Long-term effects of breastfeeding

A SYSTEMATIC REVIEW

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Introduction

Breastfeeding has well-established short-term benefits, particularly the reduction of morbidity and mortality due to infectious diseases in childhood. A pooled analysis of studies carried out in middle/low income countries showed that breastfeeding substantially lowers the risk of death from infectious diseases in the first two years of life (*1*).

Based on data from the United Kingdom Millennium Cohort, Quigley et al (*2*) estimated that optimal breastfeeding practices could prevent a substantial proportion of hospital admissions due to diarrhea and lower respiratory tract infection. A systematic review by Kramer et al (*3*) confirmed that exclusive breastfeeding in the first 6 months decreases morbidity from gastrointestinal and allergic diseases, without any negative effects on growth. Given such evidence, it has been recommended that in the first six months of life, every child should be exclusively breastfed, with partial breastfeeding continued until two years of age (*4*).

Building upon the strong evidence on the short-term effects of breastfeeding, the present review addresses its long-term consequences. Current evidence, mostly from high income countries, suggests that occurrence of non-communicable diseases may be programmed by exposures occurring during gestation or in the first years of life (*5–7*). Early diets, including the type of milk received, is one of the key exposures that may influence the development of adult diseases.

In 2007, we carried out a systematic review and meta-analysis on the long-term consequences of breastfeeding. The Department of Maternal, Newborn, Child and Adolescent Health of the World Health Organization has now commissioned an update of this review. The following long-term outcomes were reviewed: blood pressure, type-2 diabetes, serum cholesterol, overweight and obesity, and intellectual performance. These outcomes are of great interest to researchers, as made evident by the number of publications identified: 60 new publications were identified since 2006. This report describes the methods, results and conclusions of this updated review.

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··· CHAPTER 2 ···

Methodological issues

Randomized controlled trials, if properly designed and conducted, provide the best evidence on a causal association between an exposure – such as breastfeeding – and a health or developmental outcome. Randomization increases the likelihood that results will not be affected by confounding (*1*). Additionally, existing guidelines propose standards for conducting, analyzing and reporting clinical trials, which helps increase the validity of the evidence (*2*).

On the other hand, the recognition of the short-term benefits of breastfeeding, briefly described in **Chapter 1**, constitutes an ethical challenge to the design of randomized trials aimed at assessing its long-term consequences. Currently, it would be considered unethical to randomly allocate subjects not to receive breastmilk. In contrast, in the early 1980s the evidence on the short-term benefits of breastfeeding was not so clear-cut. At that time, preterm infants admitted to neonatal units could be ethically allocated at random to receive banked breastmilk or formula. Follow-up of these subjects in adolescence has provided experimental evidence on the long-term effects of breastfeeding (*3–5*).

An alternative to individual randomization to breastfeeding is to allocate groups of mothers to receive – or not to receive – breastfeeding counseling. In Belarus, the Promotion of Breastfeeding Trial (*6*) randomly assigned maternity hospitals and their affiliated polyclinics to the Baby-Friendly Hospital Initiative. The proportion of infants exclusively breastfed at 3 and 6 months was substantially higher among infants from the intervention group. This trial is ethically sound because mothers were randomly assigned to receive intense breastfeeding promotion, compared to usual care in the hospitals. The follow-up of this study has provided invaluable evidence on the long-term consequence of breastfeeding (*7–8*). On the other hand, compliance to the intervention was far from universal, only 43.3% of the infants in the intervention group were exclusively breastfed at 3 months compared to 6.4% in the comparison arm, and therefore both groups represent a mixture of breastfeeding practices. As a consequence, the effect of breastfeeding itself on outcomes is underestimated, and statistical power is reduced.

Because of the small number of randomized controlled trials with sufficient follow-up time, most of the evidence on the long-term effects of breastfeeding is derived from observational studies. Prospective birth cohort studies are the next-best design in terms of strength of evidence.

Below, we discuss the strengths and weaknesses of observational studies, as well as approaches that may help overcome their main shortcomings.

Factors affecting internal validity

Losses to follow-up

If losses to follow-up are high, selection bias may be introduced. This may affect both randomized and observational studies. In order to assess the study susceptibility to selection bias, baseline data,

such as breastfeeding duration, should be compared between those subjects who were followed up and those who were not. If attrition rates are not related to breastfeeding duration or other baseline characteristics, selection bias is unlikely (*9*). However, not every study provides such information.

Misclassification

When assessment of exposure or the outcomes is inaccurate, misclassification may occur. Misclassification may be differential or non-differential.

Retrospective studies are more susceptible to recall bias and direction of bias may change. For example, Huttly et al (*10*) observed that Brazilian mothers of high socioeconomic status tended to overestimate the breastfeeding duration, whereas among poor mothers this was not the case. This differential recall of breastfeeding duration would tend to overestimate the benefits of breastfeeding because high socioeconomic status is associated with a lower risk of chronic non transmissible diseases.

On the other hand, if the measurement error is not related to exposure or outcome, non-differential misclassification occurs. Such bias underestimates the measure of association, and, therefore, reduces the likelihood of reporting a significant association. Indeed, in a meta-analysis on the relationship between maternal smoking in pregnancy and breastfeeding duration, the odds ratio for weaning at 3 months was inversely related to the length of recall for exposure and outcome (*11*).

Unfortunately, very few of the studies included in this review address these issues. We attempted to address it by stratifying studies according to the length of recall of breastfeeding information, but admittedly this is only a proxy for misclassification.

Confounding

Confounding is one of the challenges in interpreting the evidence of observational studies. Even large studies that managed to measure the possible confounders may still be affected by residual confounding, if the confounder variables were not properly measured or adjusted for. Some methods have been suggested to improve causal inference. These include comparison of siblings in within-family analyses, which allow controlling for unmeasured maternal and family variables (socioeconomic status, maternal variables) as well as for self-selection bias, because these characteristics are shared among siblings. Usually, sibling studies assess the effect of discordance on breastfeeding duration or complementary feeding on the outcome. Gillman et al (*12*) used this design to investigate the association between breastfeeding and overweight (see **Chapter 5**). A limitation of these studies, is that heterogeneity in breastfeeding duration is smaller among siblings than that observed among unrelated individuals and the sample size for the sibling analysis are smaller, decreasing statistical power.

Another strategy involves the comparison of observational studies with a different confounding structure. In this approach, if an association is causal, the association should be observed in every setting, in spite of differing confounding structures. Brion et al (*13*) compared the effect of breastfeeding on blood pressure, body mass index and intelligence quotients in two cohorts, one in the United Kingdom (ALSPAC) where breastfeeding duration is positively associated with family income, and another in Brazil (Pelotas) where there is no such association. In ALSPAC, even after controlling for confounding for socioeconomic status, breastfeeding was inversely related to blood pressure and body mass index and positively with performance in intelligence tests. On the other hand, in Pelotas, breastfeeding was only associated with higher performance in intelligence tests. Therefore, the observed effect of breastfeeding on blood pressure and body mass index may be due to residual confounding,

whereas the higher performance in intelligence tests among subjects who were breastfed is likely to be causal. This approach should be further used; replication of an association across different settings with heterogeneous confounding structure would improve causal inference in observational studies.

Self-selection

In high-income settings, breastfeeding mothers are more likely to be health-conscious, and, therefore, also more likely to promote healthy habits to their infants, including prevention of obesity, promotion of physical activity and intellectual stimulation. For example, cognitive stimulation and emotional support is higher among children who are breastfed (*14*). Because stimulation and emotional support are positively associated with performance in intelligence tests and cognition, studies assessing the long-term consequences of breastfeeding on performance in intelligence tests should adjust their estimates to home stimulation. In this situation, the self-selection bias is measured by proxy, and treated as a confounder.

Even when it is not possible to adjust for proxies for self-selection, this possibility should be considered when interpreting the results.

Adjustment for potential mediating factors

Several studies on the long-term consequences of breastfeeding present estimates of effect that are adjusted for variables that may represent pathways in the causal chain leading from breast feeding to the outcomes being studied. In this review, the most common example was the inclusion of adult weight measures when studying outcomes such as diabetes, hypertension or cholesterol levels, which themselves are influenced by weight.

Adjustment for such mediating factors will tend to underestimate the overall effect of breastfeeding, and the adjusted estimate will only represent the part of the effect that is not mediated by current weight (*15*).

