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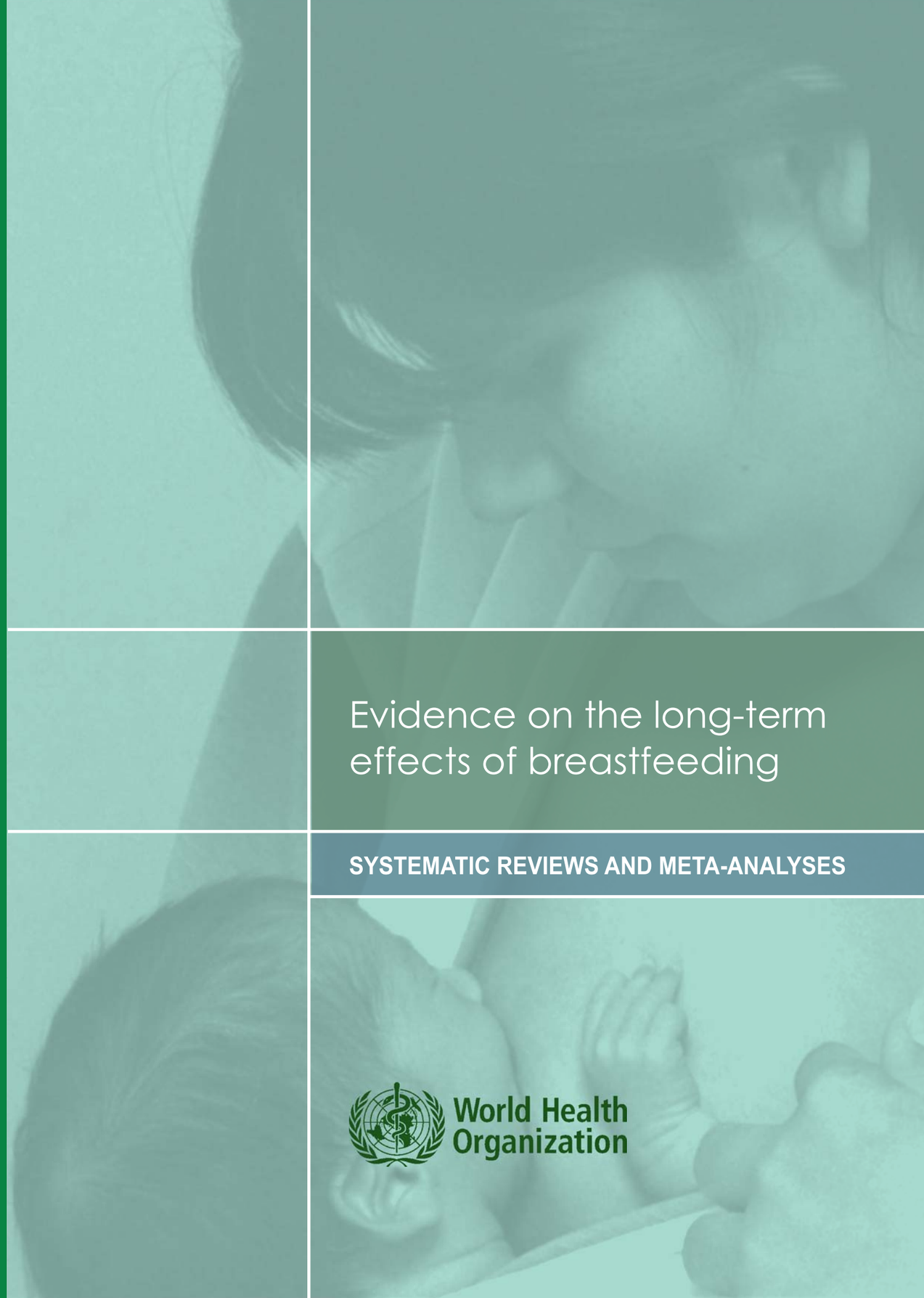
EVIDENCE ON THE LONG-TERM EFFECTS OF BREASTFEEDING: SYSTEMATIC REVIEWS AND META-ANALYSES WHO



Evidence on the long-term effects of breastfeeding

SYSTEMATIC REVIEWS AND META-ANALYSES

World Health Organization

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SYSTEMATIC REVIEWS AND META-ANALYSES

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Contents

Executive summary

Background: Breastfeeding presents clear short-term benefits for child health, mainly protection against morbidity and mortality from infectious diseases. On the other hand, there is some controversy on the long-term consequences of breastfeeding. Whereas some studies reported that breastfed subjects present a higher level of school achievement and performance in intelligence tests, as well as lower blood pressure, lower total cholesterol and a lower prevalence of overweight and obesity, others have failed to detect such associations.

Objectives: The primary objective of this series of systematic reviews was to assess the effects of breastfeeding on blood pressure, diabetes and related indicators, serum cholesterol, overweight and obesity, and intellectual performance.

Search strategy: Two independent literature searches were conducted at the World Health Organization in Geneva, Switzerland, and at the University of Pelotas in Brazil, comprising the MEDLINE (1966 to March 2006) and Scientific Citation Index databases.

Selection criteria: We selected observational and randomized studies, published in English, French, Portuguese and Spanish, assessing the effects of breastfeeding on blood pressure, obesity/overweight, total cholesterol, type-2 diabetes, and intellectual performance. Studies that restricted the measurement of outcomes to infancy were excluded from the meta-analyses. The type of comparison group used (e.g. never breastfed or breastfed for less than *x* months) did not constitute a selection criterion.

Data extraction and analysis: Two reviewers independently evaluated study quality, using a standardized protocol, and disagreement was resolved by consensus rating. Fixed and random-effects models were used to pool the effect estimates, and a random-effects regression was used to assess several potential sources of heterogeneity.

Effect on blood pressure: We included 30 and 25 estimates for systolic and diastolic blood pressure, respectively. In a random-effects model, systolic (mean difference: -1.21 mmHg; 95% confidence interval (CI): -1.72 to -0.70) and diastolic blood pressures (mean difference: -0.49 mm Hg; 95% CI: -0.87 to -0.11) were lower among breastfed subjects. Publication bias was evident, with smaller studies reporting a greater protective effect of breastfeeding. However, even among studies with $\geq$1000 participants a statistically significant effect of breastfeeding was observed (mean difference in systolic blood pressure: -0.59 mmHg; 95% CI: -1.00 to -0.19). Adjustment for confounding was also a source of heterogeneity between study results, but even among those studies controlling for several socioeconomic and demographic variables, systolic (mean difference: -1.19; 95% CI: -1.70 to -0.69) and diastolic (mean difference: -0.61; 95% CI: -1.12 to -0.10) blood pressures were lower among breastfed subjects. Publication bias and residual confounding may be responsible for part (but not all) of the observed effect of breastfeeding on blood pressure.

Effect on serum cholesterol: Breastfed subjects presented lower mean total cholesterol in adulthood (mean difference: -0.18; 95% CI: -0.30 to -0.06 mmol/L), whereas for children and adolescents the association was not statistically significant. Age at assessment of cholesterol explained about 60% of the heterogeneity between studies, whereas study size, control for confounding, year of birth and

categorization of breastfeeding duration did not play a significant role. The evidence suggests that breastfeeding is related to lower cholesterol levels and this association is not due to publication bias or residual confounding.

Effect on overweight and obesity: We obtained 39 estimates of the effect of breastfeeding on prevalence of overweight/obesity. In a random-effects model, breastfed individuals were less likely to be considered as overweight and/or obese, with a pooled odds ratio of 0.78 (95% CI: 0.72–0.84). Control for confounding, age at assessment, year of birth, and study design did not modify the effect of breastfeeding. Because a statistically significant protective effect was observed among those studies that controlled for socioeconomic status and parental anthropometry, as well as with $\geq$1500 participants, the effect of breastfeeding was not likely to be due to publication bias or confounding.

Effect on type-2 diabetes: We identified five papers that evaluated the relationship between breastfeeding duration and type-2 diabetes. Breastfed subjects were less likely to present type-2 diabetes (pooled odds ratio: 0.63; 95% CI: 0.45–0.89).

Effect on intelligence and schooling: For the assessment of performance in intelligence tests, we obtained data from eight studies that controlled for intellectual stimulation at home and collected information on infant feeding in infancy, in which the duration of breastfeeding was of at least one month among breastfed subjects. Performance in intelligence tests was higher among those subjects who had been breastfed (mean difference: 4.9; 95% CI: 2.97–6.92). Positive studies included a randomized trial. Regarding school performance in late adolescence or young adulthood, three studies showed a positive effect of breastfeeding.

Limitations: Because nearly all studies included in the analyses are observational, it is not possible to completely rule out the possibility that these results may be partly explained by self-selection of breastfeeding mothers or by residual confounding. Publication bias was assessed by examining the effect of study size on the estimates and was found not to be important for most outcomes. Very few studies were available from low/middle-income countries, where the effect of breastfeeding may be modified by social and cultural conditions.

Reviewers' conclusions: The available evidence suggests that breastfeeding may have long-term benefits. Subjects who were breastfed experienced lower mean blood pressure and total cholesterol, as well as higher performance in intelligence tests. Furthermore, the prevalence of overweight/obesity and type-2 diabetes was lower among breastfed subjects. All effects were statistically significant, but for some outcomes their magnitude was relatively modest.

I. Introduction

Breastfeeding brings clear short-term benefits for child health by reducing mortality and morbidity from infectious diseases. A collaborative reanalysis of studies conducted in middle/low-income countries reported a reduced risk of mortality from infectious diseases among breastfed infants, up to the second birthday (*1*). Kramer et al (*2*) reviewed the evidence on the effects on child health and growth of exclusive breastfeeding for 6 months. Infants who were exclusively breastfed for 6 months presented lower morbidity from gastrointestinal and allergic diseases, while showing similar growth rates to non-breastfed children.

Based on such evidence, WHO (*3*) and UNICEF (*4*) now recommend that every infant should be exclusively breastfed for the first six months of life, with continued breastfeeding for up to two years or longer. In this review we address the long-term consequences of breastfeeding on adult health and intellectual development.

Current interest in the long-term consequences of early life exposures has been fuelled by the original finding of Barker et al (*5*) that size at birth and in infancy was related to the development of adult diseases – including diabetes, hypertension and cardiovascular conditions. These findings led to the fetal origin hypothesis, which postulates that adverse intrauterine conditions would be responsible for fetal malnutrition and low birthweight, a process that would also increase the susceptibility to chronic diseases in adulthood. Indeed, epidemiological studies in several countries have reported increased risks of chronic diseases (*6-8*) among adults who were small at birth.

Because many studies on the long-term consequences of intrauterine growth may be affected by confounding variables – particularly socioeconomic status – and by inappropriate statistical analyses, some authors challenge whether or not these associations are causal (*9*). On the other hand, Lucas et al (*10*) pointed out that methodological flaws in studies of intrauterine growth may have deflected attention from important postnatal exposures – such as infant growth and feeding patterns – that could also be related to the development of chronic diseases.

The notion that nutrition during early phases of human development can alter organ function, and thereby predispose – or programme – individuals to a later onset of adult disease, is an area of considerable interest to researchers and of great concern to public health. This idea originates from the more general concept in developmental biology which was defined by Lucas as "programming" (*11*). This is defined as the process whereby a stimulus or insult applied at a critical or sensitive period of development results in a long-term or permanent effect on the structure or function of the organism. This hypothesis is currently described as the "developmental origins of health and disease" (*12*).

Over 400 scientific publications are available on the association between breastfeeding and health outcomes beyond infancy. Some researchers claim that the benefits of breastfeeding include increased school achievement or performance in intelligence tests, reduced mean blood pressure, lower total cholesterol, and a lower prevalence of overweight and obesity. On the other hand, other studies have failed to detect such associations. The evidence on long-term effects of breastfeeding may be important for further promotion of this healthy practice throughout the world.

The Department of Child and Adolescent Health and Development in the World Health Organization commissioned the present systematic review of the available evidence on long-term consequences of breastfeeding. The following long-term outcomes of public health importance were examined: blood pressure, diabetes and related indicators, serum cholesterol, overweight and obesity, and intellectual performance. These outcomes are of great interest to researchers, as evidenced by the number of publications identified. This report describes the methods, results and conclusions of this review.

II. General methodological issues in studies of the long-term effects of breastfeeding

Study design

The strength of scientific inference depends on the internal validity of the study. Randomized controlled trials, if properly designed and conducted, are considered as the gold standard of design validity, being less susceptible than other designs to selection and information bias, as well as to confounding (*13*). Furthermore, there are clearly defined standards for conducting and reporting on randomized clinical trials, all intended to increase the validity of their results and interpretation (*14*).

As mentioned previously, breastfeeding has clear short-term benefits – i.e. it reduces morbidity and mortality from infectious diseases (*1*) – and it is now unethical to randomly allocate infants to breastmilk or formula. However, about 20 years ago the evidence supporting breastfeeding was not so clear-cut and randomized trials could be carried out. In a British study from 1982, pre-term infants were randomly assigned to formula or banked breastmilk; recent follow-up of these subjects has provided an opportunity to assess whether breastfeeding can programme the later occurrence of risk factors for cardiovascular diseases (*15*).

Most recently, in the Promotion of Breastfeeding Intervention Trial (*16*) in Belarus, maternal hospitals and their corresponding polyclinics were randomly assigned to implement or not to implement the Baby-Friendly Hospital Initiative. Duration and exclusivity of breastfeeding were higher in the intervention group (*16*). Because breastfeeding promotion was randomized, rather than breastfeeding *per se*, the trial was ethically sound. Follow-up of these children will provide an excellent opportunity for studying the long-term effects of breastfeeding. It should be noted, however, that the Belarus study has relatively low statistical power because compliance with breastfeeding promotion was far from perfect.

Search for evidence on the long-term consequences of breastfeeding should not be restricted to randomized trials, because of their small number. It must involve tracking down the best available studies with rigorous design; prospective birth cohort studies should be considered as the next best design in terms of strength of evidence. It has been shown that the results of meta-analysis of well-designed observational studies, with either cohort or case-control design, can be remarkably similar to that of randomized controlled trials on the same topic (*17*). Nevertheless, birth cohort studies are susceptible to self-selection and confounding, issues that will be discussed below.

In the next section, the main methodological issues affecting these studies will be described, as well as the strategies used to minimize the impact of these limitations on the findings of the present review.

Factors affecting the internal validity of individual studies

In the context of studies on long-term consequences of breastfeeding, the following issues should be considered.

Losses to follow-up

A major source of bias in cohort studies as well as randomized controlled trials with long-term outcomes relates to the need for follow-up of individuals for a period of time after exposure in order to assess the occurrence of the outcomes of interest. If a large proportion of subjects are lost during follow-up, the study's validity is reduced. Baseline data, such as breastfeeding status, should be examined to determine whether there are systematic differences between subjects who were followed up and those who were not; if the losses are similar according to the baseline characteristics, selection bias is unlikely (*18*).

Misclassification

When the methods used for obtaining information on either infant feeding or the outcomes are inaccurate, misclassification may occur. This may take two forms: differential and non-differential misclassification.

Misclassification of breastfeeding duration is more likely in retrospective than in prospective designs. Huttly et al (*19*), in a prospective study, compared the actual breastfeeding duration with the duration reported retrospectively by the mothers. They observed a systematic bias towards reporting longer durations of breastfeeding for wealthier and more educated mothers, while those from low socioeconomic status families did not tend to err more in one direction than in the other. Because high socioeconomic status is related to a lower prevalence of cardiovascular diseases, such differential misclassification would exaggerate the long-term benefits of breastfeeding.

On the other hand, in nondifferential misclassification, measurement error is independent of exposure or outcome status. This leads to a dilution of the actual effect, because some breastfed subjects are classified as non-breastfed and vice-versa. Consequently, one is less likely to detect an association, even if one really exists.

Confounding by socioeconomic status

Socioeconomic status is one of the most important confounders in studies on the long-term effects of breastfeeding. In most societies, breastfeeding rates differ among social groups (*20*). The direction of confounding by socioeconomic status may vary between high-income and low/middle-income populations. In high-income countries, breastfeeding mothers tend to be of higher educational and socioeconomic status (*21*); other things being equal, their offspring will have a lower prevalence of cardiovascular risk factors and higher educational attainment because they belong to the upper social classes. Consequently, confounding by socioeconomic status may overestimate the beneficial effects of breastfeeding.

On the other hand, in low/middle-income settings breastfeeding is often more common among the poor (*22*). Thus, confounding by socioeconomic status may underestimate the beneficial effects of breastfeeding – for example, on educational attainment – because breastfed subjects will tend to be poorer. Depending on the association between cardiovascular risk factors and wealth in these societies, confounding can act in either direction. For example, if high cholesterol levels are more frequent among the rich, the protective effect of breastfeeding will be overestimated.

Even if confounding factors are controlled through multivariable analyses, there is a possibility of residual confounding. Inaccurate measurement of confounders, as well as incorrect specification of statistical models, may preclude full adjustment for confounding and lead to estimates of the impact of breastfeeding that are biased. For example, if information on family income is not precise, control for this imperfect variable will not fully account for the confounding effect of true income.

