Chapter 12

PROTECTIVE EFFECT OF BREAST-FEEDING AGAINST OBESITY IN CHILDHOOD: CAN A META-ANALYSIS OF PUBLISHED OBSERVATIONAL STUDIES HELP TO VALIDATE THE HYPOTHESIS?

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1. INTRODUCTION

In recent years the relationship between breast-feeding and childhood obesity has been a focus of interest. Since 2000 16 studies regarding this issue have been published - some have found a protective effect, while others have not.

The conclusions drawn from these data regarding the potential protective effect of breast-feeding on childhood obesity diverge. While a narrative review of Dewey suggests an effect of breast-feeding[1], an editorial in the British Medical Journal cites two recent studies without such an effect and cites inconclusive evidence.[2] A recent meta-analysis suggested a small but significant protective effect of breast-feeding.[3] The objective of this paper is to discuss the strengths and limitations of the meta-analysis approach and to summarise the results of our meta-analysis.

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1.1 Why does it make sense to conduct a meta-analysis?

The assumption in a meta-analysis is that all studies measure the same exposure and effect. In this case different odds ratios are explained by chance and are related to differences in the size of the study. The meta-analysis summarises the effects of the included studies. Statistical power is increased to allow for more precise estimates.

1.2 What are the limitations of a meta-analysis on breast-feeding and childhood obesity?

The reported studies do not only differ with respect to sample size but also with regard to a number of other study characteristics. The studies included used different approaches to measure the exposure "breast-feeding".[4-12] Most of the studies compare children in the broad categories "never breastfed" with children "ever breastfed" while some studies use other more elaborate definitions of breast-feeding taking account of the exclusiveness and duration of breast-feeding. Also the assessment of potential confounders and the definition of the outcome are not consistent over the different studies. Overweight or obesity was defined by BMI percentiles $\geq$ 90, 95 or 97 with varying reference populations. Testing for heterogeneity can be conducted to rule out bias generated by these different approaches.

Publication bias; (small) studies which do not show a significant effect are less likely to be published.[13] Publication bias can be detected by a funnel plot. For example a measure of the effect of breast-feeding on childhood obesity (for example the log of the odds ratios) can be plotted against a measure of precision reflecting the study size (for example the inverse of the standard error of the log odds ratio). It is assumed that the point estimates for more powerful studies will be closer to the pooled estimate. The plot therefore constitutes a funnel, the tip being formed by the more powerful studies (Figure 12-1). The objective is to assess symmetry as an indicator of the absence of publication bias. A funnel plot regression analysis can also be conducted. This is likely to have sufficient power if the number of studies included is 20 or more.[13] In this approach the degree of funnel plot asymmetry can be measured as the intercept from a linear regression of the standardised effect sizes against precision. In the absence of publication bias this intercept will be zero.

Inclusion criteria for a meta-analysis may account for selection bias if knowledge of results of eligible studies leads to the exclusion of studies with negative findings. To minimise selection bias inclusion criteria should be defined *a priori* in a study protocol and eligibility should be assessed by at least two independent observers not familiar with the study results.

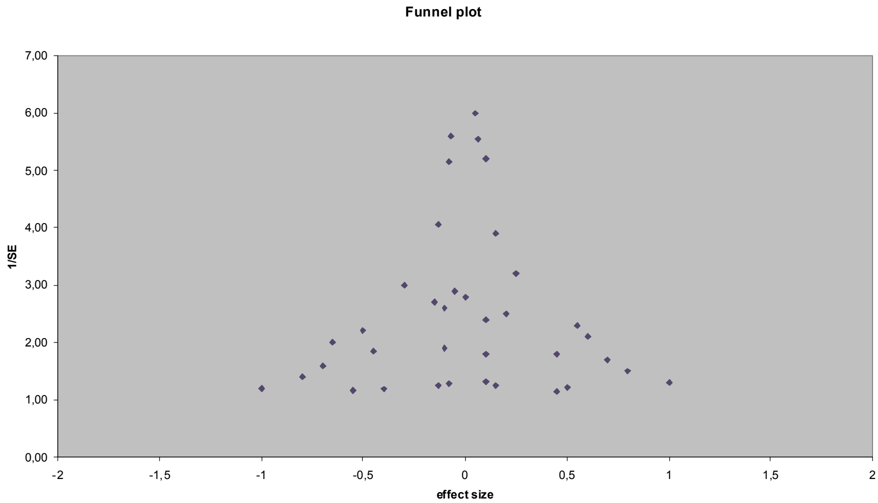

Figure 12-1. Typical funnel plot generated from simulated studies.

1.3 Does a meta-analysis take us further towards causality?

Meta-analyses can never be better than the primary studies included. If residual confounding is a problem of the observational studies there will also be potential residual confounding in the meta-analysis. For example, breast-feeding might be a surrogate for other exposures that could not be assessed or adjusted for. Parental overweight, smoking and socio-economic status are related to both breast-feeding and to childhood obesity and may account for confounding. Estimates of these factors are used in the analysis in order to adjust for confounding. However the estimates of these potential confounders may not be precise enough for full adjustment (residual confounding). Residual confounding may also arise from unknown factors - associated both with the exposure and the outcome - for which data have not been collected.