Main sources of heterogeneity among studies

Heterogeneity among studies is unavoidable, and the question is not whether heterogeneity is present, but if it seriously undermines the conclusions. Well-conducted meta-analyses should incorporate a detailed investigation of potential sources of heterogeneity (*16*). The following possible sources of heterogeneity were considered for all reviews in the present meta-analyses.

Year of birth

Studies on the long-term consequence of breastfeeding have included subjects born at different times in the past. During this period, the diets of non-breastfed infants in 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 (*17*), with high sodium concentrations and levels of cholesterol and fatty acids that were similar to those in mature breastmilk. By the 1950s, commercially prepared formulas became increasingly popular. At this time, formulas tended to have high sodium concentrations and low levels of iron and essential fatty acids. Starting in the 1980s, sodium content was reduced and nowadays the majority of formulas have levels that are similar to those in breastmilk (*18*). Therefore, the year of birth of the studied population may affect the long-term effects of breastfeeding, representing a source of heterogeneity among studies. This possibility was investigated in the present review.

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. As previously mentioned, length of recall is related to misclassification of breastfeeding duration. Some studies suggest that bias tends to increase with the time elapsed since weaning, with mothers who breastfed for a short period being more likely to exaggerate breastfeeding duration, while the opposite is observed for women who breastfed for long periods (*10,19*). Therefore, length of recall is a potential source of heterogeneity among studies.

Source of information on breastfeeding duration

Studies on the long-term effect of breastfeeding have usually assessed infant feeding by maternal recall, while others relied on information collected by health workers, or on the subjects' own reports. Marmot et al (*20*) reported that misclassification of the subjects' own infant feeding is higher among subjects who were bottle-fed. The direction of such bias will depend whether or not classification error is associated with factors related to morbidity in adulthood.

Categories of breastfeeding duration

Studies on the long-term effect of breastfeeding have compared different groups according to breastfeeding duration. Some studies compared ever-breastfed subjects to those never breastfed, whereas other studies compared subjects breastfed for less than a given number of months to those breastfed for longer periods. The comparison of ever versus never breastfed makes sense if the first hours of life are considered as a critical window for the programming effect of breastfeeding, for example if an epigenetic mechanism is being postulated (*21*). On the other hand, if there is no critical-window effect, but rather a cumulative effect of breastfeeding, studies that compared ever vs. never breastfed subjects will tend to underestimate any association. The classification of breastfeeding duration is another factor to be considered in heterogeneity analyses.

Study setting

Most of the studies on the long-term consequences of breastfeeding have been carried out in high-income countries. The findings from these studies may not hold for populations exposed to different environmental and nutritional factors because of differences in the type of milk fed to non-breastfed infants. In high-income countries, the babies usually receive industrialized formula, whereas many non-breastfed infants in low and middle income countries receive whole or diluted animal milk.

Most exposures in epidemiological studies (for example, smoking, alcohol drinking, environmental pollutants or specific dietary items) entail a comparison with a group that is not exposed to these risk or protective factors. In contrast, young infants who are not breastfed subjects – the "unexposed" – must receive some type of feeding, and are thus exposed to a variety of foodstuffs, such as industrialized formula, animal milk or traditional weaning foods. The heterogeneity of the unexposed group in breastfeeding studies must be taken into account. This issue is related to the age of the cohort, discussed above, and to the setting of the study, e.g. high or low-income country.

Whenever possible, in light of the information provided by the studies' authors, we tried to assess the role of these variables in the interpretation of the present review.

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··· CHAPTER 3 ···

Search methods

The search methods were exactly the same as in the previous review we published in 2007. Because that review covered articles published before 2006, we updated the search with articles published from 2006 (to allow late inclusion in databases) to September 2011.

Selection criteria for studies

We searched for observational and randomized studies, published in English, French, Spanish or Portuguese that evaluated the associations between breastfeeding and the following outcomes: blood pressure; total cholesterol; overweight/obesity; type-2 diabetes; and performance in intelligence tests. Because we were assessing the long-term effects of breastfeeding, studies in infants were excluded.

Studies that did not use an internal comparison group were excluded. We did not apply any restrictions on the type of categorization of breastfeeding (never versus breastfed, breastfed for more or less than a given number of months, exclusively breastfed for more or less than a given number of months). Instead, as discussed in the previous section, the type of categorization of breastfeeding was considered as possible source of heterogeneity among the studies.

Type of outcome measures

In the present systematic review and meta-analysis, we searched for manuscripts that have assessed 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;
- Performance in intelligence tests: mean difference in performance in intelligence (developmental) tests.

Search strategy

In order to minimize the likelihood of selection bias, we tried to identify as many relevant studies as possible. We carried two independent literature searches, using the terms described below. Initially, we searched Medline (2006 to September 2011) using the following terms for breastfeeding: breastfeeding; breast feeding; breastfed; breastfeed; bottle feeding; bottle fed; bottle feed; infant feeding; human milk; formula milk; formula feed; formula fed; weaning.

Every breastfeeding term was combined with each of the following terms for the 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.

The titles and abstracts of studies initially selected were scanned to exclude those that were obviously irrelevant. The full text of the remaining studies was retrieved and relevant articles were identified. In addition to the electronic search, reference lists of the articles identified was searched, and we perused the Web of Science Citation Index for manuscripts citing the identified articles. Attempts were made to contact the authors of all studies that did not provide sufficient data to estimate the pooled effect. We also contacted the authors to clarify any queries on the study methodology or result.

··· CHAPTER 4 ···

Review methods

In this section we cover methodological aspects related to assessment of study quality, data abstraction and analysis.

Assessment of study characteristics

The following study characteristics were abstracted. These were used for two purposes, namely assessing study quality and examining reasons for heterogeneity among studies. Some studies did not provide information on all characteristics.

TABLE 4.1
Characteristics abstracted from each study

Characteristic	Categorization
Sample size	Continuous
Follow-up rates (if applicable)	Continuous
Type of study	Randomized trial Birth cohort Other
Length of recall of breastfeeding duration	< or >= 3 years
Categorization of breastfeeding	Never versus ever < or >= than X months (any breastfeeding) < or >= than X months (exclusive breastfeeding)
Source of breastfeeding information	Records Interview with the subject Interview with the mother
Control for confounding	None Socioeconomic and demographic variables Socioeconomic, demographic and maternal variables (anthropometry, intellectual stimulation, intelligence, etc, depending on the outcome under study)
Control for potential mediating variables	Yes No
Type of study population	Low income Middle income High income
Year of birth of subjects	Continuous
Age at outcome assessment	Continuous

Data abstraction

Data on the above characteristics were extracted from each study using a standardized protocol. This information was collected by two independent reviewers, with disagreements being resolved by consensus rating.

Data analysis

Pooled effect estimates

In the meta-analyses, effect measures were presented as weighted mean differences for continuous outcomes and pooled odds ratio for dichotomous outcomes. Definition of exposure to breastfeeding followed the classification used in each study. A negative mean difference denoted that breastfed subjects presented a lower value of continuous variables, whereas for dichotomous variables an odds ratio < 1 indicated that breastfed subjects presented a lower odds of the outcome.

Fixed or random-effects model

To pool the studies estimates, we used a fixed and a random-effects model. Under the fixed-effect model, we assume that there is one true effect size and, therefore, the difference among studies results is due to random variation. In the fixed-effect model, studies are weighted by their precision (inverse of the standard error) (*1*). On the other hand, under the random-effects model we assume that the true effects also vary, and thus the pooled effect needs to take into consideration an additional source of variation. In the random-effect model, studies are weighted by their precision plus the estimate of the between studies variance (heterogeneity) (*2*). By incorporating a second source of variability (variance between studies) in the estimate of the variance, the confidence interval in the random-effect model is wider than that for the fixed-effect model. Because the between studies variance is the same for every study, the random-effect model gives greater weight to smaller studies as compared to the fixed-effect model.

In the present meta-analyses, heterogeneity among studies was assessed with the Q-test and I-square; if either method suggests that between-studies variability was higher than that expected by chance, a random-effects model was used (*2*). Otherwise, a fixed-effect model is recommended. In this series of meta-analyses, heterogeneity was evident for all outcomes, and thus random-effects models were used throughout.