As discussed above, the direction of residual confounding may vary between high-income and less developed settings. These differences will be explored when analysing the results of this review for each outcome.

Self-selection

Even within the same social group, mothers who breastfeed are likely to be more health-conscious than those who do not breastfeed. This may also lead them to promote other healthy habits among their children, including prevention of overweight, promotion of physical exercise and intellectual stimulation. This may be particularly true in high-income populations. Because these maternal attributes are difficult to measure, it is not possible to include them in the analyses as confounding factors. Nevertheless, this possibility should be taken into account when interpreting the study's results.

Adjustment for potential mediating factors

Several studies on the long-term consequences of breastfeeding have adjusted their estimates for variables that may represent mediating factors, or links, in the causal chain leading from breastmilk to the outcomes. Adjustment for

mediating factors will tend to underestimate the overall effect of breastfeeding, e.g. adjusting for weight at the time of blood pressure measurement when evaluating the association between breastfeeding and blood pressure in later life. The "adjusted" estimate will reflect the residual effect of breastfeeding which is not mediated by current weight (*23*).

Main sources of heterogeneity among studies

Current epidemiological practice places limited value on the findings of a single study. Evidence is built by pooling the results from several studies, if possible from different populations, either through systematic reviews or meta-analyses.

A major concern regarding systematic reviews and meta-analyses is the extent to which the results of different studies can be pooled. Heterogeneity of studies is unavoidable, and may even be positive as it enhances generalizability. The question is not whether heterogeneity is present, but if it seriously undermines the conclusions being drawn. Rigorous meta-analyses should incorporate a detailed investigation of potential sources of heterogeneity (*24*). In the present meta-analyses, the following possible sources of heterogeneity were considered for all reviews.

Year of birth

Studies on the long-term effect of breastfeeding have included subjects born during several decades in the last century. During this period, the diets of non-breastfed infants in now high-income countries have changed markedly. In the first decades of the 20th century, most non-breastfed infants received formulations based on whole cow's milk or top milk (*25*), with a high sodium concentration and levels of cholesterol and fatty acids that are similar to those in mature breastmilk. By the 1950s, commercially prepared formulas became increasingly popular. At this time, formulas tended to have a high sodium concentration and low levels of iron and essential fatty acids. Only after 1980, the sodium content was reduced and nowadays the majority of formulas have levels that are similar to those in breastmilk (*26*). Therefore, the period of the study cohorts' births may affect the long-term effects of breastfeeding, being a source of heterogeneity among the studies.

Length of recall of breastfeeding

Misclassification of breastfeeding duration has been discussed above. Feeding histories were often assessed retrospectively and the length of recall has varied widely among studies. According to the above-mentioned study by Huttly et al (*19*) in southern Brazil, as many as 24% of the mothers misclassified the duration of breastfeeding, and misclassification increased with the time elapsed since weaning. Other studies have also reported poor maternal recall of breastfeeding duration (*27-29*). As in Brazil, Promislow et al (*27*) reported from the United States that mothers who breastfed for a short period were more likely to exaggerate breastfeeding duration, while the opposite was observed for women who breastfed for long periods. Length of recall is therefore a potential source of heterogeneity among studies.

Source of information on breastfeeding duration

The vast majority of the studies reviewed assessed infant feeding by maternal recall, while others relied on information collected by health workers or on the subjects' own reports. Marmot et al (*30*), in England, observed that about 65% of subjects correctly recalled whether they had been breastfed or formula-fed, and bottle-fed subjects were more likely to report wrongly that they had been breastfed. If misclassification were independent of other factors related to morbidity in adulthood, such as socioeconomic status, this misclassification would be non-differential and would tend to underestimate the long-term effects of breastfeeding.

Categories of breastfeeding duration

Among the reviewed studies, most compared ever-breastfed subjects to those who were never breastfed. Other studies compared subjects breastfed for less than a given number of months, often 2-3 months (including those who were never breastfed), to those breastfed for longer periods. Few studies treated breastfeeding duration as a continuous or ordinal variable with

several categories, thus allowing dose-response analyses. Furthermore, breastfeeding patterns (exclusive, predominant, or partial) have rarely been assessed.

Studies comparing ever versus never breastfed subjects may be subject to misclassification. The study by Huttly et al (*19*) showed that mothers who had actually breastfed for up to 4 weeks often reported, at a later time, that they never breastfed.

The comparison of ever versus never breastfed makes sense if the early weeks of life are regarded as a critical period for the programming effect of breastfeeding on adult diseases (*31*). On the other hand, if there is no critical window and breastfeeding has a cumulative effect, comparisons of ever versus never breastfed infants will lead to substantial underestimation of the effect of breastfeeding.

Study setting

Nearly all studies on the long-term consequences of breastfeeding have been conducted in high-income countries and in predominantly Caucasian populations. The findings from these studies may not hold for other populations exposed to different environmental and nutritional conditions, such as ethnic minorities in high-income countries (*32*) or populations from less developed countries.

Among studies carried out in the last few decades, the type of milk fed to non-breastfed infants would have varied substantially between high-income countries (where most babies receive industrialized formulas) and those from low- and middle-income countries (where whole or diluted animal milk is often used).

In this sense, lack of breastfeeding is an unusual variable in epidemiological studies. For exposures to, for example, smoking, alcohol or environmental risks, the reference category is made up of those who are unexposed. In the case of breastfeeding, however, those "unexposed" to it are themselves exposed to a number of other foodstuffs, including animal milk, industrialized or home-made formulas, or traditional weaning foods. Because alternative foods vary markedly from one setting to another, the effects of breastfeeding may be particularly affected by where the study was carried out. The location (area, country) of the study is therefore a potential modifier of the effect of breastfeeding.

Adjustment for potential mediating factors

This issue has been discussed above. Inappropriate adjustment was investigated as a potential source of heterogeneity among studies.

III. Search methods

Selection criteria for studies

In the present meta-analyses, we selected observational and randomized studies, published in English, French, Spanish or Portuguese, examining the long-term effects of breastfeeding on the following outcomes: blood pressure, overweight or obesity, cholesterol, type-2 diabetes, and intellectual performance. Studies restricted to outcome measurement in infants were excluded from the meta-analyses.

Only those studies with internal comparison groups were included. The type of comparison group used (never breastfed, breastfed for less than *x* months, etc.) did not constitute an eligibility criterion, but, as discussed above, the way in which breastfeeding was categorized was investigated as a potential source of heterogeneity among the studies.

Types of outcome measures

According to the objectives of the present review, we looked for studies with the following outcomes:

- *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 non-breastfed subjects;
- *type-2 diabetes*: odds ratio comparing breastfed and non-breastfed subjects (or alternatively, mean difference in blood glucose levels);
- *intellectual performance*: mean attained schooling and performance scores in developmental tests.

Search strategy

In order to prevent selection bias (*33*) by capturing as many relevant studies as possible, two independent literature searches were conducted: one at the Department of Child and Adolescent Health and Development in the World Health Organization (R.B.) and another at the Federal University of Pelotas in Brazil (B.L.H.).

Medline (1966 to March 2006) was searched using the following terms for breastfeeding duration: breastfeeding; breast feeding; breastfed; breastfeed; bottle feeding; bottle fed; bottle feed; infant feeding; human milk; formula milk; formula feed; formula fed; weaning.

We combined the breastfeeding terms, with the following terms for each of the studied outcomes:

- *Cholesterol*: cholesterol; LDL; HDL; triglycerides; or blood lipids.
- *Type-2 diabetes*: diabetes; glucose; or glycemia.
- *Intellectual performance*: schooling; development; or intelligence.
- *Blood pressure*: blood pressure; hypertension; systolic blood pressure; or diastolic blood pressure.
- *Overweight or obesity*: overweight; obesity; body mass index; growth; weight; height; child growth.

In addition to the electronic search, the reference lists of the articles initially identified were searched, and we also perused the Scientific Citation Index for papers citing the articles identified. Attempts were made to contact the authors of all studies that did not provide sufficient data to estimate the pooled mean effects. We also contacted the authors to clarify any queries on the study's methodology.

IV. Review methods

Assessment of study quality

Eligible studies were evaluated for methodological quality prior to consideration of their results. The following *a priori* criteria for quality assessment were used:

a. Losses to follow-up (%)
b. Type of study
   (0) Observational
   (1) Randomized
c. Birth cohort
   (0) No
   (1) Yes
d. Length of recall of breastfeeding duration
   (0) ≥3 years
   (1) <3 years
e. Source of information on breastfeeding
   (0) Records
   (1) Interviews with subjects
   (2) Mothers
f. Control for confounding
   (0) None
   (1) Socioeconomic or demographic variables
   (2) Socioeconomic and demographic variables
   (3) Socioeconomic, demographic variables and maternal anthropometry
g. Control for possible mediating variables
   (0) Yes
   (1) No

Data abstraction

Data from each study were extracted using a standardized protocol to assess the mode of feeding, outcome, potential sources of heterogeneity and assessment of study quality. With respect to the assessment of study quality, each study was independently evaluated by two reviewers for each of the quality items, with disagreements resolved by consensus rating.

Data analysis

Pooled effect estimate

Effect measures were reported as i) weighted mean differences and their 95% confidence interval (CI) for continuous outcomes, and ii) pooled odds ratios and 95% CI for dichotomous outcomes. Subjects were classified as either breastfed or non-breastfed, according to the specific classification used in each study. For the 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 presented lower odds of the outcome.

Fixed or random-effects model

Fixed-effect models assume that each study estimates the same true population value for the effect of interest, and thus that differences between their results can be fully accounted for by sampling variation; in this model, individual studies are simply weighted by their precision (*34*). On the other hand, random-effects models assume that population effects also vary, and thus need to be accounted for as an additional source of variation. The random-effects model (*35*) gives greater weight to smaller studies, resulting in a wider confidence interval than fixed-effects models. In the latter, an important statistical question is whether variability among studies is greater than would be expected with the play of chance. In the present meta-analyses, the Q-test was used to assess the heterogeneity among studies (*36*); if significant, the between-studies variability was higher than expected by chance, and this required the use of a random-effects model (*35*).

Publication bias

Studies showing statistically significant associations are more likely to appear in print, to be published in English, and to be cited by others

papers. Therefore, such articles are more likely to be identified and included in a meta-analysis. Publication bias is more likely to affect small studies, since the greater amount of time and money spent in larger studies makes them more likely to be published, even when the results are not statistically significant (*34*).

In the present meta-analyses, funnel plot and Egger's test were employed to assess whether there was any evidence of publication bias (*37*). We did not use the Begg test (*38*) because the regression method (Egger's test) showed a better performance for detection of funnel plot asymmetry (*39*). Furthermore, we stratified the analyses according to study size, in order to assess the potential impact of publication bias on the pooled estimate.

Assessing heterogeneity

The next step after obtaining pooled results is to assess whether certain study characteristics may explain the variability between results. In the present meta-analyses we used a random-effects regression model developed by Berkey et al (*40*) for evaluation of sources of heterogeneity. In this approach, if the data are homogeneous or if heterogeneity is fully explained by the covariates, the random-effects model is reduced to a fixed-effect. This analysis was performed using the METAREG command within STATA. In these random-effects regression (meta-regression) models, each of the items used to assess study quality was considered as a covariate, instead of using an overall quality score. This allows the identification of aspects of the study design, if any, which may be responsible for the heterogeneity between studies (*41*). Furthermore, the following study characteristics were also included as covariates in random-effects regression:

a. Definition of breastfeeding
b Birth year
c Age at outcome assessment:
  (0) 1–9 years
  (1) 10–19 years
  (2) >19 years
d. Study size (n)
e. Provenance (high-income country / middle/low-income country).

As discussed in the Introduction, the present review was aimed at assessing the long-term consequences of breastfeeding on five different outcomes. This resulted in five separate meta-analyses which are described below.

V. Results and discussion

Review 1 - Breastfeeding and blood pressure in later life

High blood pressure in adulthood is associated with increased risk of ischaemic heart disease and stroke (*42*,*43*). It has been suggested that adult blood pressure is influenced by early life exposures, such as intrauterine growth, catch-up growth, and infant feeding (*44*).

Biological plausibility

Three possible biological mechanisms for a possible programming effect of breastfeeding on blood pressure have been proposed.

Differences in sodium content between breastmilk and formula

As previously discussed (section on general methodological issues), until the 1980s the sodium content of breastmilk in Western countries was much lower than that of formulas (*26*). Because low sodium intake is related to lower blood pressure (*45*), it has been suggested that differences in sodium content between breastmilk and formula would be one of the mechanisms for the programming of later blood pressure.

However, evidence on the existence of an effect of early salt intake on later blood pressure is controversial. Whitten & Stewart (*46*) reported that blood pressure at eight years of age was not correlated with sodium intake at the age of eight months. In another study, Singhal et al (*47*) followed pre-term infants who had been randomly assigned to receive two different types of infant formulas which differed greatly in salt content. Blood pressure at age 13-16 years was independent of the type of formula the subject had received, but was lower among the breastfed subjects. On the other hand, Geleijnse et al (*48*) reported that adjusted systolic blood pressure at age of 15 years was 3.6 mmHg (95% CI: -6.6 to -0.5) lower in children assigned to a low sodium diet in the first 6 months of life. Therefore, there is no consensus on whether the sodium content of infant diets may lead to higher blood pressure in the future.

Fatty acid content of breastmilk

Long-chain polyunsaturated fatty acids are present in breastmilk, but not in most brands of formula (*49*); these substances are important structural components of tissue membrane systems, including the vascular endothelium (*50*). Evidence suggests that dietary supplementation with long-chain polyunsaturated fatty acids lowers the blood pressure in hypertensive subjects (*51*). Furthermore, Forsyth et al (*52*) reported that blood pressure at 6 years was lower among formula-fed children who had been assigned to a formula supplemented with long-chain polyunsaturated fatty acids than among those randomized to a standard formula. This is, therefore, a potential mechanism for a possible effect of breastfeeding.

Obesity

The effect of early infant feeding on blood pressure might also be mediated by overweight or obesity in adulthood, as this is a risk factor for hypertension (*53*). On the other hand, as discussed below, the evidence suggests that breastfeeding has only a small protective effect against excess weight. Whether or not this small effect may influence blood pressure levels remains to be proven.

In conclusion, of the three postulated mechanisms, only the fatty acid content of breastmilk appears to be supported by the literature, but there may well be other mechanisms that are currently unknown.

Specific methodological issues

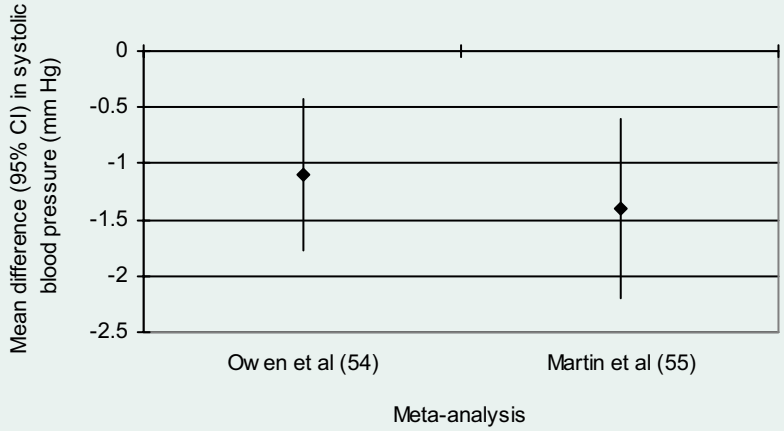
General methodological issues affecting studies of the long-term consequences of breastfeeding were addressed above. An additional issue is that several studies included adjustment for current weight, body mass index or ponderal index in their multivariate analyses. Had breastfeeding been associated with adult weight, adjustment for the latter would lead to an underestimation of its true effect on blood pressure. However, as discussed in section 1.3 above, there is no strong evidence of a breastfeeding effect on adult weight, and therefore one would not expect adjustment for weight to change the association with blood pressure.

Overview of the existing meta-analyses

We reviewed two existing meta-analyses on the influence of breastfeeding on blood pressure in later life (*54*,*55*).

The meta-analysis by Owen et al in 2003 (*54*) obtained information from 25 studies, including those in which blood pressure was measured in infancy. Meta-regression analysis was used to evaluate whether there were differences in the mean effect of breastfeeding according to the subject's age, year of birth, study size, length of recall for information on breastfeeding duration (for retrospective studies), and adjustment for current body size.

Figure 1.1. Mean difference in systolic blood pressure between breastfed and non breastfed subjects



The meta-analysis by Martin et al in 2005 (*55*) included 15 studies that related breastfeeding to blood pressure measured after the age of 12 months. Meta-regression analysis was used to evaluate whether the mean effect of breastfeeding varied according to the subject's age when the blood pressure was measured, year of birth, study size, length of recall of breastfeeding duration, follow-up rates, and whether or not confounding variables were adjusted for.

Breastfeeding and systolic blood pressure

Figure 1.1 shows that, in spite of the difference in the admission criteria, the effect size in both meta-analyses was similar, systolic blood pressure being significantly lower among breastfed infants.