1.4 Methods and main results of a recent meta-analysis on breast-feeding and childhood obesity

Cohort, cross-sectional or case-control studies were included in this meta-analysis[3]. Only studies with adjustment for at least three potential confounding factors such as birthweight, dietary factors, physical activity, parental overweight, parental smoking and socio-economic status were included. Other inclusion criteria were: comparable risk estimates such as odds ratio or relative risk had to be reported; age at the last follow-up had to be between 5 and 18 years; feeding-mode had to have been assessed and reported; and obesity as the outcome had to be defined by BMI percentiles ≥ 90, 95 or 97 to allow for comparison of studies. Inclusion criteria were defined *a priori* by a person initially not familiar with the study results.

A systematic computerised literature search of published studies for breast-feeding, obesity and children was conducted. Identification of further studies was carried out through handsearches in the references of original articles and reviews.

The pooled odds ratios of the eligible studies were calculated, heterogeneity was tested to determine whether the studies were measuring the same effects and stratified 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. The potential impact of inclusion of other studies - not matching the inclusion criteria for the meta-analysis - on the pooled estimates was also assessed.

Nine studies with more than 69000 participants met the inclusion criteria. The adjusted odds ratio for breast-feeding on childhood obesity was 0.78, 95% CI (0.71, 0.85) in the fixed-effects model. The results of the included studies were homogeneous (Q-test for heterogeneity, $p>0.3$). Stratified analyses showed no significant differences regarding different study types, age groups, definition of breast-feeding or obesity and number of confounding factors adjusted for (Table 12-1).

Table 12-1. Stratified 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	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 Percentile	0.79 (0.68, 0.91)
	≥97th Percentile	0.76 (0.65, 0.89)

*From: Arenz *et al* [3]

The funnel plot was asymmetrical due to one particular study. Funnel plot regression gave no indication of publication bias, however the statistical power might have been insufficient due to the small number of included studies.

It is difficult to definitely rule out publication bias. 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.

To assess potential selection bias a pooled estimate of all eligible studies which reported adjusted odds ratios with confidence intervals was calculated (including those studies excluded from the original meta-analysis because individuals were either too young or too old to meet the original inclusion criteria.[14,15]). In this analysis the AOR of 0.77 (95%CI: 0.72, 0.82) was similar to the base case.

In conclusion our meta-analysis indicates that breast-feeding has a small but consistent protective effect on obesity risk in childhood. Since it is difficult to rule out residual confounding and publication bias there remains some uncertainty. Regarding publication bias we felt reassured when we looked at unpublished data from candidates for the Bavarian school entry examinations in 1999 and 2002 and compared the observed effect estimates for breast-feeding on childhood obesity to the original publication based on data from 1997.[4] Whilst in 1999 no significant protective effect could be seen, in 2002 the effect became significant again (Table 12-2).

Table 12-2. Adjusted odds ratios for breast-feeding and overweight or obesity in candidates for school entrance examinations in Bavaria.

Year	Adjusted odds ratio and 95%CI for breast-feeding	
	Overweight	Obesity
1997	0.79 (0.68, 0.93)	0.75 (0.57, 0.98)
1999	0.84 (0.66, 1.06)	0.91 (0.60, 1.38)
2002	0.79 (0.63, 0.99)	0.70 (0.47, 1.04)

1.5 Why is it still tempting to assume that breast-feeding prevents childhood obesity?

There are some hints for biological plausibility of a protective effect of breast-feeding including behavioural and hormonal mechanisms and differences in macronutrient intake. Formula-fed infants have higher plasma-insulin concentrations compared to breast-fed infants. This could stimulate fat deposition and lead to early development of adipocytes.[16] Bioactive factors in breast-milk might modulate growth factors which inhibit adipocyte differentiation *in vitro*. [17-18] Protein intake and energy metabolism is lower in breast-fed than in formula-fed infants.[19] A longitudinal study showed a significant positive association between early protein intake and later BMI, suggesting that a higher amount of protein intake early in life might increase the risk of obesity in later life.[20] In animal studies the availability of protein during fetal and early postnatal development was found to have a long term effect on glucose metabolism and body composition.[21-22]

If true, a causal relationship between breast-feeding and childhood obesity might be relevant at the population level. Even a small protective effect with an odds ratio near one would have a large public health impact which is reflected in the population attributable risk (PAR: reduction in the prevalence of childhood obesity by breast-feeding of all children) and the population attributable risk fraction (PARF: fraction of formula-fed children with obesity where obesity could have been prevented by breast-feeding of all children). Data from the Bavarian school entry examinations in 4916 children with an overweight prevalence of 10.4% showed a breast-feeding prevalence of 76.3% and an adjusted odds ratio for breast-feeding of 0,75 resulting in a potential reduction in the prevalence of overweight from 10.4 to 9.6% if all instead of 76% of the children would have been breastfed (population attributable risk). In this setting 7.3% of the risk for childhood overweight could be explained by not breast-feeding (population attributable risk fraction).

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