Publication bias

Studies reporting statistically significant associations are more likely to be published, and to be cited by others articles. Therefore, these results tend to be included in systematic-review, whereas small studies with negative findings are less often published. Publication bias is more likely to affect small studies because the great amount of resources (time and money) spent in larger studies makes them more likely to be published, regardless of their results (*1*). In meta-analysis, publication bias is a type of selection bias.

In the present meta-analyses, funnel plots and Egger's test were employed to assess the presence of publication bias (*3*). Furthermore, the analysis was stratified according to study size, in order to assess the impact of publication bias on the pooled estimate.

Assessing heterogeneity

The last phase of the analyses relied on meta-regression to assess the contribution of study characteristics to between-study variability (*4*). In this approach, if the data are homogenous or if the heterogeneity is fully explained by the covariates, the random-effects model is reduced to a fixed-effect model. This analysis was performed using the METAREG command within STATA. Each of the items listed in **Table 4.1** were included as covariates in the meta-regression, one at a time, rather than using an overall score. This approach allows the identification of aspects of study design that were responsible for heterogeneity between studies (*5*).

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··· CHAPTER 5 ···

Overweight and obesity

Overweight/obesity increases the risk of several non-communicable diseases, including diabetes, cancer and cardiovascular disease. It has been suggested that breastfeeding may prevent the development of overweight/obesity, not only in early life but also on the long-term (*1*).

Biological plausibility

Several mechanisms have been proposed for a protective effect of breastfeeding against obesity. Protein intake as well as energy metabolism are lower among breastfed subjects (*2*), and it has been suggested that higher protein intake in infancy is associated to the development of later obesity (*3*).

Another possibility is that breastfed and formula-fed infants have different hormonal responses to feeding, with formula leading to a greater insulin response resulting in fat deposition and increased number of adipocytes (*4*).

Finally, it has been proposed that differences in dietary preferences could explain such association. Scholtens et al (*5*) reported that at 7 years of age, Dutch children who had been breastfed for more than 16 weeks had a higher intake of fruit and vegetables than those who were never breastfed. The latter were also less likely to consume white bread, soft drinks, chocolate bars and fried snacks. However, the same study showed that adjustment for diet at 7 years did not change the magnitude of the association between breastfeeding and obesity, thus suggesting that healthier diet among breastfed subjects is not an important pathway.

Specific methodological issues

Methodological issues affecting studies of the long-term consequences of breastfeeding were addressed in **Chapter 2**. As will be discussed in greater detail in **Chapter 9** (breastfeeding and intelligence), breastfeeding mothers are likely to be more health-conscious, and, therefore, to promote healthy habits, which are likely to prevent overweight and obesity later in childhood.

In addition, two methodological issues should be taken into account when studying overweight/obesity as the outcome – use of continuous BMI or of prevalence of overweight or obesity as the outcome, and adjustment for maternal BMI.

Breastfeeding may reduce the variance of weight distribution, decreasing the prevalence of both overweight and underweight in later life (*6,7*). As a consequence, the mean body mass index may not be affected by breastfeeding, in spite of a reduction in the prevalence of overweight/obesity. Studies that only reported an effect on mean BMI were not included in the present meta-analyses, because it would not be possible to combine their results with those reported here. Nevertheless, a previous meta-analysis by Owen et al (*8*) found a very small effect of breastfeeding on mean BMI (-0.04 kg/m^2) in such studies.

Maternal pregestational overweight/obesity is negatively associated with breastfeeding incidence and duration (*9–13*) and positively associated with offspring weight (*14*). For this reason, confounding by maternal anthropometry may overestimate the benefit of breastfeeding.

Overview of existing meta-analysis

In 2007, we carried out a systematic review and meta-analysis that assessed the long-term consequences of breastfeeding duration, in which overweight/obesity was one of the outcomes assessed. In that review, subjects who had been breastfed were less likely to be overweight and/or obese [pooled odds ratio: 0.78 (95% confidence interval: 0.72; 0.84)]. This association was not modified by the presence of control for confounding, year at birth, and age at assessment of body weight. Publication bias was observed, but the pooled effect among large studies (≥ 1500 participants) was similar to that observed in the overall analysis, suggesting that the publication bias did not overestimate of the mean effect

Update of the 2007 meta-analysis

In the present update, the search strategy was the same as in the systematic review published in 2007. We identified 33 new manuscripts that reported the effect of breastfeeding on the prevalence of overweight and/or obesity. Below, we will describe the findings from those new studies whose sample size was > 2000 participants. Smaller studies were also included in the meta-analyses but are not described individually.

Al-Qaoud et al (*15*) evaluated Kuwaiti pre-school children aged 3–6 years, and reported that those who had been breastfed presented higher odds of obesity [1.29 (95% confidence interval: 0.88; 1.90)], but the confidence interval included the unity.

Neutzling et al (*16*) evaluated subjects who have been followed since birth in 1993, in Pelotas, a southern Brazilian city. At 11 years, obesity was more frequent among those children who had been breastfed [odds ratio: 1.34 (95% confidence interval: 0.45; 3.91)]. As in the Kuwaiti study, the confidence interval included the unity.

Procter et al (*17*) linked data on Kansas families from the Pediatric Nutrition Surveillance System and Pregnancy Nutrition Surveillance System, from 1998 to 2002. Breastfeeding for ≥ 9 weeks was not related to overweight/obesity at 4 years [odds ratio: 0.95 (95% confidence interval: 0.75; 1.22)].

Huus et al (*18*) analyzed data from a birth cohort study from Southeast Sweden. At 5 years of age, children who had been exclusively breastfed for ≥ 4 months were somewhat less likely to be considered as obese [odds ratio: 0.82 (95% confidence interval: 0.55; 1.23)] than those who were exclusively breastfed for < 4 months. Again, the confidence interval included the unity.

Scholtens et al (*19*) evaluated 7 year-old children who had been enrolled in a birth cohort study primarily aimed at assessing asthma and mite allergy. Children who had been breastfed for > 16 weeks were less likely to be overweight/obese [odds ratio: 0.76 (95% confidence interval: 0.52; 1.11)], a non-significant difference.

In an English birth cohort study, Toschke et al (*20*) observed that the odds ratio of overweight/obesity was of 1.14 (95% confidence interval: 0.91; 1.43) among those children who had been breastfed for ≥ 6 months in relation to those who had never been breastfed.

Shields et al (*21*) analyzed data from a birth cohort in Brisbaine, Australia, reporting that obesity at 21 years was not related to duration of breastfeeding.

Michels et al (*22*) reported that among women aged 37–54 years, the odds of obesity was similar among subjects who had been exclusively breastfed for > 6 months, compared to those who had never been breastfed [odds ratio: 0.94 (95% confidence interval: 0.83; 1.07).

Fall et al (*23*) in the COHORTS collaboration, a consortium comprising five birth cohort studies from low and middle income countries (Brazil, Guatemala, India, Philippines and South Africa), observed that those subjects who were ever breastfed were less likely to be overweight/obese [odds ratio: 0.84 (95% confidence interval: 0.67; 1.06)], a non-significant difference.

Our meta-analyses covered 71 manuscripts that provided 75 estimates on the association between breastfeeding and overweight/obesity (**Table 5.1**). For cohort studies that provided estimates on the effects of breastfeeding for the same subjects at different age ranges, we included only the most recent follow-up in the main meta-analysis. On the other hand, in the meta-analyses stratified by age groups, we used more than one report from the same study if the results referred to different age ranges. **Figure 5.1** shows that the studies were clearly heterogeneous, and a random-effects model was thus used. Subjects who were breastfed were less likely to be considered as overweight/obese [pooled odds ratio: 0.76 (95% confidence interval: 0.71; 0.81)].

Table 5.2 shows that there was no effect modification by length of recall of breastfeeding, study setting or categorization of breastfeeding. On the other hand, the protective effect of breastfeeding was smaller in studies that assessed the prevalence of overweight/obesity in adults [pooled odds ratio: 0.89 (95% confidence interval: 0.84; 0.96)] rather than in children or adolescents. Other study characteristics also modified the association: the protective effect of breastfeeding was smaller in cohort studies, in studies whose subjects were born before 1980 and in those including adjustment for socioeconomic status, birth condition (birthweight or gestation age) and parental anthropometry. In the meta-regression analysis, three variables explained part of the variance among studies: study size (38.8% of the variance); study design (18.1% of the variance); and age at assessment of BMI (12.6% of the variance).