However, there was evidence of publication bias; the effect size decreased with increasing study size. Owen et al (*54*) noted that studies with fewer than 300 participants reported a mean difference in systolic blood pressure of -2.05 mmHg (95% CI: -3.30 to -0.80) when comparing breastfed and non breastfed infants, whereas among studies with more than 1000 subjects the mean difference was -0.16 mmHg (95% CI: -0.60 to 0.28). Martin et al (*55*) also reported similar differences in mean effect according to study size.

In terms of heterogeneity among studies, the magnitude of the effect was independent of the subjects' age. On the other hand, Martin et al (*55*) observed that the protective effect of breastfeeding was higher among those born in or before 1980 (mean difference: -2.7 mmHg) compared with those born after (mean difference: -0.8 mmHg), whereas Owen et al (*54*) failed to observe such an association.

Martin et al (*55*) noticed that only 6 of the 15 studies included in their meta-analysis had controlled for confounding by socioeconomic status and maternal variables (body mass index,

smoking). In a clear demonstration of the importance of adjustment for confounding, in two of the three studies that reported crude and adjusted estimates, adjustment reduced the crude estimates in more than 30% (Table 1.1). With regard to control for possible mediating factors, Owen et al (*54*) reported that control for body size at the time of blood pressure assessment had no effect in the results of 10 studies (12 observations) that included such analyses. This is in agreement with our earlier argument that – given the weak association between breastfeeding and adult weight – such control would not affect the final results.

Unlike for systolic blood pressure, there was no evidence of publication bias. The mean effect of breastfeeding on diastolic blood pressure was similar among studies with 1000 or more participants (mean difference: -0.4 mmHg; 95% CI: -0.9 to 0.1) and smaller studies (<1000 participants) (mean difference: -0.6 mmHg; 95% CI: -1.5 to 0.2).

Table 1.1. Studies included in the Martin et al (*55*) meta-analysis that provided crude and adjusted estimates of difference in systolic blood pressure between breastfed and non breastfed subjects

Study	Mean difference in systolic blood pressure in mm Hg (SE)		Covariates included in the multivariate model
	Crude	Adjusted	
Martin 2004 (56)	-1.2 (SE* 0.4)	-0.8 (SE 0.4)	Sex, age, room temperature, solids introduced, maternal factors (schooling, social class, age at birth of the child, hypertension, pre-pregnancy BMI, height), paternal BMI, child's height
Martin 2005 (57, 58)	-0.33 (SE 1.1)	-0.11 (SE 1.1)	Age, birth order, father's social class, social class in adulthood
Lawlor 2004 (59)	-1.0 (SE 0.3)	-1.2 (SE 0.4)	Age, sex, parental factors (age, BMI, smoking in pregnancy, schooling, marital status), family income, birthweight, adiposity

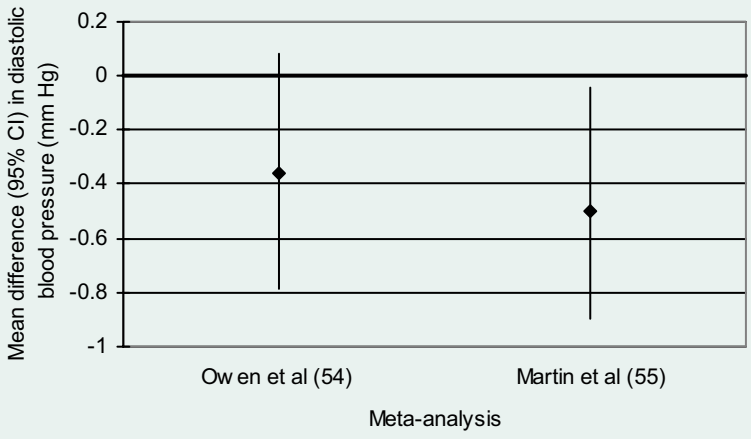
* SE: Standard error of mean difference

Age and year of birth were not related to variability in the study results. On the other hand, those studies that relied on maternal recall of breastfeeding beyond infancy showed smaller differences between breastfed and formula-fed groups than studies with shorter recall.

Breastfeeding and diastolic blood pressure

Figure 1.2 shows that in the meta-analysis by Owen et al (*54*) the difference in diastolic blood pressure between breastfed and non-breastfed infants was not statistically significant (mean difference: -0.36 mmHg; 95% CI: -0.79 to 0.08 mmHg). On the other hand, Martin et al (*55*) found that mean diastolic blood pressure was significantly lower among breastfed infants (mean difference: -0.5 mmHg; 95% CI: -0.9 to -0.04 mmHg).

Figure 1.2. Mean difference in diastolic blood pressure between breastfed and non breastfed subjects



Studies not included in the previous meta-analyses

We have identified four recently published studies that have not been included in the published meta-analyses. Below are summarized the findings from these studies.

Martin et al (*57*) studied a cohort of 1580 men living in Caerphilly, South Wales, who were aged 45-59 years when examined between 1979 and 1983. Information on breastfeeding duration was obtained from the subjects' mothers or a close female relative. Difference in systolic blood pressure between breastfed and bottle-fed subjects was -0.11 mmHg (95% CI: -2.28 to 2.06) and for diastolic blood pressure -0.21 mmHg (95% CI: -1.67 to 1.25).

Martin et al also studied (*58*) a historic cohort based on a follow-up of the subjects who participated in a 1-week survey of diet and health when aged 0 to 19 years, between 1937 and 1939. This study was conducted in 16 centres in England and Scotland. Information on breastfeeding duration was obtained from the subject's mother at the time of the survey on diet and health. Differences between breastfed and non-breastfed subjects were -1.62 mmHg (95% CI: -6.66 to 3.41) and -0.74 mmHg (95% CI: -3.06 to 1.57) for systolic and diastolic blood pressure, respectively.

Lawlor et al (*60*) evaluated random samples of schoolchildren aged 9 years and similar samples of 15-year-olds from Estonia (n=1174) and Denmark (n=1018). Even after controlling for possible confounding variables, the systolic blood pressure was lower among those children who had ever been exclusively breastfed (difference: -1.7 mmHg; 95% CI: -3.0 to -0.5).

In a recently published paper, Horta et al (*61*) observed in a cohort of over 1000 15-year-olds in Pelotas (Brazil) that breastfeeding was not related to systolic (difference -1.31 mmHg; 95% CI: -3.92 to 1.30) or diastolic blood pressure (difference -0.64 mmHg; 95% CI: -2.91 to 1.63).

Update of existing meta-analysis

A new meta-analysis was carried out which included the four recently published studies described above, all the papers in previously published meta-analyses, and those identified by the two independent literature searches at WHO and at the University of Pelotas. It was possible to include 30 estimates on the effect of breastfeeding on systolic blood pressure, and 25 on diastolic blood pressure (Table 1.2). Fig. 1.3 and 1.4 show the forest plot for systolic and diastolic blood pressures, respectively. Systolic (mean difference: -1.21 mmHg; 95% CI: -1.72 to -0.70) and diastolic blood pressures (mean difference: -0.49 mmHg; 95% CI: -0.87 to -0.11) were both lower among those subjects who had been breastfed. Random-effects models were used in both analyses because heterogeneity among studies was statistically significant.

Similar to the previously published meta-analyses, publication bias was clearly present. Table 1.2 shows that the mean difference was inversely related to the study size, with larger studies reporting a smaller protective effect of breastfeed-ing. This was more marked for systolic than for diastolic blood pressure. This is confirmed by examination of the funnel plots which are clearly asymmetrical, with small studies reporting a higher protective effect of breastfeeding. (Fig. 1.5 and 1.6)

Conclusion

According to Owen et al (*54*), the association between breastfeeding and lower blood pressure was mainly due to publication bias, and any effect of breastfeeding was modest and of limited clinical or public health relevance. In spite of not being able to exclude residual confounding and publication bias, Martin et al (*55*) concluded that breastfeeding was negatively associated with blood pressure. They argued that even a small protective effect of breastfeeding would be important from a public health perspective. For example, a reduction in mean population blood pressure of 2 mmHg could lower the prevalence of hypertension by up to 17%, the number of coronary heart disease events by 6%, and stroke by 15%. Three large studies were published since the last review, two of which found no association and one found a protective effect of breastfeeding.

Both meta-analyses may have been affected by publication bias. Small studies with negative results are less likely to be published, and this

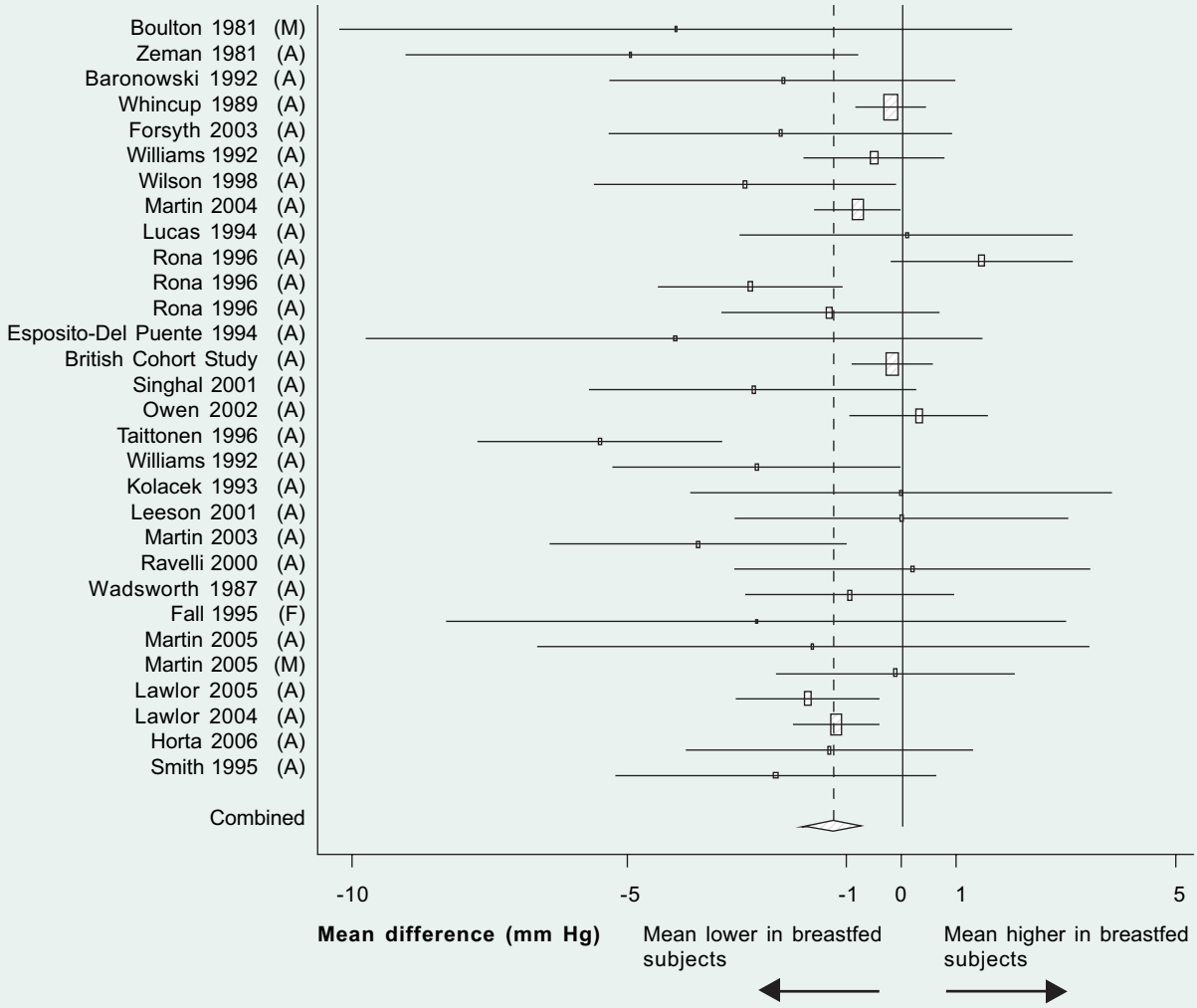
Table 1.2. Breastfeeding and blood pressure in later life: studies included in the meta-analysis in ascending order of subjects' age at which outcome was measured.

Author, year (reference)	Study design	Year of birth of subjects	Age at blood pressure measurement	Gender	Comparison groups	Mean difference in mm Hg (Standard error of mean difference)	
						Systolic blood pressure	Diastolic blood pressure
Boulton 1981(62)	Cross-sectional	1976-9	1 year	All	Breastfed for ≥3 months (n=14) vs. Formula fed from <3 months (n=47)	-4.11 (SE 3.12)	Not stated
Smith 1995 (63)	Cohort	1990	1 year	All	Ever breastfed vs. Never breastfed	-2.29 (SE 1.49)	Not stated
Zeman 1981 (64)	Cross-sectional	Not stated	8-26 months	All	Breastfed (n=42), vs. Bottle fed (n=13)	-4.91 (SE 2.10)	0.33 (SE 0.90)
Baronowski 1992 (65)	Cross-sectional	1981-3	3-4 years	All	Exclusively breastfed for >3 months (n=60) vs. Bottle fed (n=185)	-2.17 (SE 1.61)	0.48 (SE 1.42)
Lawlor 2004 (59)	Cohort	1981-4	5 years	All	Breastfed for ≥6 months (n=1191) vs. Breastfed for <6 months (n=2528)	-1.19 (SE 0.4)	Not stated
Whincup 1989 (66)	Cross-sectional	1979-83	5-8 years	All	Exclusively breastfed for first 3 months (n=1221) vs. Bottle fed (n=1787)	-0.20 (SE 0.33)	-0.26 (SE 0.23)
Forsyth 2003 (52)	Cohort	1992	5 years	All	Breastfed (n=83) vs. Formula fed (n=71)	-2.2 (SE 1.6)	-3.4 (SE 1.4)
Williams 1992 (67)	Cohort	1972-3	7 years	All	Exclusively breastfed {median 28 wk} (n=192) vs. Bottle fed (n=327)	-0.5 (SE 0.66)	-0.7 (SE 0.61)
Wilson 1998 (68)	Cohort	1983-6	6-9 years	All	Exclusively breastfed for >15 wk (n=74) vs. Bottle fed (n=105)	-2.84 (SE 1.40)	-1.79 (SE 1.23)
Martin 2004 (56)	Cohort	1991-2	6-9 years	All	Ever breastfed (n=5586) vs. Never breastfed (n=1141)	-0.8 (0.4)	-0.6 (0.3)
Lucas 1994 (69)	Randomized controlled trial	1982-5	7-8 years	All	Allocated to banked breastmilk (n=66) vs. Allocated to preterm formula (n=64)	0.1 (SE 1.55)	-0.7 (SE 1.32)
Rona 1996 (70)	Cross-sectional (England 1993 sample)	1983-5	8-9 years	All	Exclusively breastfed for ≥3 mo (n=157) vs. Bottle fed (n=308)	1.46 (SE 0.84)	2.54 (SE 0.76)
Rona 1996 (70)	Cross-sectional (England 1994 sample)	1984-6	8-9 years	All	Exclusively breastfed for ≥3 mo (n=213) vs. Bottle fed (n=318)	-2.75 (SE 0.86)	-2.34 (SE 0.75)
Rona 1996 (70)	Cross-sectional (Scotland 1994 sample)	1983-6	8-9 years	All	Exclusively breastfed for ≥3 mo (n=124) vs. Bottle fed (n=273)	-1.29 (SE 1.01)	-0.97 (SE 0.84)
Esposito-Del Puente 1994 (71)	Cross-sectional	1980-2	9-11 years	All	Breastfed (n=43) vs. Bottle fed (n=17)	-4.13 (SE 2.86)	0.11 (SE 0.86)

Table 1.2. (continued)

Author, year (reference)	Study design	Year of birth of subjects	Age at blood pressure measurement	Gender	Comparison groups	Mean difference in mm Hg (Standard error of mean difference)	
						Systolic blood pressure	Diastolic blood pressure
Lawlor 2005 (60)	Cross-sectional	Not stated	9-15 years	All	Exclusively breastfed vs. Not exclusively breastfed	-1.7 (SE 0.66)	Not stated
British Cohort Study (72)	Cohort	1970	10 years	All	Breastfed for ≥3 months (n=951) vs. Never breastfed (n=5133)	-0.16 (SE 0.38)	-0.21 (SE 0.33)
Singhal 2001 (47)	Randomized controlled trial	1982-5	13-16 years	All	Allocated to banked breastmilk (n=66) vs. Allocated to preterm formula (n=64)	-2.7 (SE 1.52)	-3.2 (SE 1.31)
Owen 2002 (54)	Cross-sectional	1982-6	13-16 years	All	Exclusively breastfed ≥3 months (n=980) vs. Exclusively bottle fed (n=951)	0.32 (SE 0.64)	-0.17 (SE 0.35)
Taittonen 1996 (73)	Cohort	1962-74	12-24 years	All	Breastfed >3 months (n=760) vs. Bottle fed (n=150)	-5.48 (SE 1.14)	Not stated
Horta 2006 (61)	Cohort	1982	15 years	All	Breastfed (n=966) vs. Bottle fed (n=85)	-1.31 (SE 1.33)	-0.64 (SE 1.16)
Williams 1992 (67)	Cohort	1972-3	18 years	All	Exclusively breastfed {median 28 wk} (n=197) or bottle fed (n=319)	-2.63 (SE 1.34)	-2.66 (SE 1.36)
Kolacek 1993 (74)	Cohort	1968-9	18-23 years	All	Exclusively breastfed ≥3 months (n=199) vs. Never breastfed (n=78)	0.00 (SE 1.96)	0.75 (SE 1.40)
Leeson 2001 (75)	Cross-sectional	1969-75	20-28 years	All	Breastfed (n=149) vs. Bottle fed (n=182)	0.0 (SE 1.55)	-1.0 (SE 0.94)
Martin 2003 (76)	Cohort	1972-4	23-27 years	All	Lowest (n=193) vs. Highest quartile (n=79) of dried formula milk consumption at age 3 months	-3.7 (SE 1.38)	-1.4 (SE 0.97)
Ravelli 2000 (77)	Cohort	1943-7	48-53 years	All	Exclusively breastfed (n=520) vs. Bottle fed (n=105)	0.2 (SE 1.65)	0.9 (SE 1.08)
Wadsworth 1987 (78)	Cohort	1946	53 years	All	Exclusively breastfed for ≥3 months (n=1507) vs. Never breastfed (n=628)	-0.94 (SE 0.97)	-0.32 (SE 0.37)
Fall 1995 (79)	Cohort	1920-30	60-71 years	Female	Exclusively breastfed (n=862) vs. Bottle fed (n=68)	-2.64 (SE 2.88)	-0.96 (SE 1.38)
Martin 2005 (57, 58)	Cohort	1920-38	45-59 years	Male	Breastfed (n=1159) vs. Bottle fed (n=417)	-0.11 (SE 1.11)	-0.21 (SE 0.74)
Martin 2005 (58)	Cohort	1918-39	63-82 years	All	Breastfed (n=272) vs. Bottle fed (n=90)	-1.62 (SE 2.57)	-0.74 (SE 1.18)

Figure 1.3. Mean difference in systolic blood pressure in mm Hg (and its 95% confidence interval) between breastfed and non-breastfed subjects in different studies. Whether the estimate was for males (M), females (F) and all (A) is indicated in parenthesis



leads to an overestimate of the pooled mean difference due to selective inclusion of small positive studies.

