitivity analysis, homogeneity between the studies stratified by different definitions of breast-feeding could not be rejected.

Residual confounding

Although only studies with adjustment for at least three confounding variables were included in this meta-analysis, residual confounding remains a potential limitation. Residual confounding is present if a confounding factor cannot be assessed with sufficient precision and randomization is not feasible. This represents a widespread problem in epidemiological research.[13,41] Socioeconomic status in particular is likely to confound the relationship between breast-feeding and childhood obesity. The number of indicators to assess socioeconomic status used in the studies considered varied: in those using one indicator only there might be residual confounding. Even in the study of Bergmann *et al*,[3] however, which used all three indicators parental education, profession and income, socioeconomic status could not fully explain the protective effect of breastfeeding on childhood obesity, supporting the findings of Liberatos *et al*,[14] that parental education is a highly relevant indicator of socioeconomic status.

In our meta-analysis potential confounding factors as birth weight, maternal overweight, maternal smoking and socioeconomic status contributed to a difference between adjusted and crude OR of up to 0.14 in the individual studies. Even in the three studies, in which the investigators adjusted for more than six potential confounding factors, the protective effect of breast-feeding remained significant with a pooled OR of 0.78, however (Table 3). This indicates that further adjustment for more relevant variables might reduce the calculated effect, but the protective effect of the breast-feeding is unlikely to be reduced to zero.

Publication bias

The funnel plot of the included studies showed an asymmetric pattern, which was due to the particular study of Bergmann *et al*.[3] This study is diverging to the left-hand side. The funnel plot regression, however, indicated no significant publication bias. Both approaches have limitations. The shape of a funnel plot can show great variation depending on the way of construction.[42] We used the method suggested by Sterne *et al*.[43] The validity of the regression method is limited because of low statistical power in meta-analyses of less than 20 studies.[43]

To assess potential selection bias, a pooled estimate of all eligible studies that reported AORs with confidence intervals—including also studies excluded from the original meta-analysis[2–10,18,26]—was calculated. The AOR of 0.77 (95% CI: 0.72, 0.82) was similar to the base case including only studies matching the inclusion criteria[3–10,18] (AOR 0.78). Nevertheless publication bias cannot be excluded definitely, because some studies, which found no significant effect in a crude analysis, did not report adjusted estimates and therefore had to be excluded from the meta-analysis. Including these studies might reduce the protective effect of breast-feeding; however, most of the recently published studies with weak or absent effects in the crude analysis presented estimates with adjustment for confounding.[5,7,10,11,18,26]

Possible mechanisms

The inverse association between breast-feeding and obesity suggests a role for breast-feeding in the reduction of obesity prevalence in later life. Possible explanations were extensively discussed in earlier studies, reviews and editorials[12,44] and include behavioural and hormonal mechanisms and differences in macronutrient intake. Higher plasma-insulin concentrations in bottle-fed compared to breast-fed infants could stimulate fat deposition and lead to early development of adipocytes.[45] Bioactive factors in breast-milk might modulate growth factors, which inhibit adipocyte differentiation *in vitro*.[46,47] Furthermore, protein intake and amount of energy metabolisation is lower in breastfed than in formula-fed infants.[48] A longitudinal study showed a significant association between early protein intake and later BMI,[49] suggesting that a higher protein intake early in life might increase the risk of later obesity. In animal studies the availability of protein during fetal and early postnatal development was found to have a long-term effect on the metabolic programming of glucose metabolism and body composition in later life.[50,51] These pathways—alone or in combination—provide plausible explanations for a protective effect of breast-feeding against obesity.

Conclusion

This meta-analysis indicates that breast-feeding is associated with a small but consistent protective effect against obesity risk in later childhood.

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