We further explored the influence of study design in a meta-regression analysis. When study size was not in the model, cohort studies produced odds ratios estimates that were 20% (95% confidence interval: 3%; 41%) higher than cross- sectional studies; the corresponding odds ratios were 0.83 and 0.68, indicating less protection in cohort than cross-sectional studies. After controlling for study size this ratio was reduced to 12% (95% confidence interval: -2%; 28%).Therefore, the observed effect modification by study design was partially explained by differences in sample size, with cohort studies in general being larger than case-control studies.

The presence of effect modification by study size, with small studies reporting larger effects of breastfeeding, suggests the possibility of publication bias. Indeed, the funnel plot is quite asymmetrical (**Figure 5.2**) Egger's test was statistically significant (p-value 0.003).

Our meta-analysis compared groups of children classified according to breastfeeding practices. We did not include the only general population controlled trial on this issue, in which maternity hospitals in Belarus were randomized to receive breastfeeding promotion or no intervention. It was not possible to incorporate results from this study because they compared two groups using intent-to-treat analyses, rather than comparing breastfed versus non breastfed children. This study showed no difference between the intervention and control arms at the age of 6.5 years in terms of BMI or adiposity measures (*24*).

Conclusion

In this updated meta-analysis, we observed an association between breastfeeding and lower prevalence of overweight/obesity later in life. Nevertheless, some methodological issues should be taken into consideration in the assessment of the evidence. A small-study effect (publication bias) is an important issue, tending to overestimate the benefits of breastfeeding. Among studies with ≥ 1500 participants the protective effect of breastfeeding was relatively modest [0.85 (95% confidence interval: 0.80; 0.91)].

Residual confounding is another issue that should be addressed, because most studies were carried out in high-income countries where breastfeeding tends to be more common among the better off and more educated mothers. In these societies, overweight and obesity tend to be more prevalent among the poor, and even studies that adjusted for several socioeconomic variables may still be affected by residual confounding. Attempting to elucidate this possibility, Brion et al (*25*) compared the effects of breastfeeding on body mass index in two settings with different socioeconomic confounding structures. In England, a developed country setting, breastfeeding was protective against overweight, but in Brazil, where breastfeeding does not show a clear social gradient, no such effect was evident. This was confirmed by the negative findings of the COHORTS collaboration from low and middle-income countries (*23*). Therefore, residual confounding by socioeconomic status is an issue that should be taken into consideration in the assessment of causality. By the same token, we observed that studies with tighter control of confounding (socioeconomic factors, birth weight or gestational age, and parental anthropometry) reported smaller benefits of breastfeeding.

In order to reduce the influence of publication bias and residual confounding, we estimated the pooled effect among those studies with large sample size and that controlled for confounding by socioeconomic, birth weight or gestational age, and parental anthropometry. The pooled odds ratio in the 16 studies that fulfilled both criteria was 0.88 (95% confidence interval: 0.83; 0.93), suggesting that the protective effect of breastfeeding may be overestimated by publication bias and residual confounding.

Our conclusion is that the meta-analysis of higher-quality studies suggests a small reduction, of about 10%, in the prevalence of overweight or obesity in children exposed to longer durations of breastfeeding. Nevertheless, it is not possible to completely rule out residual confounding because in most study settings breastfeeding duration was higher in families where the parents were more educated and had higher income levels.

TABLE 5.1

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	Year of birth of subjects	Study design	Mean age at measurement	Gender	Comparison groups	Outcome	Odds ratio (95% confidence interval)
Jingxiong, 2009 (*26*)	2003–2004	Case-control	1 year	All	Exclusively breastfed for > 4 months vs. Exclusively breastfed for ≤ 4 months	Overweight or obesity	0.47 (0.25; 0.87)
Weyermann, 2006 (*27*)	2000–2001	Cohort	2 years	All	Breastfed for ≥ 6 months vs. Breastfed for < 3 months	Overweight or obesity	0.4 (0.2; 0.8)
Poulton, 2001 (*28*)	1972–1973	Cohort	3 years	All	Breastfed for > 6 months vs. Never breastfed	Overweight or obesity	0.86 (0.44; 1.65)
Armstrong, 2002 (*29*)	1995–1996	Cohort	3 years	All	Exclusively breastfed vs. Bottle fed at 6–8 months	Obesity	0.72 (0.65. 0.79)
Taveras, 2006 (*30*)	Not stated	Cohort	3 years	All	No infant formula feeding during the first 6 months of life vs. Not breastfed at 6 months	Overweight or obesity	0.33 (0.13; 0.84)
Dennison, 2006 (*31*)	1995–1999	Cross-sectional	4 years	All	Breastfed ≥ 1 month vs. Never breastfed	Obesity	0.73 (0.48; 1.13)
Strbak, 1991 (*32*)	Not stated	Cohort	4 years	All	Breastfed for > 1 month vs. Breastfed < 2 weeks	Obesity	0.84 (0.41; 1.72)
Hediger 2001 (*33*)	1983–1991	Cross-sectional	4 years	All	Ever breastfed vs. Never breastfed	Obesity	0.84 (0.62; 1.13)
Grummer-Strawn, 200 (*46*)	1988–1992	Cohort	4 years	All	Breastfed for ≥ 12 months vs. Never breastfed	Overweight or obesity	0.72 (0.65; 0.80)
Li, 2005 (*34*)	1990–1994	Cohort	4 years	All	Breastfed for ≥ 4 months vs. Never breastfed	Obesity	0.6 (0.3; 1.3)
Dubois, 2006 (*35*)	1998	Cohort	4 years	All	Breastfed for ≥ 3 months vs. Breastfed for < 3 months	Obesity	1.0 (0.7; 1.5)
Araujo, 2006 (*36*)	1993	Cohort	4 years	All	Ever breastfed vs. Never breastfed	Overweight or obesity	1.83 (0.53; 6.28)
Moschonis, 2008 (*37*)	1998–2001	Cross-sectional	4 years	All	Exclusive breastfeeding for ≥ 6 months vs. Never breastfed	Overweight or obesity	0.94 (0.65; 1.35)
Procter, 2008 (*17*)	1998	Cohort	4 years	All	Breastfed for ≥ 9 months vs. Never breastfed	Overweight or obesity	0.95 (0.75; 1.22)
Al-Qaoud, 2009 (*15*)	Not stated	Cross-sectional	4 years	All	Ever breastfed vs. Never breastfed	Obesity	1.29 (0.88; 1.90)
Komatsu, 2009 (*38*)	2002–2006	Cross-sectional	4 years	All	Exclusively breastfed for ≥ 6 months vs. Exclusively breastfed for < 6 months	Overweight or obesity	0.46 (0.15; 1.37)
Simon, 2009 (*39*)	1988–2003	Cross-sectional	4 years	All	Exclusively breastfed for ≥ 6 months vs. Exclusively breastfed for < 6 months	Overweight or obesity	0.57 (0.38; 0.86)
Balaban, 2010 (*40*)	Not stated	Case-control	4 years	All	Breastfed for ≥ 4 months vs. Breastfed for < 4 months	Overweight or obesity	0.70 (0.43; 1.16)