Lack of control for confounding is another methodological issue, as pointed out by Martin et al (*55*). Most studies did not provide estimates adjusted for confounding by socioeconomic status and maternal characteristics; in the studies that showed both adjusted and crude results, the latter tended to overestimate the protective effect of breastfeeding. The majority of these studies are from developed countries, and as previously discussed, the direction of confounding may vary according to the level of economic development of the population.

In summary, the present updated meta-analyses show that there are small but significant protective effects of breastfeeding on systolic and diastolic blood pressure. Publication bias is unlikely to explain this finding because a significant protective effect was observed even among the larger studies. However, residual confounding cannot be excluded because of the marked reduction in effect size after adjustment for known confounders.

Figure 1.4. Mean difference in systolic blood pressure in mm Hg (and its 95% confidence interval) between breastfed and non-breastfed subjects in different studies. Whether the estimate was for males (M), females (F) and all (A) is indicated in parenthesis

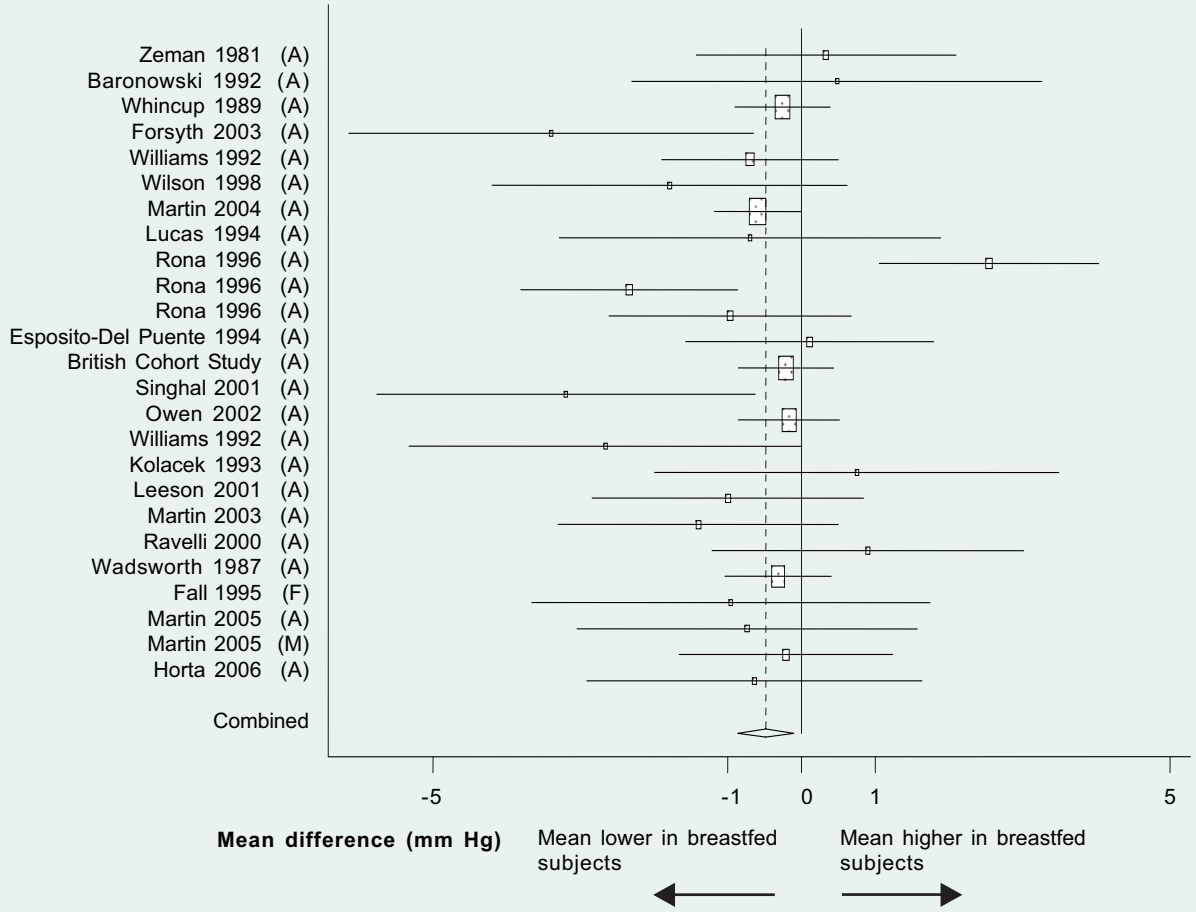


Figure 1.5. Funnel plot showing mean difference in systolic blood pressure (mm Hg) by standard error of mean difference

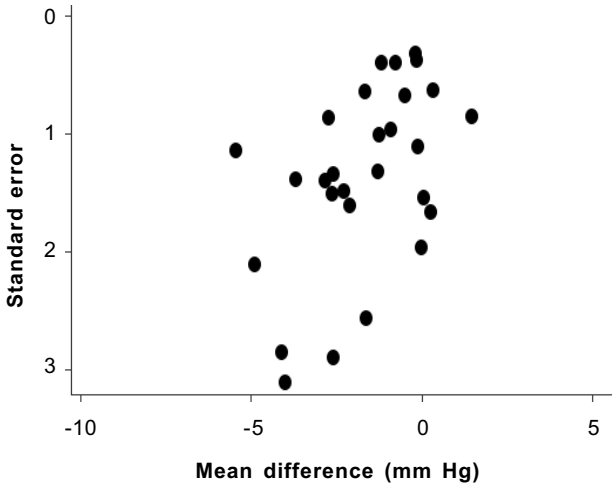


Figure 1.6. Funnel plot showing mean difference in diastolic blood pressure (mm Hg) by standard error of mean difference

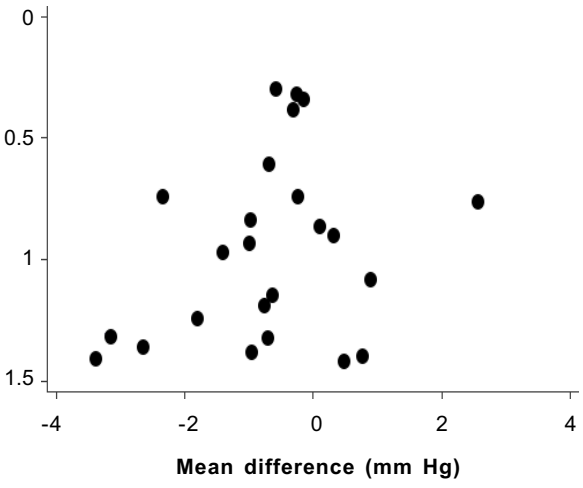


Table 1.3. Breastfeeding and blood pressure in later life: Random-effects meta-analyses by subgroups

Subgroup analysis	Systolic blood pressure			Diastolic blood pressure		
	Number of estimates	Mean difference (95% confidence interval)	P value	Number of estimates	Mean difference (95% confidence interval)	P value
By age group						
1 to 9 years	14	-1.06 (-1.70 to -0.42)	0.04	11	-0.54 (-1.27 to 0.19)	0.14
9 to 19 years	8	-1.81 (-3.13 to -0.50)	0.007	6	-0.53 (-1.22 to 0.17)	0.14
>19 years	8	-0.95 (-1.97 to 0.07)	0.07	8	-0.38 (-0.90 to 0.15)	0.16
By study size						
<300 participants	10	-2.45 (-3.52 to -1.38)	0.001	9	-0.87 (-1.83 to 0.08)	0.07
300-999 participants	11	-1.52 (-2.80 to -0.23)	0.02	9	-0.59 (-1.71 to 0.52)	0.30
≥1000 participants	9	-0.59 (-1.00 to -0.19)	0.004	7	-0.33 (-0.61 to -0.04)	0.02
By year of birth of subjects						
Before 1980	13	-1.42 (-2.44 to -0.39)	0.007	11	-0.40 (-0.78 to -0.02)	0.04
After 1980	16	-1.03 (-1.61 to -0.45)	0.001	13	-0.61 (-1.27 to 0.04)	0.06
By length of recall of breastfeeding						
<3 years	19	-1.23 (-1.63 to -0.82)	0.001	14	-0.59 (-0.94 to -0.23)	0.001
≥3 years	11	-1.01 (-1.97 to -0.06)	0.04	10	-0.36 (-1.02 to 0.30)	0.28
By categorization of breastfeeding						
Ever breastfed	14	-0.83 (-1.35 to -0.32)	0.002	13	-0.49 (-0.89 to -0.10)	0.01
Breastfed for a given number of months	16	-1.42 (-2.22 to -0.63)	0.001	12	-0.47 (-1.10 to 0.16)	0.14
By control for confounding						
None	11	-1.73 (-3.17 to -0.30)	0.02	9	-0.59 (-1.39 to 0.22)	0.15
Adjusted for socioeconomic status	12	-0.92 (-1.71 to -0.14)	0.02	12	-0.44 (-1.04 to 0.17)	0.16
Adjusted for socioeconomic and demographic variables	7	-1.19 (-1.70 to -0.69)	0.001	4	-0.61 (-1.12 to -0.10)	0.02
Study setting						
High-income country	26	-1.15 (-1.68 to -0.62)	0.001	22	-0.54 (-0.95 to -0.14)	0.009
Middle/Low-income country	4	-1.93 (-3.61 to -0.26)	0.02	3	0.13 (-1.12 to 1.37)	0.20
Total	30	-1.21 (-1.72 to -0.70)		25	-0.49 (-0.87 to -0.11)	

Concentrations of total cholesterol and LDL cholesterol (low-density lipoprotein) are important risk factors for coronary heart disease (*80*). It has been suggested that total cholesterol and LDL cholesterol may be programmed by early life exposures, such as rapid early growth (*81*) and infant feeding (*82*).

Biological plausibility

The cholesterol content is markedly higher in breastmilk than in most commercially available formulas. High cholesterol intake in infancy may have a long-term programming effect on synthesis of cholesterol by down-regulation of hepatic hydroxymethylglutaryl coenzyme A (HMG-CoA) (*83*). This hypothesis is supported by studies with animals, which showed that early exposure to increased levels of cholesterol is associated with decreased cholesterol levels at a later age. Indeed, Devlin et al (*84*) reported that HMG-CoA reductase was higher ($P < .05$) in formula-fed than in milk-fed piglets, whereas LDL receptor mRNA was not independent of early diet. HMG-CoA is the rate-limiting enzyme in synthesis of cholesterol from acetate, and HMG-CoA reductase inhibitors, the so-called statins, have an important cholesterol-lowering effect (*85*).

Therefore, nutritional programming by the high cholesterol content of breastmilk has been proposed as a potential mechanism for the association between breastfeeding duration during infancy and lower cholesterol levels in later ages.

Specific methodological issues

General methodological issues affecting studies of the long-term consequences of breastfeeding were addressed in the Introduction. An additional issue affecting studies of cholesterol levels is that four studies included in their multivariate analyses an adjustment for weight, body mass index or ponderal index measured at the same time as cholesterol levels. Had breastfeeding been associated with adult weight, adjustment for the latter would lead to an underestimation of its true effect on cholesterol. However, as discussed in the review on the long-term effects of breastfeeding on blood pressure, the evidence suggests that the effect of breastfeeding on adult weight is weak, and therefore one would not expect an adjustment for weight to change the association with cholesterol.

Overview of the evidence

A previous meta-analysis (*82*) on this association showed that mean total cholesterol in infancy was higher among those breastfed (mean difference: 0.64; 95% CI: 0.50 to 0.79 mmol/L), whereas among adults the total cholesterol was lower among those who had been breastfed (mean difference -0.18; 95% CI: -0.30 to -0.06 mmol/L).

The electronic search carried out at WHO yielded 37 potentially relevant publications, 23 of which provided data on the mean difference in total cholesterol between breastfed and non-breastfed subjects. From these 23 studies, 28 estimates of total cholesterol were derived, of which 18 included both genders and two were gender specific. No additional studies were identified by the independent search at the University of Pelotas. Table 2.1 presents a description of the studies included in the present meta-analysis, and Figure 2.1 shows the distribution of the studies' results. There was strong evidence of heterogeneity between studies ($P = 0.003$), and the mean difference using a random-effects model was -0.03 (95% CI: -0.10 to 0.03), suggesting no overall association between breastfeeding and cholesterol levels.

However, Table 2.2 shows marked effect modification by age group. In adults (>19 years), breastfed subjects had mean total cholesterol levels 0.18 mmol/L (95% CI: 0.06 to 0.30 mmol/L) lower than those who were bottle-fed, and there was no heterogeneity between studies ($P = 0.86$). For children and adolescents, the association was not significant. Figure 2.2 shows the forest plot for studies in adults.

Other subgroup analyses were carried out. Studies with a length of recall of breastfeeding duration $\geq$3 years resulted in lower mean total

Table 2.1. Breastfeeding and blood cholesterol in later life: studies included in the meta-analysis in ascending order of subjects' age at which outcome was measured

Author, year (reference)	Study design	Year of birth of subjects	Age at cholesterol measurement	Gender	Comparison groups	Mean difference in total cholesterol mmol/L (SE)
Jooste 1991 (86)	Cohort	1981-6	1 year	All	Exclusively breastfed (n=110) vs. Formula fed (n=201) for the first 3 months	-0.07 (SE 0.09)
Mize 1995 (87)	Cohort	Not stated	1 year	All	Ever breastfed (n=23) vs. Formula fed from birth (n=33)	0.35 (SE 0.21)
Freedman 1992 (88)	Cross-sectional	1972-90	1-4 years	All	Ever breastfed (n=2232) vs. Bottle fed (n=1796)	0.03 (SE 0.02)
Friedman 1975 (89)	Cross-sectional	Not stated	1.5-2 years	All	Breastfed (n=31) vs. Bottle fed (n=55)	0.02 (SE 0.19)
Ward 1980 (90)	Cross-sectional	1974	2.5-3 years	All	Breastfed for ≥1 month (n=28) vs. Bottle fed (n=46)	0.25 (SE 0.13)
Routi 1997 (91)	Cohort	1990-2	3 years	All	Breastmilk only source of milk at 7 months (n=295) vs. Formula only source of milk at 7 months (n=324)	0.12 (SE 0.06)
Huttunen 1983 (92)	Cohort	1975	5 years	All	Exclusively breastfed for 6 months (n=35) vs. Formula feeding started between 1 to 6 months (n=32)	0.2 (SE 0.11)
Elaraby 1985 (93)	Cross-sectional	Not stated	5-10 years	All	Breastfed for >6 months (n=50) vs. Artificially fed (n=50)	-0.57 (SE 0.21)
Plancoulaine 2000 (94)	Cross-sectional	1981-7	5-11 years	Male Female	Breastfed (n=111) vs. Formula fed (n=131) Breastfed (n=101) vs. Formula fed (n=118)	-0.3 (SE 0.13) 0 (SE 0.16)
Crawford 1981 (95)	Cohort	1969-70	6 years	All	Exclusively breastfed (n=32) vs. Exclusively formula-fed (n=16) at 3 months	-0.04 (SE 0.20)
Hodgson 1976 (96)	Cohort	1962-5	7-12 years	Male Female	Exclusively breastfed (n= 12) vs. Formula fed (n=10) for the first 3 months Exclusively breastfed (n= 18) vs. Formula fed (n=10) for the first 3 months	0.54 (SE 0.34) 0.23 (SE 0.27)
Fomon 1984 (97)	Cohort	1966-71	8 years	Male Female	Breastfed (n=70) vs. Formula fed (148) Breastfed (n=76) vs. Formula fed (105)	-0.13 (SE 0.09) 0.03 (SE 0.12)
Hromodova 1997 (98)	Cohort	Not stated	12-13 years	All	Breastfed (n=44) vs. Formula fed (n=13)	-0.09 (SE 0.27)
Owen 2002 (82)	Cross-sectional	1982-6	13-16 years	All	Exclusively breastfed (n= 620) vs. Exclusively formula fed (n=542) for the first 3 months	-0.02 (SE 0.04)
Singhal 2004 (99)	Randomized controlled trial	1982-5	13-16 years	All	Allocated to banked breastmilk (n=66) vs. Allocated to preterm formula (n=64)	-0.4 (SE 0.20)
Friedman 1975 (89)	Cross-sectional	Not stated	15-19 years	All	Breastfed (n=86) vs. bottle fed (n=94)	0.03 (SE 0.25)

Table 2.1. (continued)

Author, year (reference)	Study design	Year of birth of subjects	Age at cholesterol measurement	Gender	Comparison groups	Mean difference in total cholesterol mmol/L (SE)
Kolacek 1993 (100)	Cohort	1968-9	18-23 years	Male Female	Exclusively breastfed (n=35) vs. Formula fed (n=17) Exclusively breastfed (n=52) vs. Formula fed (n=14)	-0.2 (SE 0.32) -0.2 (SE 0.31)
Leeson 2001 (75)	Cross-sectional	1969-75	20-28 years	All	Any breastfeeding (n=149) vs. Exclusively bottle fed (n=182)	-0.18 (SE 0.11)
Marmot 1980 (30)	Cohort	1946	31-32 years	Male	Exclusively breastfed for 5 months (n=57) vs. Exclusively formula fed (n=20)	-0.1 (SE 0.25)
				Female	Exclusively breastfed for 5 months (n=68) vs. Exclusively formula fed (n=27)	-0.5 (SE 0.23)
Ravelli 2000 (77)	Cohort	1943-7	48-53 years	All	Exclusively breastfed (n=520) vs. Partly or exclusively bottle fed (n=105) in the first 10 days	-0.16 (SE 0.11)
Martin 2005 (58)	Cohort	1918-39	63-82 years	Male	Breastfed (n=272) vs. Bottle fed (n=90)	0.12 (SE 0.28)
Fall 1992 (101)	Cohort	1920-30	59-70 years	Male	Exclusively breastfed (n=344) vs. Formula fed (n=25)	-0.32 (SE 0.25)
Fall 1995 (79)	Cohort	1920-30	60-71 years	Female	Exclusively breastfed (n=208) vs. Formula fed (n=11)	0.12 (SE 0.43)

cholesterol for subjects who were breastfed, although the difference was not statistically significant. Adjustment for body size at the time of cholesterol assessment was a source of heterogeneity between studies; the protective effect of breastfeeding was restricted to studies that adjusted for body size (mean difference: -0.20; 95% CI: -0.33 to -0.06). Both types of heterogeneity, however, could be explained by the age ranges of the study subjects because longer recall and adjustment for current size were more frequent in studies of adults. Age at assessment of serum cholesterol explained 59.7% of the overall heterogeneity; further adjustment for body size and length of recall did not provide further explanation for heterogeneity in the random-effects model.

Concerning publication bias, the funnel plot is quite symmetrical, with small studies tending to report either positive or negative effects of breastfeeding, with no evidence of bias. Indeed, Egger's test was not statistically significant (P=0.16). Furthermore, Table 2.2 shows that the mean difference in total cholesterol was independent of study size.

Conclusion

This meta-analysis suggests that the association between breastfeeding and total cholesterol varies according to age. Whereas no significant effect was observed in children or adolescents, mean cholesterol levels among adults who were breastfed were 0.18 mmol/L (6.9 mg/dl) lower than among non-breastfed subjects. This association did not seem to be due to either publication bias or confounding. The median level of cholesterol in the adult studies included in the review was about 5.7 mmol/L; the observed reduction associated with breastfeeding corresponds to about 3.2% of this median.

Figure 2.1. Mean difference in total cholesterol in mmol/L (and its 95% confidence interval) between breastfed and non-breastfed subjects in different studies. Whether the estimate was for males (M), females (F) and all (A) is indicated in parenthesis

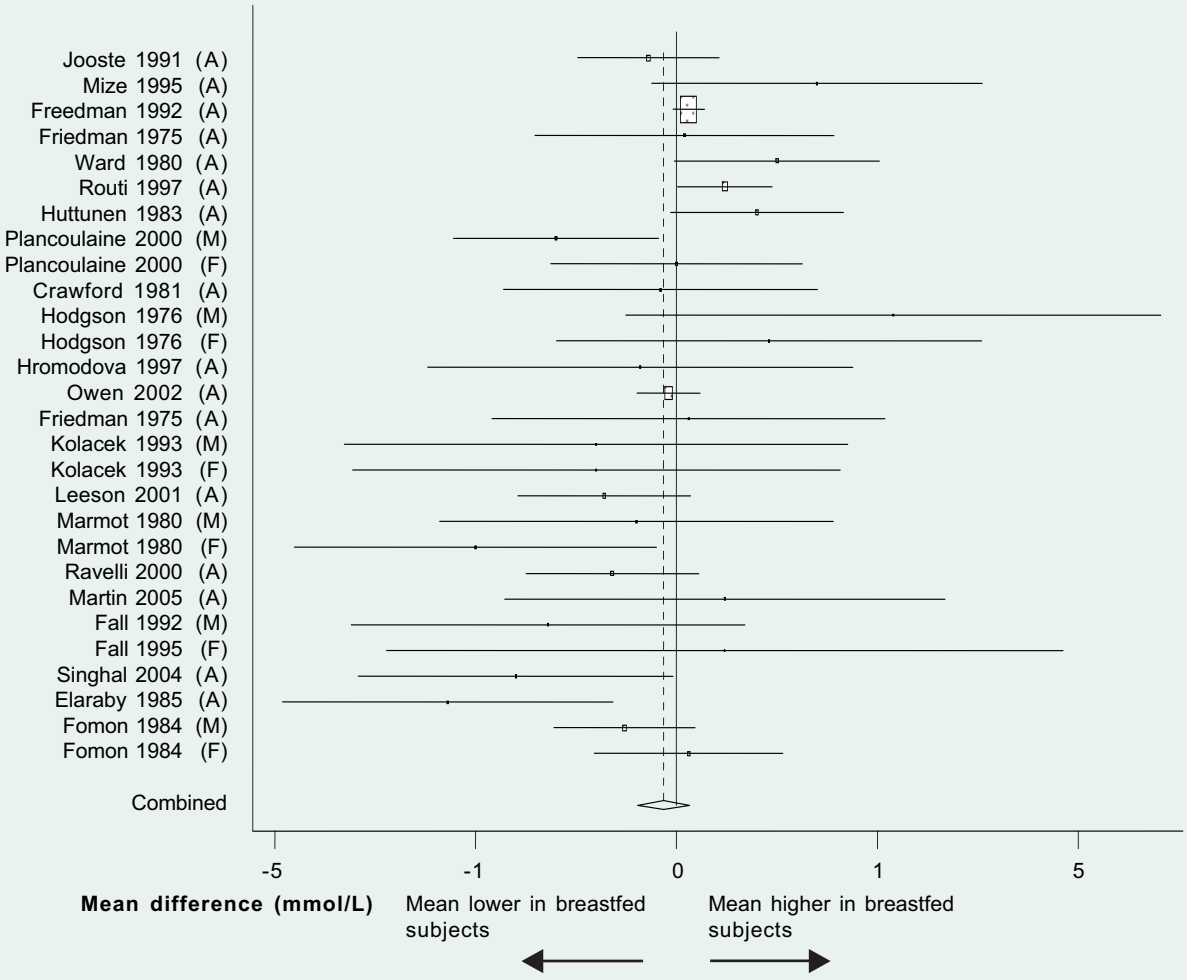


Figure 2.2. Mean difference in total cholesterol in mmol/L (and its 95% confidence interval) between breastfed and non-breastfed subjects during adult life. Whether the estimate was for males (M), females (F) and all (A) is indicated in parenthesis

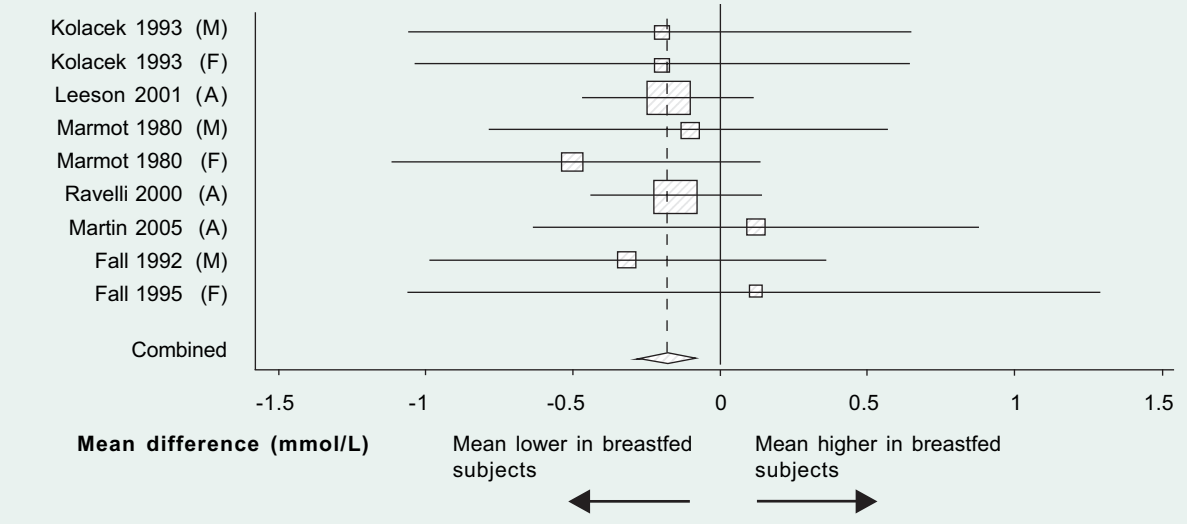


Figure 2.3. Funnel plot showing mean difference in total cholesterol (mmol/L) by standard error of mean difference

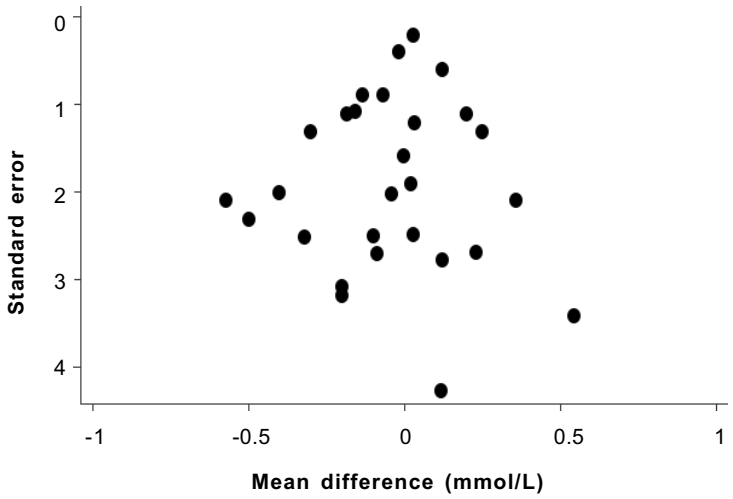


Table 2.2. Breastfeeding and blood cholesterol in later life: Random-effects meta-analyses of cholesterol levels by subgroup

Subgroup analysis	Number of estimates of total cholesterol	Mean difference (95% confidence interval)	P value
By age group			
1 to 9 years	15	0.02 (-0.06 to 0.11)	0.63
9 to 19 years	4	-0.07 (-0.21 to 0.08)	0.37
>19 years	9	-0.18 (-0.30 to -0.06)	0.004
By study size			
<300 participants	20	-0.04 (-0.16 to 0.07)	0.47
≥300 participants	8	-0.01 (-0.08 to 0.06)	0.74
By year at birth			
Before 1980	17	-0.06 (-0.18 to 0.06)	0.32
After 1980	7	-0.02 (-0.10 to 0.06)	0.64
By study design			
Cross-sectional	18	-0.01 (-0.10 to 0.09)	0.88
Cohort	9	-0.05 (-0.14 to 0.05)	0.35
By length of recall of breastfeeding			
<3 years	21	0.00 (-0.07 to 0.08)	0.95
≥3 years	7	-0.13 (-0.27 to 0.01)	0.07
By categorization of breastfeeding			
Ever breastfed	17	-0.07 (-0.16 to 0.01)	0.08
Breastfed for a given number of months	11	0.01 (-0.11 to 0.13)	0.82
By control for confounding			
None	23	-0.04 (-0.14 to 0.06)	0.45
Adjusted for socioeconomic and demographic variables	5	-0.02 (-0.09 to 0.05)	0.55
By control for current measure of body size			
No	24	-0.01 (-0.07 to 0.06)	0.91
Yes	4	-0.20 (-0.33 to -0.06)	0.006
Total	28	-0.03 (-0.10 to 0.03)	

It has been proposed that breastfeeding promotion might be an effective way to prevent the development of obesity (*102*).

Biological plausibility

Several possible biological mechanisms for a protective effect of breastfeeding against overweight and obesity have been proposed.

Differences in protein intake and energy metabolism may be one of the biological mechanisms linking breastfeeding to later obesity. Lower protein intake and reduced energy metabolism were reported among breastfed infants (*103*). Rolland-Cachera et al (*104*) observed that higher protein intakes in early life, regardless of the type of feeding, was associated with an increased risk of later obesity.

Another possibility is that breastfed and formula-fed infants have different hormonal responses to feeding, with formula feeding leading to a greater insulin response resulting in fat deposition and increased number of adipocytes (*105*).

Finally, limited evidence suggests that breastfed infants adapt more readily to new foods such as vegetables, thus reducing the caloric density of their subsequent diets (*106*).

Specific methodological issues

General methodological issues affecting studies of the long-term consequences of breastfeeding were addressed in the Introduction. In addition, the following methodological issues should be taken into account when studying overweight/obesity as the outcome.

Definition of overweight/obesity

Although different criteria and percentiles have been used in the definition of obesity, the results of the studies have been similar. Arenz et al (*107*) reported no difference in mean effect among studies using the 90th, 95th or 97th percentile to define obesity. Therefore, differences in the definition of overweight/obesity should not be considered as a major methodological flaw in this meta-analysis. Existing cut-offs for overweight/obesity will have to be reassessed in the light of the new WHO Growth Standards.

Mean body mass index or prevalence of overweight/obesity

Grummer-Strawn suggested that breastfeeding may be associated both with a lower prevalence of overweight/obesity and with underweight in later life, due to a smaller variance of weight-related indices in subjects who were breastfed (*32*). Therefore, the mean body mass index would remain unchanged but breastfeeding would still have an effect on the upper tail of the body mass index distribution - that is, on the prevalence of overweight/obesity.

Overview of existing meta-analyses

The protective effect of breastfeeding against childhood obesity was initially proposed by Kramer in 1981 (*108*). More recently, several studies were published on this topic. We identified four systematic reviews on the relationship between breastfeeding and overweight.

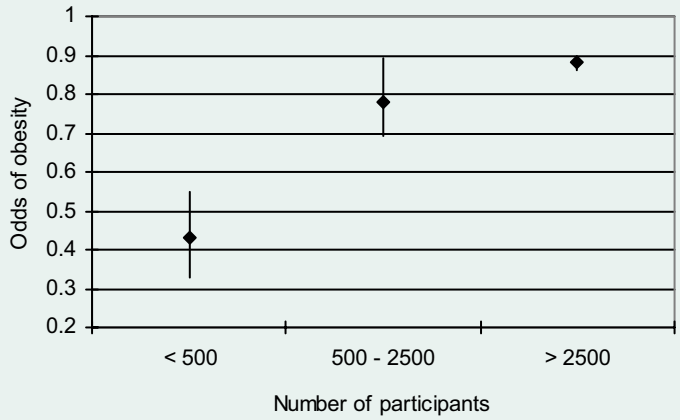
In 2004, Arenz et al (*107*) were the first to publish a systematic review of the evidence concerning the protective effect of breastfeeding duration against childhood obesity. To be included in their meta-analysis, the studies had to fulfill the following criteria:

- Analyses had to be adjusted for at least three of the following possible confounders: birth weight, parental overweight, parental smoking, dietary factors, physical activity, and socioeconomic status.
- Odds ratios or relative risks had to be reported.
- Age at the last follow-up had to be between 5 and 18 years.
- Obesity had to be defined by body mass index percentiles $\geq$90, 95 or 97.