Author, Year	Year of birth of subjects	Study design	Mean age at measurement	Gender	Comparison groups	Outcome	Odds ratio (95% confidence interval)
Gewa, 2010 (*41*)	2002–2006	Cross-sectional	4 years	All	Breastfed for > 24 months vs. Breastfed for < 12 months	Overweight or obesity	0.55 (0.32; 0.94)
Twells, 2010 (*42*)	2001	Cross-sectional	4 years	All	Exclusively breastfed for ≥ 3 months vs. Never breastfed	Obesity	0.66 (0.45; 0.97)
O'Callaghan, 1997 (*43*)	1981–1984	Cohort	5 years	All	Ever breastfed vs. Never breastfed	Obesity	0.71 (0.43; 1.25)
von Kries, 1999 (*44*)	1991–1992	Cross-sectional	5 years	All	Ever breatfed vs. Never breastfed	Obesity	0.75 (0.57; 0.98)
He, 2000 (*45*)	1989–1993	Case control	5 years	All	Breastfed vs. Never breastfed	Obesity	1.18 (0.91; 1.54)
Scaglioni, 2000 (*46*)	1991	Cohort	5 years	All	Ever breastfed vs. Never breastfed	Overweight or obesity	0.66 (0.25; 1.78)
Burdette, 2006 (*47*)	Not stated	Cohort	5 years	All	Ever breastfed vs. Never breastfed	Overweight or obesity	0.79 (0.44; 1.46)
Schaefer-Graf, 2006 (*48*)	1995–2000	Cross-sectional	5 years	All	Breastfed for > 3 months vs. Breastfed for ≤ 3 months	Overweight or obesity	0.55 (0.33; 0.91)
Huus, 2008 (*18*)	1997–1999	Cohort	5 years	All	Exclusively breastfed for ≥ 4 months vs. Exclusively breastfed for < 4 months	Obesity	0.82 (0.55; 1.23)
Wadsworth, 1999 (*49*)	1946	Cohort	6 years	All	Ever breastfed vs. Never breastfed	Obesity	0.83 (0.65; 1.04)
Thorsdottir, 2003 (*50*)	Not stated	Cohort	6 years	Male	Breastfed for ≥ 6 months vs. Breastfed for < 6 months	Overweight or obesity	0.33 (0.13; 0.83)
Li, 2003 (*51*)	1983–1987	Cross-sectional	6 years	All	Breastfed for > 9 months vs. Breastfed for < 1 week	Obesity	0.61 (0.28; 1.32)
Bergmann, 2003 (*52*)	1990	Cohort	6 years	All	Breastfed for ≥ 3 months vs. Breastfed for < 3 months	Obesity	0.46 (0.23; 0.92)
Richter, 1981 (*53*)	1957–1959	Cohort	7 years	All	Ever breastfed vs. Never breastfed	Obesity	0.73 (0.51; 1.07)
Scholtens, 2007 (*19*)	1996–1997	Cohort	7 years	All	Breastfed for > 16 weeks vs. Breastfed for ≤ 16 weeks	Overweight or obesity	0.76 (0.52; 1.11)
Buyken, 2008 (*54*)	1984–1999	Cohort	7 years	M	Breastfed for > 4 months vs. Never breastfed	Overweight or obesity	0.70 (0.27; 1.74)
				F	Breastfed for > 4 months vs. Never breastfed	Overweight or obesity	1.11 (0.50; 2.44)
Kwok, 2010 (*55*)	1997	Cohort	7 years	All	Exclusively breastfed for ≥ 3 months vs. Never breastfed	Overweight of obesity	1.09 (0.83; 1.43)
Eid, 1970 (*56*)	1961	Cohort	8 years	All	Breastfed vs. Bottle fed	Obesity	0.42 (0.11; 1.61)
Maffeis, 1994 (*57*)	Not stated	Cross-sectional	8 years	All	Not stated	Obesity	0.91 (0.69; 1.21)
Liese, 2001 (*58*)	1985–1987	Cross-sectional	9 years	All	Ever breastfed vs. Never breastfed	Overweight or obesity	0.66 (0.52; 0.87)
Frye, 2003 (*59*)	1978–1994	Cross-sectional	9 years	All	Exclusively breastfed for > 12 weeks vs. Never breastfed	Obesity	0.60 (0.40; 0.90)

Author, Year	Year of birth of subjects	Study design	Mean age at measurement	Gender	Comparison groups	Outcome	Odds ratio (95% confidence interval)
Mai, 2007 (*60*)	1995	Case-control	9 years	All	Exclusively breastfed for ≥ 12 weeks vs. Exclusively breastfed for < 12 weeks	Overweight or obesity	0.55 (0.39; 0.77)
Toschke, 2007 (*20*)	1991–1992	Cohort	9 years	All	Breastfed for ≥ 6 months vs. Never breastfed	Obesity	1.40 (0.92; 2.14)
Toschke, 2002 (*61*)	1977–1985	Cross-sectional	10 years	All	Ever breastfed vs. Never breastfed	Obesity	0.80 (0.66; 0.96)
Sung, 2003 (*62*)	1990	Cross-sectional	10 years	All	Breastfed vs. Bottle fed	Overweight or obesity	0.45 (0.27; 0.78)
Siqueira, 2007 (*63*)	1990–1998	Cross-sectional	10 years	All	Ever breastfed vs. Never breastfed	Obesity	0.49 (0.24; 0.98)
Poulton, 2001 (*28*)	1972–1973	Cohort	11 years	All	Breastfed for > 6 months vs. Never breastfed	Overweight or obesity	0.36 (0.1; 1.28)
Panagiotakos, 2008 (*64*)	Not stated	Cross-sectional	11 years	Male	Breastfeeding for > 3 months vs. Never breastfed	Overweight or obesity	0.28 (0.09; 0.84)
				Female	Breastfeeding for > 3 months vs. Never breastfed	Overweight or obesity	0.19 (0.06; 0.65)
Neutzling, 2009 (*16*)	1993	Cohort	11 years	All	Ever breastfed vs. Never breastfed	Obesity	1.34 (0.45; 3.91)
Sabanayagam, 2009 (*65*)	Not stated	Cohort	11 years	All	Ever breastfed vs. Never breastfed	Overweight or obesity	1.14 (0.80; 1.63)
Papandreou, 2010 (*66*)	Not stated	Cross-sectional	11 years	All	Breastfeeding for ≥ 3 months vs. Breastfed for < 3 months	Overweight or obesity	0.21 (0.11; 0.79)
Gillman 2001 (*1*)	Not stated	Cross-sectional	12 years	All	Mostly or only breastfed vs. Mostly or only formula fed	Obesity	0.78 (0.66; 0.91)
Li, 2005 (*34*)	1982–1985	Cohort	12 years	All	Breastfed for ≥ 4 months vs. Never breastfed	Obesity	0.6 (0.3; 1.6)
Fallahzadeh, 2009 (*67*)	Not stated	Cross-sectional	12 years	All	Breastfeeding for ≥ 24 months vs. Breastfeeding for < 12 months	Obesity	0.53 (0.31; 1.01)
Li, 2003 (*51*)	1973–1982	Cross-sectional	13 years	All	Breastfed for > 9 months vs. Breastfed for < 1 week	Obesity	0.73 (0.23; 2.27)
Elliott, 1997 (*68*)	1977–1980	Cohort	14 years	All	Breastfed for ≥ 2 months vs. Breastfed for < 2 months	Overweight or obesity	0.51 (0.22; 1.16)
Shields, 2006 (*69*)	1981–1984	Cohort	14 years	All	Breastfed for ≥ 4 months vs. Never breastfed	Obesity	0.92 (0.6; 1.5)
Woo, 2008 (*70*)	Not stated	Cross-sectional	14 years	Black	Breastfeeding for > 4 months vs. Never breastfed	0.50 (0.20; 1.27)	
				White	Breastfeeding for > 4 months vs. Never breastfed	Overweight or obesity	0.48 (0.32; 0.74)
Metzger, 2010 (*71*)	Not stated	Cohort	14 years	All	Ever breastfed vs. Never breastfed	Overweight or obesity	0.44 (0.03; 0.85)
Kramer, 1981 (*72*)	Not stated	Case-control	15 years	All	Ever breastfed vs. Never breastfed	Obesity	0.44 (0.21; 0.93)

Author, Year	Year of birth of subjects	Study design	Mean age at measurement	Gender	Comparison groups	Outcome	Odds ratio (95% confidence interval)
Kramer, 1981 (*72*)	Not stated	Case-control	15 years	All	Ever breastfed vs. Never breastfed	Obesity	0.29 (0.11; 0.75)
Tulldahl, 1999 (*73*)	1979	Cohort	15 years	All	Breastfed for > 2 months vs. Breastfed for ≤ 2 months	Overweight or obesity	0.66 (0.44; 0.98)
Victora, 2003 (*74*)	1982	Cohort	18 years	Male	Breastfed for ≥ 1 month vs. Breastfed for < 1 month	Obesity	0.73 (0.50; 1.07)
Poulton, 2001 (*28*)	1972–1973	Cohort	21 years	All	Breastfed for > 6 months vs. Never breastfed	Overweight or obesity	0.79 (0.46; 1.34)
Shields, 2010 (*21*)	1981–1983	Cohort	21 years	All	Breastfed for > 4 months vs. Never breastfed	Obesity	0.93 (0.63; 1.39)
Fall, 2011 (*23*)	1969-1990	Cohort	25 years	All	Ever breastfed vs. Never breastfed	Overweight or obesity	0.84 (0.67; 1.06)
Parsons, 2003 (*75*)	1958	Cohort	33 years	Males	Breastfed for > 1 month vs. Never breastfed	Obesity	0.93 (0.74; 1.17)
				Females	Breastfed for > 1 month vs. Never breastfed	Obesity	0.84 (0.67; 1.05)
Kvaavik, 2005 (*76*)	1966	Cohort	33 years	All	Breastfed for ≥ 4 month vs. Never breastfed	Obesity	0.34 (0.12; 1.01)
Parikh, 2009 (*77*)	Not stated	Cohort	41 years	All	Ever breastfed vs. Never breastfed	Obesity	0.75 (0.47; 1.21)
Michels, 2007 (*22*)	1947–1964	Cohort	45 years	Female	Exclusively breastfed for > 6 months vs. Never breastfed	Obesity	0.94 (0.83; 1.07)
Rudnicka, 2007 (*78*)	1958	Cohort	45 years	All	Breastfed for > 1 month vs. Never breastfed	Obesity	0.85 (0.75; 0.97)
Eriksson, 2003 (*79*)	1934–1944	Cohort	61 years	All	Breastfed for > 8 months vs. Breastfed for < 2 months	Obesity	1.10 (0.88; 1.37)
O'Tierney, 2009 (*80*)	1934–1944	Cohort	62 years	All	Breastfed for ≥ 8 months vs. Breastfed for < 2 months		0.75 (0.50; 1.11)