Only nine studies were included in this meta-analysis; 19 were not eligible. The main reasons for exclusion were failure to report adequately adjusted estimates and a definition of obesity that did not match the study criteria. Other authors (see below) were more flexible in accepting different definitions of overweight, and were able to include a larger number of studies in their meta-analyses.

Analyses were stratified according to the following study characteristics: type of design, age group, definition of breastfeeding, number of variables included in the multivariable analysis, and definition of obesity.

Figure 3.1. Odds ratio of obesity according to study size, modified from Owen et al.



Their pooled odds ratio was 0.78 (95% CI: 0.71–0.85), and there was no sign of heterogeneity among the nine studies. The protective effect of breastfeeding was independent of the following study characteristics: study design (cohort or cross-sectional); age at obesity assessment ($\leq$6 years or >6 years); definition of breastfeeding (never vs. ever or other definition); and definition of obesity (95th or 97th percentile). On the other hand, the protective effect of breastfeeding was slightly more pronounced in studies that adjusted their estimates for less than 7 variables (pooled odds ratio: 0.69; 95% CI: 0.59–0.81), compared to those that adjusted for 7 or more variables (pooled odds ratio: 0.78; 95% CI: 0.70–0.87).

The funnel plot was clearly asymmetric, with small studies tending to report a higher protective effect of breastfeeding duration. This is a strong suggestion of publication bias.

Owen et al published two meta-analyses. In the first (*109*), the authors managed to obtain odds ratio estimates from 28 of 61 studies reporting on the relationship between breastfeeding and obesity. Unlike the Arenz meta-analysis (*107*), Owen et al (*109*) included studies that provided only crude odds ratios and were flexible in terms of the definition of obesity. Meta-regression analysis was used to investigate differences in the pooled odds ratio according to study size, age group at outcome measurement, year of birth and attrition rate, definition of obesity, and length of recall for information on breastfeeding duration.

Figure 3.1 shows that small studies tended to report stronger protective effects of breastfeeding (pooled odds ratio: 0.43; 95% CI: 0.33–0.55) than larger studies (pooled odds ratio: 0.88; 95% CI: 0.86–0.90).

This protective effect may be due to confounding by socioeconomic status and parental body composition. In developed countries, women who breastfeed tend to have higher socioeconomic status and may therefore be more "nutrition-conscious" (*21*). Owen et al (*109*) identified 6 studies whose estimates were adjusted for the following confounders: socioeconomic status, parental BMI, and maternal smoking. In these studies, adjustment for confounding reduced the pooled odds ratio from 0.86 (95% CI: 0.81–0.91) to 0.93 (95% CI: 0.88–0.99). This suggests that at least part of the effect of breastfeeding on body composition is due to confounding by socioeconomic status and parental body composition, and that crude estimates should not be included in the meta-analysis. Even after adjustment for socioeconomic status, the possibility of residual confounding cannot be ruled out.

Other methodological characteristics of the studies, such as obesity definition and maternal recall of breastfeeding duration, were not related to differences in the studies' results.

As in the meta-analysis by Arenz et al (*107*), publication bias was evident with small studies reporting a stronger protective effect of

breastfeeding (Fig. 3.1). Selective reporting was also evident; studies that failed to report odds ratios were much less likely to conclude that breastfeeding was associated with a reduced risk of obesity (1 of 35 studies), compared with studies that did provide odds ratios (18 of 29 studies); this difference was statistically significant (P <0.001). However, because studies that did not report odds ratios were smaller than those that presented such information, Owen et al (*109*) pointed out that their inclusion would have a minimal impact on the pooled odds ratio.

The third meta-analysis was published by Harder et al (*110*). Unlike the other analyses, they attempted to assess the effect of duration of breastfeeding on the risk of overweight (*107,109*), in search of a possible dose-response association. Fourteen studies providing results on more than one category of breastfeeding duration were identified and included in the meta-analysis. Subgroup analyses according to the definition of obesity and age at outcome assessment were performed.

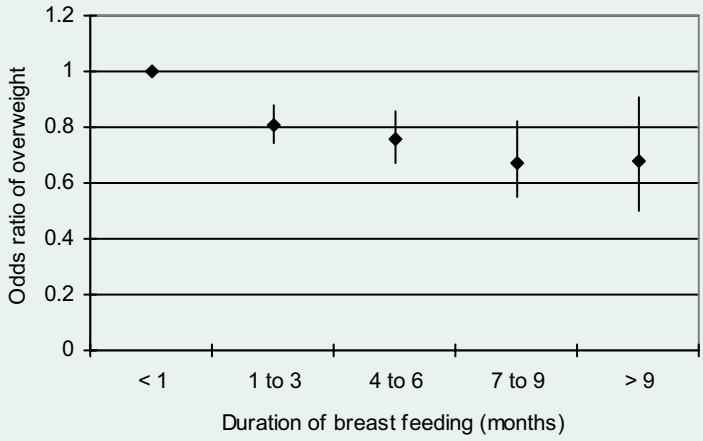
Fig. 3.2 shows that the odds ratio of being overweight decreased continuously with increasing duration of breastfeeding, reaching a plateau after 9 months of breastfeeding. Furthermore, trend analysis by a random-effect model showed that each month of increase in breastfeeding duration was associated with a 4% decrease in the odds of overweight (OR: 0.96; 95% CI: 0.94–0.98).

Because previously published meta-analyses (*107,109,110*) treated overweight/obesity as dichotomous variables, Owen et al (*111*) conducted a fourth meta-analysis to assess the effect of breastfeeding on mean BMI. The authors of the 70 identified studies were asked to provide information on mean differences in BMI, according to breastfeeding duration; these estimates were adjusted for age, socioeconomic status, maternal BMI, and maternal smoking in pregnancy.

In the fixed-effects model including 36 studies, breastfed subjects had lower mean BMI (mean difference: -0.04; 95% CI: -0.05, -0.02). In spite of efforts to prevent publication bias, the mean difference was greater among small studies (mean difference: -0.12; 95% CI: -0.29, 0.04) as compared to larger ones (mean difference: -0.03; 95% CI: -0.04, -0.01).

Despite the authors' request, only 11 studies provided estimates that were adjusted for age, socioeconomic status, maternal smoking and body mass index; among these studies, the crude mean difference of -0.12 (95% CI: -0.16, -0.08) disappeared in the adjusted analyses (mean difference: -0.01; 95% CI: -0.05, 0.03). This result reinforces the importance of controlling for confounding by socioeconomic status and maternal body mass index when assessing the long-term effect of breastfeeding duration on body composition.

Figure 3.2. Breastfeeding duration and odds ratio of overweight



Update of existing meta-analyses

A new meta-analysis was carried out including the recently published studies described above, all the papers included in previously published meta-analyses, and those identified by the two independent literature searches at WHO and at the University of Pelotas. It was possible to include 33 studies with 39 estimates on the effect of breastfeeding on prevalence of overweight/obesity (Table 3.1). The forest plot shows that results were clearly heterogeneous (Fig. 3.3). In a random-effects model, including all studies, breastfed individuals were less likely to be considered as overweight/obese, and the pooled ratio was 0.78 (95% CI: 0.72–0.84).

Table 3.1. Breastfeeding and overweight/obesity in later life: studies included in the meta-analysis in ascending order of subjects' age at which outcome was measured

Author, year (reference)	Study design	Year of birth of subjects	Age measured	Gender	Comparison groups	Outcome	Odds ratio (95% confidence interval)
Strbak 1991 (114)	Cohort	Not stated	1-7 years	All	Breastfed for >1 months (n=741) vs. Breastfed <2 weeks (n=165)	Obesity	0.84 (0.41–1.72)
Li 2005 (115)	Cohort	1990-4	2-6 years	All	Breastfed for ≥4 months vs. Never breastfed (n=923)*	Obesity	0.6 (0.3–1.3)
He 2000 (116)	Case-control	1989-93	3-6 years	All	Breastfeeding vs. no breastfeeding (n=465)*	Obesity	1.18 (0.91–1.54)
Poulton 2001 (117)	Cohort	1972-3	3 years	All	Breastfed for >6 months vs. Never breastfed (n=677)*	Overweight or obesity	0.86 (0.44–1.65)
Armstrong 2002 (118)	Cohort	1995-6	3 years	All	Exclusively breastfed (n=8751) vs. Bottle fed at 6-8 weeks (n=23449)	Obesity	0.72 (0.65–0.79)
Hediger 2001 (119)	Cross-sectional	1983-91	3-5 years	All	Ever breastfed (n=1158) vs. Never breastfed (n=1498)	Overweight only Obesity	0.63 (0.41–0.96) 0.84 (0.62–1.13)
Grummer-Strawn 2004 (32)	Cohort	1988-92	4 years	All	Breastfed for ≥12 months (n=293) vs. Never breastfed (n=7084)	Overweight or obesity	0.72 (0.65–0.80)
Dubois 2006 (120)	Cohort	1998	4 years	All	Breastfed for ≥3 months (n=710) vs. Breastfed for <3 months (n=740)	Obesity	1.0 (0.7–1.5)
Araujo 2006 (121)	Cohort	1993	4 years	All	Ever breastfed (n=1221) vs. Never breastfed (n=52)	Overweight or obesity	1.83 (0.53–6.28)
Li 2003 (122)	Cross-sectional	1983-87	4-8 years	All	Breastfed for >9 months (n=194) vs. Breastfed <1 week (n=505)	Obesity	0.61 (0.28–1.32)
Maffeis 1994 (A) (123)	Cross-sectional	Not stated	4-12 years	All	Not stated	Obesity	0.91 (0.69–1.21)
Scaglioni 2000 (124)	Cohort	1991	5 years	All	Ever breastfed (n=124) vs. Never breastfed (n=23)	Overweight or obesity	0.64 (0.24–1.70)
O'Callaghan 1997 (125)	Cohort	1981-4	5 years	All	Ever breastfed (n=3119) vs. Never breastfed (n=790)	Obesity	0.71 (0.43–1.25)
Burdette 2006 (126)	Cohort	Not stated	5 years	All	Ever breastfed (n=231) vs. Never breastfed (n=82)	Overweight or obesity	0.66 (0.25–1.78)
Von Kries 1999 (127)	Cross-sectional	1991-2	5-6 years	All	Ever breastfed (n=5184) vs. Never breastfed (4022)	Overweight or obesity Obesity	0.79 (0.68–0.93) 0.75 (0.57–0.98)
Frye 2003 (128)	Cross-sectional	Not stated	5-14 years	All	Exclusively breastfed for >12 weeks (n=762) vs. Never breastfed (n=1955)	Overweight or obesity Obesity	0.90 (0.70–1.10) 0.60 (0.40–0.90)

* total sample

Table 3.1. (continued)

Author, year (reference)	Study design	Year of birth of subjects	Age measured	Gender	Comparison groups	Outcome	Odds ratio (95% confidence interval)
Wadsworth 1999 (129)	Cohort	1946	6 years	All	Ever breastfed (n=2873) vs. Never breastfed (858)	Overweight only Obesity	0.94 (0.73–1.20) 0.88 (0.59–1.32)
Thorsdottir 2003 (130)	Cohort	Not stated	6 years	Male	Breastfed for ≥6 months vs. Breastfed for <6 months (n=61)*	Overweight or obesity	0.33 (0.13–0.83)
Bergmann 2003 (131)	Cohort	1990	6 years	All	Breastfed for ≥3 months (n=607) vs. Breastfed for <3 months (n=280)	Overweight only Obesity	0.53 (0.31–0.89) 0.46 (0.23–0.92)
Reilly 2005 (132)	Cohort	1991-2	7-8 years	All	Exclusively breastfed for ≥2 months (n=2211) vs. Never breastfed (n=1153)	Obesity	1.22 (0.87–1.71)
Eid 1970 (133)	Cohort	1961	8 years	All	Not stated	Obesity	0.42 (0.11–1.61)
Liese 2001 (134)	Cross-sectional	1985-7	9-10 years	All	Ever breastfed (n=1754) vs. Never breastfed (n=354)	Overweight or obesity	0.66 (0.52–0.87)
Sung 2003 (A) (135)	Cross-sectional	1990	9-12 years	All	Not stated	Overweight or obesity	0.45 (0.27–0.78)
Toschke 2002 (136)	Cross-sectional	1977-85	6-14 years	All	Ever breastfed (n=30641) vs. Never breastfed (n=3127)	Overweight or obesity Obesity	0.80 (0.71–0.90) 0.80 (0.66–0.96)
Poulton 2001 (117)	Cohort	1972-3	11 years	All	Breastfed for >6 months vs. Never breastfed (n=591)*	Overweight	0.36 (0.1–1.28)
Li 2003 (122)	Cross-sectional	1973-82	9-18 years	All	Breastfed for >9 months (n=67) vs. Breastfed <1 week (n=471)	Obesity	0.73 (0.23–2.27)
Gillman 2001 (137)	Cross-sectional	Not stated	9-14 years	All	Mostly or only breastfed (n=4510) vs. Mostly or only formula fed (n=2248)	Overweight only Obesity	0.95 (0.84–1.07) 0.78 (0.66–0.91)
Li 2005 (115)	Cohort	1982-5	1-14 years	All	Breastfed for ≥4 months vs. Never breastfed (n=749)*	Obesity	0.6 (0.3–1.6)
Elliott 1997 (138)	Cohort	1977-80	12-17 years	All	Breastfed for >2 months (n=73) vs. Breastfed for ≤2 months (n=63)	Overweight	0.51 (0.22–1.16)
Kramer 1981 (108)	Case-control	Not stated	12-18 years	All	Ever breastfed (n=45) vs. Never breastfed (284)	Obesity	0.44 (0.21–0.93)
Kramer 1981 (108)	Case-control	Not stated	12-18 years	All	Ever breastfed (n=60) vs. Never breastfed (332)	Obesity	0.29 (0.11–0.73)
Tulldahl 1999 (139)	Cohort	1979	15-16 years	All	Breastfed for >2 months (n=390) vs. Breastfed for ≤2 months (n=391)	Overweight or obesity	0.66 (0.44–0.98)

* total sample

Table 3.1. (continued)

Author, year (reference)	Study design	Year of birth of subjects	Age measured	Gender	Comparison groups	Outcome	Odds ratio (95% confidence interval)
Victora 2003 (140)	Cohort	1982	18 years	Males	Breastfed for ≥1 month (n=489) vs. Breastfed for <1 month (n=1666)	Obesity	0.73 (0.50–1.07)
Poulton 2001 (117)	Cohort	1972-3	21 years	All	Breastfed for >6 months vs. Never breastfed (n=687)*	Overweight	0.79 (0.46–1.34)
Kvaavik 2005 (141)	Cohort	1966	31-35 years	All	Breastfed for ≥4 months (n=121) vs. Never breastfed (n=78)	Overweight or obesity	0.64 (0.33–1.26)
						Obesity	0.34 (0.12–1.01)
Parsons 2003 (142)	Cohort	1958	33 years	Males	Breastfed for >1 month vs. Never breastfed (n=4662) *	Obesity	0.93 (0.74–1.17)
				Females	Breastfed for >1 month vs. Never breastfed (n=4625) *	Obesity	0.84 (0.67–1.05)
Richter 1981 (143)	Cohort	1957-9	Adult life	All	Ever breastfed (n=1999) vs. Never breastfed (n=386)	Obesity	0.73 (0.51–1.07)
Eriksson 2003 (144)	Cohort	1934-44	56-66 years	All	Breastfed for >8 months (n=986) vs. Breastfed for <2 months (n=607)	Obesity	1.10 (0.88–1.37)

* total sample

Table 3.2 shows that there was no marked effect modification by age group, year at birth, control of confounding, categories of breastfeeding duration, study setting, study design, and control for confounding variables. On the other hand, the study's outcome was related to heterogeneity between studies.

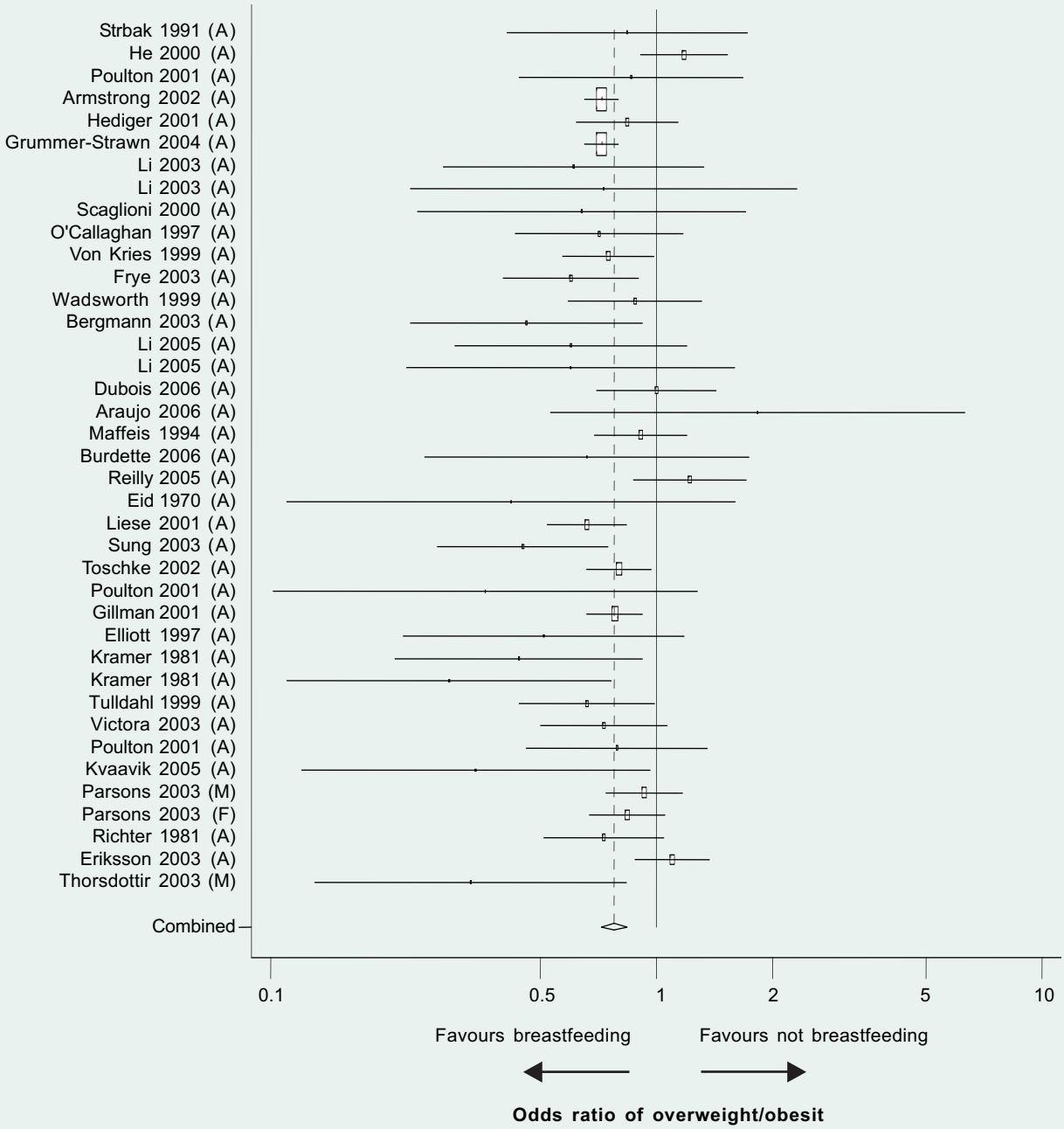
Concerning publication bias, the funnel plot is quite asymmetrical, with small studies tending to report a higher protective effect of breastfeeding. Indeed, Table 3.2 shows that the protective effect of breastfeeding was higher among small studies (<500 participants). However, studies with 500-1500 and >1500 participants had similar protective effects, which were also similar to the pooled protective effect of all studies.

Eight studies provided odds ratios for more than one outcome, such as overweight only (e.g. BMI 25-29.9), overweight plus obesity (e.g. BMI ≥25) and obesity (e.g. BMI ≥30). Six of these eight studies reported a more marked protective effect against obesity than against overweight only or overweight plus obesity. This supports a causal effect of breastfeeding.

Relevant studies not included in the meta-analyses

A frequent limitation of observational studies is inadequate adjustment for confounding by socioeconomic and maternal variables. In the absence of randomized studies, within-family analyses allow controlling for confounding by socioeconomic, maternal variables, as well as self-selection bias. Gillman et al (*112*) analysed data from 5614 sibling sets from the Growing Up Today Study to assess the association of breastfeeding with adolescent obesity within sibling sets. The overall odds of overweight in that study were smaller among subjects breastfed for at least 7 months, compared with those breastfed for 3 months or less (OR: 0.85; 95% CI: 0.71–1.00). When the analyses were limited to the 172 families in which one sibling was breastfed for at least 7 months and another for 3 months or less, the resulting odds ratio was similar to that of the overall analyses OR: 0.89; 95% CI: 0.50–1.59), but the upper 95% confidence limit was well above the unity (1). This similarity between the results obtained in the

Figure 3.3. Odds ratio and its 95% confidence interval of being considered as overweight/obese, comparing breastfed vs. non-breastfed subjects in different studies. Whether the estimate was for males (M), females (F) and all (A) is indicated in parenthesis



total sample and those from the siblings study suggests that confounding by socioeconomic status was not an important issue in this study. However, because heterogeneity in breastfeeding durations among siblings is much smaller than for unrelated individuals, the effective sample size for the within-family analysis was quite small leading to less precise estimates. Another within-family analysis from the United States (*113*) found no association between breastfeeding duration and prevalence of obesity.

Table 3.2. 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
By age group			
1 to 9 years	22	0.79 (0.71 to 0.87)	0.001
9 to 19 years	11	0.69 (0.60 to 0.80)	0.001
>19 years	6	0.88 (0.74 to 1.04)	0.13
By study size			
<500 participants	11	0.51 (0.35 to 0.75)	0.001
500–1499 participants	11	0.79 (0.66 to 0.93)	0.006
≥1500 participants	17	0.80 (0.74 to 0.87)	0.001
By year at birth			
Before 1980	13	0.83 (0.73 to 0.95)	0.008
After 1980	22	0.78 (0.72 to 0.85)	0.001
By study design			
Cross-sectional	26	0.79 (0.72 to 0.87)	0.001
Case-control	3	0.58 (0.23 to 1.45)	0.24
Cohort	10	0.75 (0.69 to 0.83)	0.001
By length of recall of breastfeeding			
<3 years	24	0.79 (0.71 to 0.87)	0.001
≥3 years	15	0.76 (0.67 to 0.86)	0.001
By categorization of breastfeeding			
Ever breastfed	12	0.75 (0.67 to 0.83)	0.001
Breastfed for a given number of months	23	0.78 (0.71 to 0.86)	0.001
By control for confounding			
None	16	0.76 (0.64 to 0.91)	0.004
Adjusted for socioeconomic status	3	0.72 (0.66 to 0.79)	0.001
Adjusted for socioeconomic status and parental anthropometry	20	0.77 (0.71 to 0.84)	0.001
By study setting			
High-income country	33	0.77 (0.71 to 0.83)	0.001
Middle/Low-income country	6	0.82 (0.62 to 1.09)	0.18
Total	39	0.78 (0.72 to 0.84)	

Table 3.3. Comparison of odds ratios for overweight only*, overweight plus obesity* and for obesity* only, in studies reporting more than one of these outcome

Study	Overweight only	Overweight plus obesity	Obesity
Hediger 2001 (119)	0.63	-	0.84
Von Kries 1999 (127)	-	0.79	0.75
Frye 2003(128)	-	0.90	0.60
Wadsworth 1999 (129)	0.94	-	0.88
Bergmann 2003 (131)	0.53	-	0.46
Toschke 2002 (136)	-	0.80	0.80
Gillman 2001 (137)	0.95	-	0.78
Kvaavik 2005 (141)	-	0.64	0.34

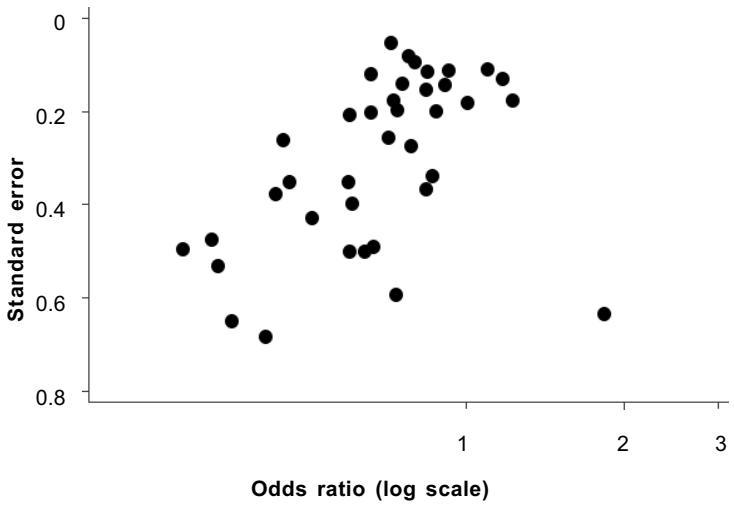
* For example in adult subjects, overweight only defined as BMI 25-29.9, overweight plus obesity defined as BMI ≥25 and obesity only defined as BMI ≥30 kg/m^2

Conclusion

The evidence suggests that breastfeeding may have a small protective effect on the prevalence of obesity. In spite of the evidence of publication bias, a protective effect of breastfeeding was still observed among the larger studies (≥1500 participants), suggesting that this association was not due to publication bias. With respect to confounding, studies that controlled for socioeconomic status and parental anthropometry also reported that breastfeeding was associated with a lower prevalence of obesity. This effect seems to be more important against obesity than against overweight.

Because the great majority of the published studies were conducted in Western Europe and North America, we are not able to assess whether this association is present in low and middle-income settings.

Figure 3.4. Funnel plot showing odds ratio for overweight/obesity by standard error of odds ratio



Biological plausibility

Two possible mechanisms for a protective effect of breastfeeding against type-2 diabetes have been proposed.

Baur et al (*145*) observed that the fasting glucose level was inversely correlated to long-chain polyunsaturated fatty acids in skeletal muscle membranes. Because long-chain polyunsaturated fatty acids are present in breastmilk, but not in most brands of formula (*49*), it has been postulated that changes in skeletal muscle membrane would play a role in the development of insulin resistance, leading to compensatory hyperinsulinaemia. Over a period of time there would be β-cell failure, resulting in the occurrence of type-2 diabetes (*146*).

Several studies (*105*,*147*,*148*) reported that formula-fed infants have higher basal and postprandial concentrations of insulin and neurotensin, which modulates insulin and glucagon release. These differences may lead to the earlier development of insulin resistance and type-2 diabetes.

These are possible mechanisms for an association between breastfeeding and diabetes. Other biological mechanisms may also exist, which are presently unknown.

Overview of the evidence

The two independent literature searches carried out at WHO and at the University of Pelotas identified five papers that assessed the association between breastfeeding duration and type-2 diabetes.

Pettitt et al (*149*) followed a cohort of Pima Indians born between 1950 and 1978. Information on infant feeding was provided by mothers in 1978. The odds ratio for type-2 diabetes between subjects who were exclusively breastfed in the first two months and those who were exclusively bottle-fed was 0.41 (95% CI: 0.18–0.93).

Ravelli et al (*77*) studied a cohort of subjects who were born between 1943 and 1947 in a university hospital in Amsterdam. Information on infant feeding at hospital discharge was collected from the medical records. The odds ratio for type-2 diabetes was 0.51 (95% CI: 0.3–0.9), comparing exclusively breastfed subjects with those who were partially or exclusively bottle-fed.

Young et al (*150*) assessed the role of prenatal and early infancy risk factors for type-2 diabetes among native Canadians. Forty-six cases were recruited from the only clinical centre for the treatment of diabetes in the province of Manitoba. Two controls were chosen for each case, from a paediatric clinic. Mean ages were 14.0 years for the cases and 12.7 years for controls. The odds ratio for type-2 diabetes between subjects who were breastfed for $\geq$6 months and those breastfed for <6 months was 0.36 (95% CI: 0.13–0.99).

Martin et al (*58*) studied a cohort of subjects recruited in 16 centres in England and Scotland, who participated in a 1-week survey of diet and health when aged <20 years between 1937 and 1939. Information on breastfeeding duration was obtained from the subjects' mothers. At a mean age of 71 years, breastfeeding was not associated with type-2 diabetes (odds ratio: 0.97; 95% CI: 0.41–2.30).

Rich-Edwards et al (*151*) studied a cohort of registered nurses in the US, who had been followed since 1976. Information on occurrence of diabetes was reported by the subjects themselves. Prevalence of diabetes was lower among breastfed (4%) compared to non-breastfed (5%) subjects.

These five studies were included in a meta-analysis. The pooled odds ratio was 0.63 (95% CI: 0.45–0.89). Fig. 4.1 shows the forest plot for this analysis.

Other relevant studies not included in the meta-analysis

Lawlor et al (*60*) evaluated a random sample of schoolchildren aged 9 and 15 years from Estonia and Denmark. Insulin resistance was estimated according to the homeostasis model assessment (HOMA), based on fasting glucose and insulin levels. Information on infant feeding was collected from the parents at the time of the

subjects' examination. After controlling for possible confounding variables, there was no association between breastfeeding and insulin resistance. Difference in HOMA index was -4% (95% CI: -13 to 5) between ever and never breastfed subjects. Also, there was no evidence of a dose-response trend.

Martin et al (*57*) also studied a cohort of men from Caerphilly, South Wales, aged 45-59 years when examined between 1979 and 1983. Information on breastfeeding duration was obtained from the subjects' mothers or a close female relative. Difference in the HOMA index between breastfed and bottle-fed subjects was 0.00 (95% CI: -0.10 to 0.10).

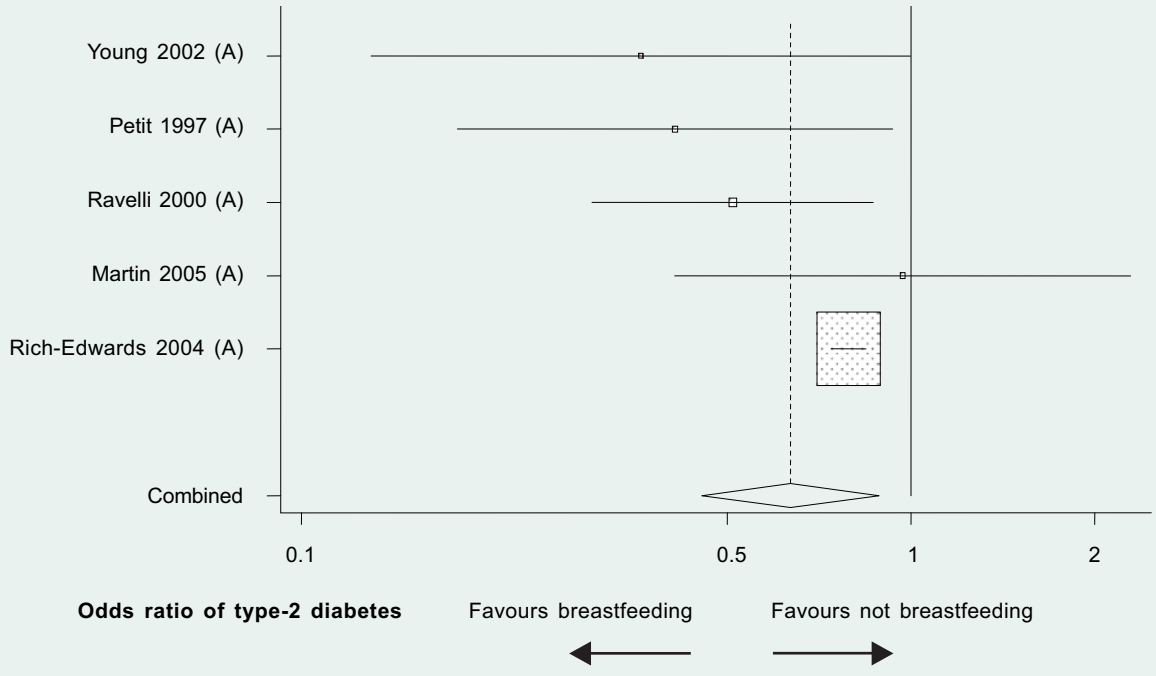
Plancoulaine et al (*94*) evaluated a sample of children aged 5 to 11 years in two small towns in northern France. Information on breastfeeding duration was obtained from the mother at the moment of the children's examination. Fasting blood glucose levels were similar among breastfed and non-breastfed children.

Singhal et al (*152*) assessed 32-33 split proinsulin concentration – a marker of insulin resistance – among subjects aged 13-16 years who were born pre-term and randomized to receive a nutrient-enriched or lower-nutrient diet. The level of 32-33 split proinsulin was lower among those subjects who were randomized to receive banked breastmilk, compared to those receiving pre-term formula; the difference was not statistically significant (P = 0.07).

Conclusion

Evidence on a possible programming effect of breastfeeding on glucose metabolism is sparse. Studies assessing the risk of type-2 diabetes reported a protective effect of breastfeeding, with a pooled odds ratio of 0.63 (95% CI: 0.45–0.89) in breastfed compared to non-breastfed subjects. On the other hand, two other studies failed to report an association between HOMA index, a measure of insulin resistance, and breastfeeding duration, and a study on fasting blood glucose levels was also negative. At this stage, it is not possible to draw firm conclusions about the long-term effect of breastfeeding on the risk of type-2 diabetes and related outcomes. Further studies are badly needed on this topic.

Figure 4.1. Odds ratio and 95% confidence interval of having type-2 diabetes in different studies, comparing breastfed vs. non-breastfed subjects. Whether the estimate was for males (M), females (F) and all (A) is indicated in parenthesis.