TABLE 5.2

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	42	0.77 (0.71; 0.83)	< 0.001
10 to 19 years	22	0.62 (0.53; 0.73)	< 0.001
≥ 20 years	11	0.89 (0.84; 0.96)	0.001
By study size			
< 500 participants	17	0.51 (0.42; 0.61)	< 0.001
500–1499 participants	24	0.65 (0.56; 0.76)	< 0.001
≥ 1500 participants	27	0.85 (0.80; 0.91)	< 0.001
By year at birth			
Before 1980	14	0.87 (0.80; 0.94)	< 0.001
After 1980	35	0.76 (0.70; 0.83)	< 0.001
By study design			
Cohort	38	0.83 (0.77; 0.89)	< 0.001
Case-control	6	0.60 (0.39; 0.92)	0.02
Cross-sectional	24	0.68 (0.60; 0.76)	< 0.001
By length of recall of breastfeeding			
< 3 years	29	0.80 (0.73; 0.88)	< 0.001
≥ 3 years	39	0.73 (0.67; 0.80)	< 0.001
By control for confounding			
None	17	0.66 (0.54; 0.82)	< 0.001
Adjusted for socioeconomic status	5	0.63 (0.52; 0.76)	< 0.001
Also adjusted for birth condition	12	0.77 (0.69; 0.86)	< 0.001
Also adjusted for parental anthropometry	34	0.81 (0.75; 0.88)	< 0.001
By setting			
High income country	48	0.76 (0.71; 0.81)	< 0.001
Middle /low income country	20	0.75 (0.64; 0.89)	0.001
By categorization of breastfeeding			
Ever breastfed	20	0.79 (0.70; 0.90)	< 0.001
Breastfed for a given number of months	35	0.74 (0.67; 0.82)	< 0.001
Exclusively breastfed for a given number of months	12	0.73 (0.62; 0.85)	< 0.001
Total	**75**	**0.76 (0.71; 0.81)**	

Note: The total number of studies does not add to 75, due to exclusion of studies with repeated report on the effect of breastfeeding (7 studies), one study with missing information on categorization of breastfeeding and 19 studies with missing information on year of birth of subjects.

FIGURE 5.1

Odds ratio and its 95% confidence interval of being considered as overweight/obese, comparing breastfed vs. not-breastfed subjects in different studies. Whether the estimate was for males (M), females (F) and all(A) is indicated in parenthesis.

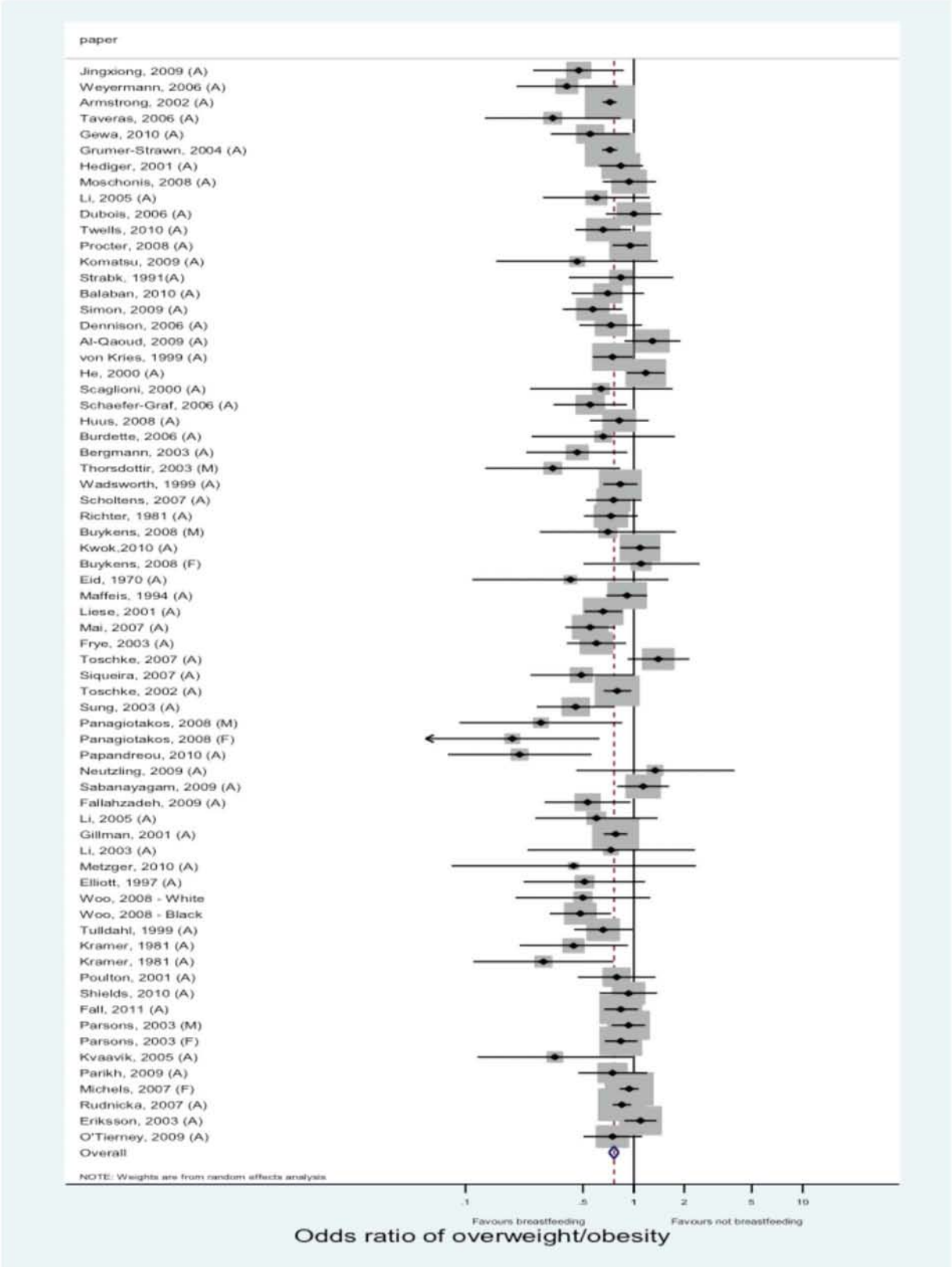
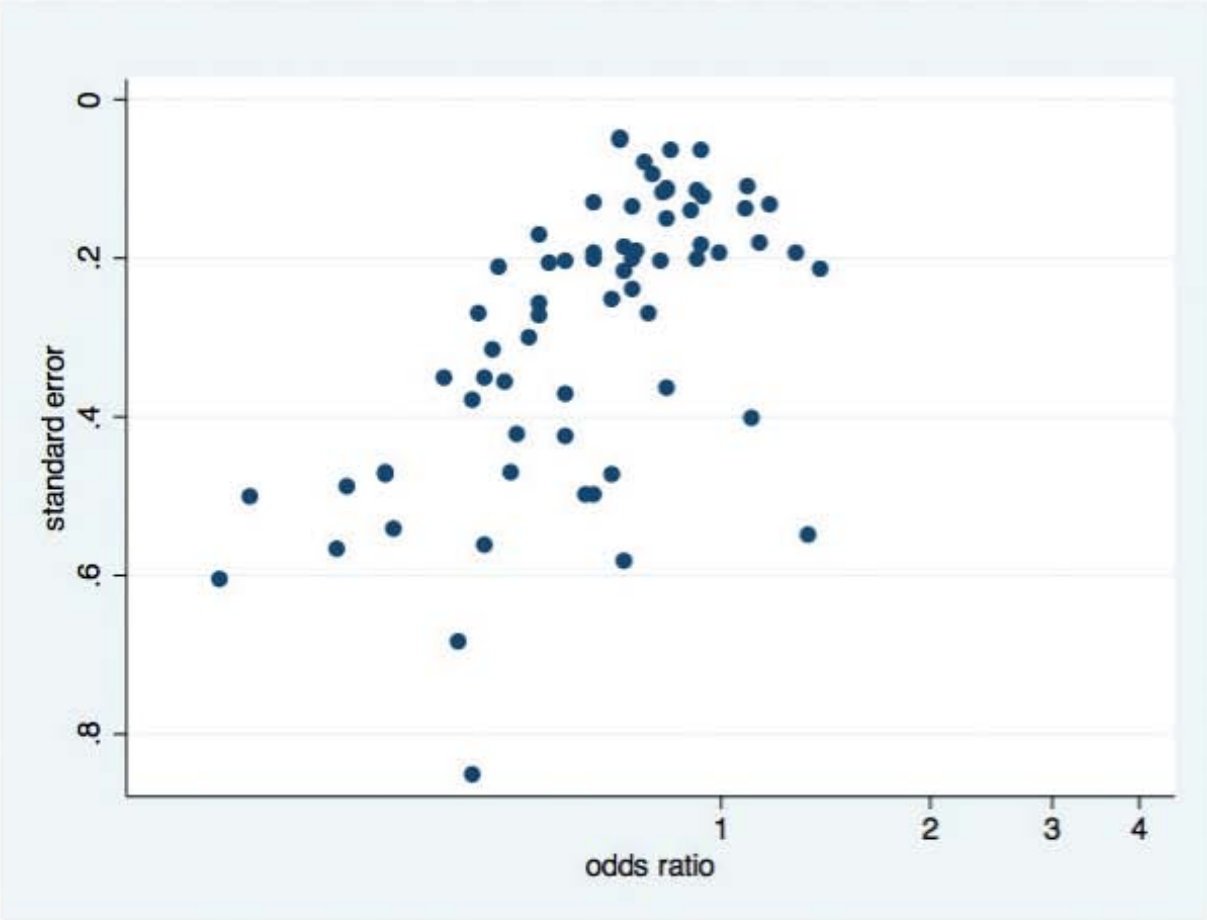