Review 5 - Breastfeeding and school achievement/intelligence levels

Biological plausibility

Long-chain polyunsaturated fatty acids are present in breastmilk, but not in most brands of formula (*49*). These fatty acids are preferentially incorporated into neural cell membranes; structural lipids constitute about 60% of the human brain. The major lipid components include docosahexaenoic (DHA) and arachidonic (AA) acids (*153*), which are important for retinal and cortical brain development (*154*). Bjerve et al (*155*) reported that the results of the Bayley mental and psychomotor development indexes correlated positively with serum DHA concentrations.

AA and DHA accumulate in the brain and retina most rapidly during the last trimester of pregnancy and the first months after birth (*156*). Their reserves are limited at birth, especially in pre-term infants, and decline rapidly when lacking in the diet (*157*). Bottle-fed infants have been shown to have lower long-chain polyunsaturated fatty acids in the phospholipids of the cerebral cortex than infants who are fed breastmilk (*158*). This is, therefore, a potential mechanism for an effect of breastfeeding on intellectual development.

In addition to the chemical properties of breastmilk, breastfeeding enhances the bonding between mother and child (*159*, *160*), which may contribute to the child's intellectual development.

Specific methodological issues

General methodological issues were addressed in the Introduction. Two points deserve special attention. Because cognition and performance in intelligence tests are positively related to the stimulation received by the child (*161*) and because breastfeeding mothers may be more prone to stimulating their children (*162*), studies assessing the long-term consequences of breastfeeding on intellectual performance should attempt to control for the quantity and quality of stimulation. In addition, in societies where breastfeeding is more common among upper social groups, the possibility of confounding by parental education level has to be addressed.

Overview of the evidence

We identified three meta-analyses that assessed the relationship between breastfeeding duration and performance in intelligence tests.

In 1999, Anderson et al (*163*) were the first to publish a meta-analysis on this topic, employing the following selection criteria:

- the study included a comparison between subjects who were mostly breastfed with those who were mostly bottle-fed;
- the outcome was measured with a widely applied test of cognitive development or ability, yielding a single score;
- subjects were examined between infancy and adolescence.

The studies were considered as including control for confounding if the estimates were adjusted for a minimum of five variables, from a list of 15 potential confounders.

Eleven studies were included in their analyses. In a random-effects model, the adjusted mean difference in cognitive function was of 3.16 (95% CI: 2.35 to 3.98) points in favour of breastfed subjects. The effect of breastfeeding was not modified by age at measurement. The benefit of breastfeeding was higher among low birthweight infants (mean difference: 5.18 points; 95% CI: 3.59 to 6.77) although a significant effect was also observed among normal birthweight subjects (mean difference: 2.66 points; 95% CI: 2.15 to 3.17).

In 2000, Drane et al (*164*) carried out a second systematic review. Articles had to fulfil the following criteria:

- subjects had to be born between 1960 and 1998;
- cognition had to be measured by using standard tests;

- breastfeeding had to be measured as a categorical variable (exclusively breastfed, partially breastfed, exclusively formula-fed) or as a "continuous variable" (duration of exclusive breastfeeding or proportion of the diet as breastmilk);
- analyses had to be adjusted for socioeconomic status and birth weight, at least.

Twenty-four studies including subjects born between 1960 and 1998 were identified, but only five (*165-169*) fulfilled the three methodological pre-requisites. Another study (*170*), which met two standards (confounding and cognition assessment) and partially met the standard for breastfeeding measurement, was also included. Four of these studies reported a positive effect of breastfeeding on cognitive development, particularly for low-birthweight subjects.

In 2002, Jain et al (*171*) published a third review. Inclusion was restricted to studies published in English, and each study was assessed for the following methodological aspects: study design, sample size, target population, quality of feeding data, control of susceptibility bias, blinding and outcome measures. Of the 40 studies identified, only nine met all criteria for quality of the feeding data; the breastfed group was specified as those who mostly breastfed, information on infant feeding was collected in infancy and by interviewing the mother or from health records, and duration of breastfeeding was of at least 1 month among the breastfed subjects. Only two of these nine studies presented estimates adjusted for socioeconomic status and stimulation at home, and their results were conflicting. Wigg et al (*172*) reported that, after controlling for socioeconomic status and quality of the child's environment, breastfed subjects presented a small advantage in the Wechsler Intelligence Scale for Children at 11-13 years of age (mean difference: 0.8; 95% CI: -1.9 to 3.5 points). Johnson et al (*173*) reported that the adjusted difference between breastfed and non-breastfed 3-year-olds in the Stanford-Binet Composite IQ Scale was 5.0 points (95% CI: 0.3 to 9.5), while in the Peabody Picture Vocabulary Test the difference was 4.6 points (95% CI: 0.7 to 8.5). Seven other studies controlled for both socioeconomic status and stimulation/interaction of the child but did not fulfil the remaining methodological criteria. Three of these studies reported that performance in the intelligence test was higher among breastfed subjects (*165,174,175*), whereas four failed to show an association (*162,176-178*). Given the conflicting results from high-quality studies, the authors stated that the evidence on the effect of breastfeeding on cognition was not convincing.

A very important study that was included in the meta-analyses carried out by Anderson et al (*163*) and by Drane et al (*164*) was a randomized trial by Lucas et al (*167*), in which newborn pre-term babies received breastmilk or formula, and a significant improvement in WISC-R was found in the former. Because of the randomized design, these differences are not likely to be due to confounding.

Update of existing meta-analysis

Jain and colleagues (*171*) restricted their interpretation to whether or not the study results had been significant. They did not discuss the direction of the effect in non-significant studies, nor did they try to pool the results in a meta-analysis. We carried out a meta-analysis including these papers, as well as three more recent articles identified in our own systematic review. According to the criteria proposed by Jain and colleagues, all estimates were adjusted for stimulation at home and fulfilled the other quality criteria. Studies restricted to very low birthweight infants were not included. The three additional studies are described below.

Quinn et al (*179*) studied a cohort of 7357 singleton children whose mothers had been enrolled in the Mater Hospital-University of Queensland Study of Pregnancy. Information on breastfeeding duration was obtained from the mother when the child was six months old. At five years, 4049 children were assessed with the Peabody Picture Vocabulary Test Revised (PPVT-R). Breastfeeding duration was positively associated with the PPVT-R score, and after controlling for confounding by socioeconomic status, birthweight, and stimulation in the home, the mean score for children breastfed for six

months or more was 8.2 (95% CI: 6.5 to 9.9) points higher for females and 5.8 (95% CI: 4.1 to 7.5) points higher for males, when compared to those never breastfed.

Clark et al (*180*) followed a cohort of children born between 1991 and 1996 in urban communities near Santiago, Chile, who were enrolled in a study on prevention of iron deficiency in healthy full-term infants. At six months, the infants were randomly assigned to receive iron supplementation. At five years, information from 784 (62.6%) subjects was gathered. Children breastfed for <2 months or >8 months had lower scores for language, motor and cognition tests than those breastfed for 2-8 months, after adjustment for socioeconomic factors and home stimulation.

Angelsen et al (*181*) reported from Norway that the odds of having a low total intelligence quotient at five years of age was higher among those children breastfed for <3 months compared to those breastfed for at least 6 months (odds ratio: 1.5; 95% CI: 1.0–2.1).

Because the Chilean and Norwegian studies did not provide results in terms of means scores, they were not included in the meta-analyses. Fig. 5.1 shows that the eight studies observed a beneficial effect from breastfeeding, which was statistically significant in six of them. Because heterogeneity among studies was statistically significant, a random-effects model was used. In the pooled analysis, performance in intelligence tests was higher among those subjects who had been breastfed (mean difference: 4.9; 95% CI: 2.97 to 6.92). Given the small number of studies, it was not possible to assess publication bias.

Studies on breastfeeding and schooling

Our systematic review resulted in only three studies on the relationship between breastfeeding and achieved schooling. Horwood & Fergusson (*168*) studied adolescents from Christchurch, New Zealand, who had been followed since birth. Even after controlling for confounding by socioeconomic status and perinatal variables (birthweight, birth order, and maternal smoking in pregnancy), increased breastfeeding duration was positively associated with academic performance in high-school leaving examinations. A lower percentage of children left high school without qualifications in the group breastfed for >8 months (14%) as compared to those breastfed for 4–7 months (16.4%), <4 months (19.2%), and not breastfed (22.2%) (overall P <0.05).

Richards et al (*182*) reported from the British 1946 birth cohort that the odds ratio for obtaining an advanced educational qualification by the age of 26 years was directly associated with breastfeeding duration, showing a dose-response relationship. The odds of obtaining an advanced educational qualification were 1.58 (95% CI: 1.15–2.18) times higher among those subjects who were breastfed for more than seven months, compared with those who were never breastfed.

Breastfeeding was also associated with increased achieved schooling among Brazilian adolescents who had been followed-up since birth (*183*). In the adjusted analyses, there was an increase in schooling with breastfeeding duration up to 12 months. Subjects breastfed for 9-11 months had achieved 8.0 (95% CI: 7.5–8.5) years of schooling, while those breastfed for less than one month had 7.2 (95% CI: 6.9–7.6) years. Children breastfed for 12 or more months attained on average 7.7 (95% CI: 7.3–8.0) years. This association is unlikely to be explained by residual confounding by socioeconomic status. In this population, there was no strong association between breastfeeding and social class, and the poorest children were those breastfed for over one year. In addition, a stratified analysis showed that breastfeeding was associated with increased schooling within all strata of family income.

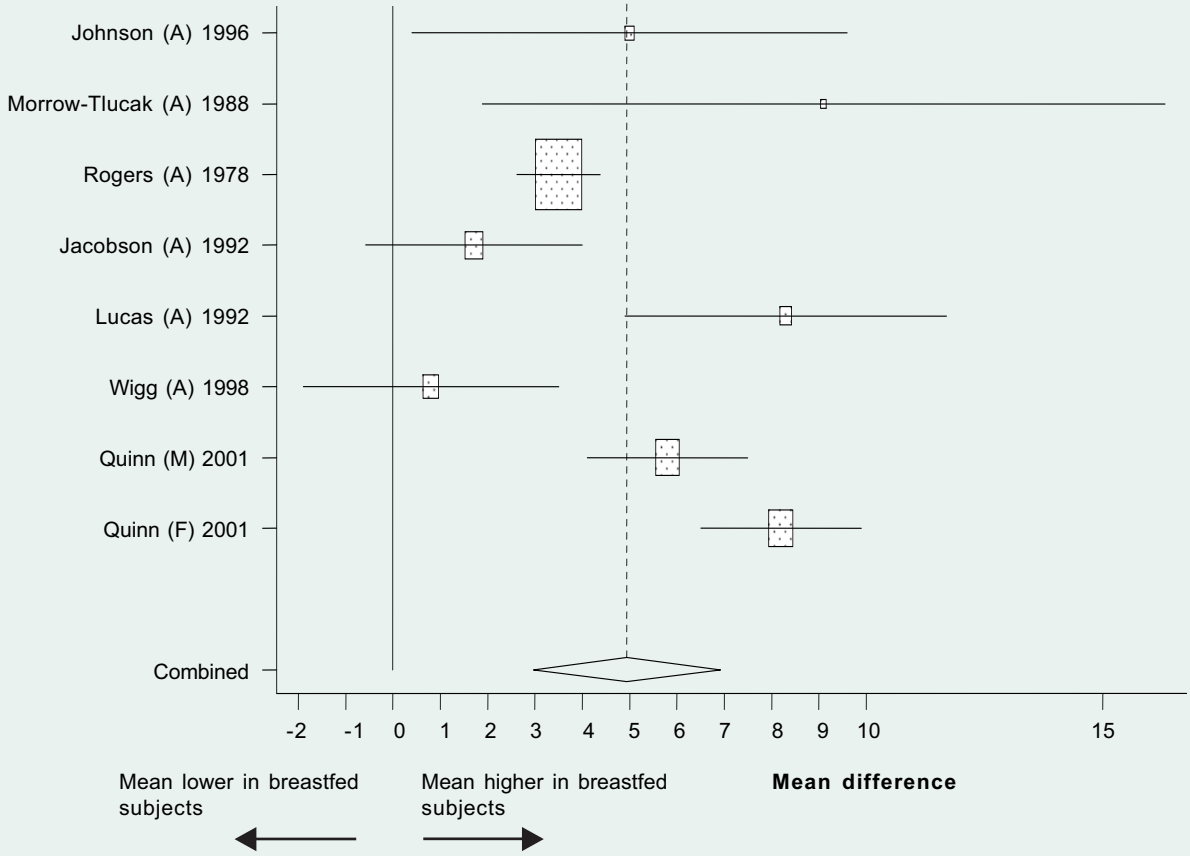
Conclusion

This meta-analysis suggests that breastfeeding is associated with increased cognitive development in childhood, in studies that controlled for confounding by socioeconomic status and stimulation at home. The practical implications of a relatively small increase in the performance in developmental tests in childhood may be open to debate. However, evidence from the only three studies on school performance in late ado-

lescence or young adulthood suggests that breastfeeding is also positively associated with educational attainment (*168*,*182*,*183*).

The issue remains of whether the association is related to the properties of breastmilk itself, or whether breastfeeding enhances the bonding between mother and child, and thus contributes to intellectual development. Although in observational studies it is not possible to disentangle these two effects, the positive results from the randomized trial carried out by Lucas et al (*167*) suggest that the nutritional properties of breastmilk alone seem to have an effect.

Figure 5.1. Mean difference in cognitive development scores and its 95% confidence interval between breastfed and non-breastfed subjects in different studies. Whether the estimate was for males (M), females (F) and all (A) is indicated in parenthesis



VI. Conclusions

The available evidence suggests that breastfeeding may have long-term benefits. Subjects who had been breastfed were found to have a lower mean blood pressure and lower total cholesterol, and showed higher performance in intelligence tests. Furthermore, the prevalence of overweight/obesity and type-2 diabetes was lower among breastfed subjects. All effects were statistically significant, but for some outcomes their magnitude was relatively modest.

The Table 6.1 summarizes the magnitude of the effects of breastfeeding based on the five meta-analyses described above. For all outcomes, except performance in intelligence tests, we provide a comparison of these effects with those observed for other public health interventions. For blood pressure, the effect of breastfeeding was smaller than those derived from other public health interventions targeted at adults, such as dietary advice, physical activity, salt restriction, and multiple risk factor interventions. On the other hand, for total cholesterol among adults, the magnitude of the breastfeeding effect was similar to that of dietary advice in adulthood. Similarly, for the prevention of type-2 diabetes, the magnitude was similar to that of diet and physical activity. Concerning obesity, whereas Summerbell et al (*184*) reported that combined dietary education and physical activity interventions were not effective in reducing childhood obesity and overweight, we noticed that breastfeeding was associated with a 22% reduction in the prevalence of overweight/obesity.

This Table is intended for illustrative purposes only. It should be interpreted with caution because it includes a comparison of the effect of actual interventions – none of them with perfect compliance levels – with the gross difference of the effect between breastfed and non-breastfed subjects, which corresponds to an intervention with 100% compliance. Only the long-term follow-up of subjects involved in breastfeeding trials will provide a more accurate estimate of the impact of breastfeeding promotion.

Table 6.1. Summary of effect of breastfeeding and comparison with other interventions

Outcome	Range of effect of other public health interventions in later life				Breastfeeding (current review)	
	Diet / Dietary advice	Exercise	Multiple risk factor intervention	Modest salt restriction	Pooled effect size (95% confidence interval)	Conclusion
Blood pressure (mean difference in mm Hg, 95% CI)						The effect of breastfeeding is significant, but smaller than the effect of other interventions.
Systolic	-2.1 (-2.8 to -1.4)	-3.84 (-4.97 to -2.72)	-4.2 (-4.6 to -3.8)	-2.03 (-2.56 to -1.50)	-1.21 (-1.72 to -0.70)	
Diastolic	-1.6 (-2.7 to -0.6)	-2.58 (-3.35 to -1.81)	-2.7 (-2.9 to -2.5)	-0.99 (-1.4 to -0.57)	-0.49 (-0.87 to -0.11)	
	ref. (*45*)	ref. (*185*)	ref. (*186*)	ref. (*187*)		
Total serum cholesterol (mean difference in mmol/L, 95% CI)	-0.13 (-0.23 to -0.03)		-0.14 (-0.16 to -0.12)		-0.18 (-0.30 to -0.06)	The effect of breastfeeding is significant and larger than the effect of other interventions.
	ref. (*45*)		ref. (*186*)			
Overweight or obesity	*Diet/dietary advice and exercise* 5/6 studies showed no effect on childhood obesity. Meta-analysis not done because of heterogeneity between studies. ref. (*184*)				Odds ratio 0.78 (0.72 to 0.84)	The effect of breastfeeding is significant (22% reduction), while other interventions showed no effect.
Type II diabetes	*Diet/dietary advice and exercise* 31-46% reduction in risk in persons with impaired glucose tolerance. ref. (*188*)				Odds ratio 0.63 (0.45 to 0.89)	The effect of breastfeeding is significant (37% reduction) and of similar magnitude to the effect of other interventions.
Intelligence test scores					Mean difference 4.9 points (2.97 to 6.92)	The effect of breastfeeding is significant, with a substantial effect size.

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