FIGURE 5.2
Funnel plot showing odds ratio for overweight/obesity by standard error of odds ratio



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··· CHAPTER 6 ···

Blood pressure

Cardiovascular diseases is the leading cause of death worldwide, and blood pressure is positively associated with the risk of stroke and ischemic heart disease (*1*). It has been suggested that the development of noncommunicable diseases may be programmed by exposures in early life (*2,3*).

Biological plausibility

Until the 1980s the sodium content of formulas in Western countries was much lower than that of breastmilk (*4*). Because sodium intake in infancy is positively associated to blood pressure (*5*), differences in sodium content between breastmilk and formula might be a potential mechanism for the programming of later blood pressure. However, evidence on such a programming effect are scarce and inconsistent (*6,7*). As a consequence, there is no consensus on whether the sodium content of infant diets is associated with later blood pressure.

Long-chain polyunsaturated fatty acids (LCPUFAs), such as docosahexanoic acid (DHA) and arachidonic acid (AA), are present in breastmilk but not in most brands of formula (*8*). These fatty acids are an important structural component of the vascular endothelium, and evidence suggests that supplementation with LCPUFAs reduces blood pressure in adult hypertensive subjects (*9*). In infants, the synthesis of DHA and AA is limited, and LCPUFAs levels in nonsupplemented formula-fed infants tends to be low. Therefore, LCPUFAs levels might be a potential mechanism for the long-term effect of breastfeeding on blood pressure. However, evidence on the long-term consequences of LCPUFA supplementation in infancy on blood pressure is controversial. Forsyth et al (*10*) reported lower blood pressure at 6 years among formula-fed children who had been assigned to receive a formula supplemented with LCPUFAs, compared to those receiving standard formula. In contrast, de Jong et al (*11*) reported that mean blood pressure levels at 9 years were similar in formula-fed infants supplemented with LCPUFAs and in a control group.

It has been suggested that breastfeeding protects against obesity (*12*). Because blood pressure is directly correlated to body weight, one would expect breastfeeding to also protect against high blood pressure. Nevertheless, **Chapter 5** of the present review suggests a weak association between breastfeeding and overweight or obesity. As a consequence, it is unlikely that prevention of obesity would consist an important mechanism for the association between breastfeeding and blood pressure.

Insulin-like growth factor 1 (IGF-1) is inversely related to blood pressure in adulthood (*13*) .3 It has been suggested that IGF-1 later in life is positively associated with breastfeeding (*14*), and consequently IGF-1 programming may constitute a pathway for the programming of later blood pressure by breastfeeding.

Summing up, although several pathways have been proposed to explain why breastfeeding might protect against high blood pressure, there is limited actual evidence on such mechanisms.

Overview of the evidence

In 2007, we carried out a systematic review and meta-analysis on the long-term consequences of breastfeeding duration, with systolic and diastolic blood pressure included among the outcomes. In that review, systolic [mean difference: -1.21 mmHg; 95% confidence interval: -1.72; -0.70)] and diastolic [mean difference: -0.49 mmHg; 95% confidence interval: -0.87; -0.11)] blood pressure were lower among breastfed subjects. Publication bias was evident and tended to overestimate the benefit of breastfeeding, as among those studies with ≥ 1000 participants the mean difference in systolic blood pressure was of -0.59 mmHg (95% confidence interval: -1.00; -0.19).

Update of the 2007 meta-analysis

We used the same search strategy as in the 2007 systematic review. The additional studies identified in this new search are described below.

Järvisalo et al (*15*) assessed endothelial function and cardiovascular risk factors among subjects aged between 24 and 39 years who have been followed for 21 years. The manuscript only provided unadjusted estimates, with systolic blood pressure being lower among females who had been breastfed, with no association among males.

Holmes et al (*16*) reported that breastfeeding was not related to blood pressure among subjects aged between 20 and 25 years who have been followed since adolescence.

de Jonge et al (*17*) observed that durations of total or exclusive breastfeeding were not associated with blood pressure at 2 years of age, even after adjustment for possible confounding variables.

Naghettini et al (*18*) evaluated factors related to blood pressure among children aged 3 to 10 years. In crude analysis, the authors reported that systolic blood pressure was lower among subjects who were predominantly breastfed for at least 6 months.

Fall et al (*19*) in the COHORTS collaboration, a consortium comprising five birth cohort studies from low and middle income countries (Brazil, Guatemala, India, Philippines and South Africa), observed that blood pressure levels were similar among ever and never breastfed subjects. Additional analyses showed a U-shaped association between breastfeeding duration and both systolic blood pressure and hypertension, with the lowest mean levels observed in subjects breastfed for 3 to 6 months.

Rudnicka et al (*20*) evaluated subjects who have been followed since birth in 1958, in England, Wales and Scotland. At 44–45 years of age, breastfeeding (never versus > 1 month) was not associated with blood pressure.

Brion et al (*21*) compared the effect of breastfeeding on blood pressure in two cohorts (Pelotas, Brazil and ALSPAC, England). Because the confounding structure differs between the two sites, this approach improves causal inference by exploring the likelihood of residual confounding. In the present meta-analysis, we incorporated only the results for the Pelotas site, as the results for ALSPAC had already been included (*22*). In Pelotas, where there is no confounding of breastfeeding by socioeconomic position, breastfeeding duration was not associated with blood pressure at the mean age of 11 years.

Evelein et al (*23*) assessed the cardiovascular effect of exclusive breastfeeding. Carotid intima-media thickness, distensibility and elastic modulus at mean age of 5 years were the main outcomes. Children who were breastfed for 3 to 6 months presented higher carotid intima-media thickness. Only unadjusted results were reported, with no association between exclusive breastfeeding and blood pressure.

Our updated meta-analysis included 36 studies that provided 37 estimates on the effect of breastfeeding on blood pressure (**Table 6.1**). **Figure 6.1** and **6.2** show the forest plot for systolic and diastolic blood pressure. Because there was marked heterogeneity among studies, a random-effect model was used to pool the estimates. Systolic [mean effect -1.02 (95% confidence interval: -1.45; -0.59)] and diastolic [mean effect -0.37 (95% confidence interval: -0.71; -0.04)] blood pressure were lower among subjects who were breastfed.

Similar to the 2007 meta-analysis, publication bias was clearly present (**Figure 6.3** and **6.4**). Furthermore, **Table 6.2** shows that sample size was inversely related to the mean difference in systolic and diastolic blood pressure. Among those studies whose sample size was ≥ 1000 participants, the mean difference between breastfed and non-breastfed subjects in systolic blood pressure was of -0.48 (95% confidence interval: -0.85; -0.12). This suggests that publication bias has contributed to overestimating the benefits of breastfeeding.

Table 6.2 also shows that the mean difference was smaller among those studies that measured blood pressure at ≥ 20 years. Year of age of the subject, length of recall of breastfeeding and study setting did not modify the effect of breastfeeding on blood pressure. On the other hand, those studies that compared ever versus never breastfed subjects, rather than those breastfed for more or less than a given cutoff in months, found slightly smaller effects on systolic blood pressure levels.

Table 6.2 also shows marked effect modification by control of confounding. For systolic blood pressure, the mean difference among those studies providing only crude estimates was -1.53 (95% confidence interval: -2.51; -0.56), whereas among those studies that adjusted for socioeconomic and demographic variables the mean difference was -0.80 (95% confidence interval: -1.38; -0.21).

We also assessed the role of the study characteristics presented in **Table 6.2** on the heterogeneity among studies. Sample size was the important characteristic, accounting for 34.9% of the overall heterogeneity.

Studies not included in the present review

Khan et al (*24*) assessed vascular function among subjects aged 11 to 14 years who have been followed since birth in Dundee, Scotland. In the crude analysis, systolic blood pressure [-3.1 (95% confidence interval:-6.16; -0.04)] and diastolic blood pressure [-1.1 (95% confidence interval: -3.82; 1.62)] were lower among breastfed subjects. Because Wilson et al (*25*) reported confounder-adjusted estimates from the same cohort at ages 6 to 9 years, we did not include the results by Khan et al (*24*).

We also did not include the cluster randomized trial on promotion of breastfeeding by Kramer et al (*26*) in Belarus, in which 16 maternity hospitals and surrounding clinics were randomly assigned to receive an intervention based in the Baby-Friendly Hospital Initiative. The prevalence of predominant and exclusive breastfeeding at 3 and 6 months was higher in the intervention group, but systolic blood pressure levels at six years of age differed by only 0.2 mmHg (standard error 1.58). For diastolic blood pressure, the difference was also 0.2 mmHg (standard error 1.02). These estimates could not be included in the meta-analyses because the analysis was based in the intention to treat analysis and both groups included breastfed and non-breastfed subjects.

Conclusion

In the assessment of the evidence on the long-term consequence of breastfeeding on blood pressure, publication bias and residual confounding are two methodological issues that must be taken into consideration. With respect to publication bias, we observed that small studies provided estimates that clearly overstated the benefits of breastfeeding. Among studies with sample sizes greater than 1000 subjects), the benefit of breastfeeding was modest.

Control of confounding by socioeconomic and demographic factors led to smaller reported effects of breastfeeding. This is consistent with the study by Brion et al (*21*) comparing two cohorts with different socioeconomic confounding structures, which is discussed above. In addition, the only randomized trial on this issue did not find an association.

In order to estimate the impact of publication bias and confounding, we pooled the estimates of seven studies with large sample sizes (> 1000 participants) that provided estimates adjusted for socioeconomic status and demographic variables. The mean effect was – 0.71 (95% confidence interval: -1.24; -0.19) for systolic and -0.27 (-0.64; 0.09) for diastolic pressure.

These findings are consistent with a small protective effect of breastfeeding against systolic blood pressure, but residual confounding cannot be ruled out.

TABLE 6.1

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	Study design	Year of birth of subjects	Mean age at blood pressure measurement	Gender	Comparison groups	Mean difference in mmHg (Standard error of mean difference)	
						Systolic blood pressure	Diastolic blood pressure
Boulton, 1981 (*27*)	Cross-sectional	1976–9	1 year	All	Breastfed for ≥ 3 months vs. Formula fed from < 3 months	-4.11 (SE 3.12)	Not stated
Zeman, 1981 (*28*)	Cross-sectional	Not stated	1 year	All	Breastfed vs. Bottle fed	-4.91 (SE 2.10)	0.33 (SE 0.90)
Jonge, 2010 (*17*)	Cohort	2002–2006	2 years	All	Ever breastfed vs. Never breastfed	-0.45 (SE 1.42)	-0.85 (SE 1.47)
Baranowski, 1992 (*29*)	Cross-sectional	1981–1983	3 years	All	Exclusively breastfed for ≥ 3 months vs. Bottle fed	-2.17 (SE 1.61)	0.48 (SE 1.42)
Forsyth, 2003 (*10*)	Cohort	1992	5 years	All	Breastfed vs. Formula fed	-2.2 (SE 1.6)	-3.4 (SE 1.4)
Lawlor, 2004 (*30*)	Cohort	1981–1984	5 years	All	Breastfed for ≥ 6 months vs. Breastfed for < 6 months	-1.19 (SE 0.4)	Not stated
Evelein, 2011 (*23*)	Cohort	2001	5 years	ÀII	Exclusively breastfed > 6 months vs. Never breastfed	-0.1 (SE 1.67)	1.7 (SE 1.39)
Whincup, 1989 (*31*)	Cross-sectional	1979–1983	7 years	All	Exclusively breast for first 3 months vs. Bottle fed	-0.20 (SE 0.33)	-0.26 (SE 0.23)
Williams, 1992 (*32*)	Cohort	1972–1973	7 years	All	Exclusively breastfed (median 28 wk) vs. Bottle fed	-0.5 (SE 0.66)	-0.7 (SE 0.61)
Naghettini, 2010 (*18*)	Cross-sectional	1996–2003	7 years	All	Predominantly breastfed ≥ 6 months vs. Predominantly breastfed < 6 months	-1.52 (SE 0.86)	Not stated
Wilson, 1998 (*25*)	Cohort	1983–1986	8 years	All	Exclusively breastfed for > 15 wk vs. Bottle fed	-2.84 (SE 1.40)	-1.79 (SE 1.23)
Martin, 2004 (*22*)	Cohort	1991–1992	6–9 years	All	Ever breastfed vs. Never breastfed	-0.8 (SE 0.4)	-0.6 (SE (0.3)
Lucas, 1994 (*33*)	Randomized controlled trial	1982–1985	8 years	All	Allocated to banked breastmilk vs. Allocated to preterm formula	0.1 (SE 1.55)	-0.7 (SE 1.32)
Rona, 1996 (*34*)	Cross-sectional (England 1993 sample)	1983–1985	9 years	All	Exclusively breastfed for ≥ 3 months vs. Bottle fed	1.46 (SE 0.84)	2.54 (SE 0.76)
Rona, 1996 (*34*)	Cross-sectional (England 1994 sample)	1984–1986	9 years	All	Exclusively breastfed for ≥ 3 months vs. Bottle fed	-2.75 (SE 0.86)	-2.34 (SE 0.75)
Rona, 1996 (*34*)	Cross-sectional (Scotland 1994 sample)	1983–1986	9 years	All	Exclusively breastfed for ≥ 3 months vs. Bottle fed	-1.29 (SE 1.01)	-0.97 (SE 0.84)
Esposito-Del Puente, 1994 (*35*)	Cross-sectional	1980–1982	10 years	All	Breastfed vs. Bottle fed	-4.13 (SE 2.86)	0.11 (SE 0.86)

Author, year	Study design	Year of birth of subjects	Mean age at blood pressure measurement	Gender	Comparison groups	Mean difference in mmHg (Standard error of mean difference)	
						Systolic blood pressure	Diastolic blood pressure
British Cohort Study, 1982 (*36*)	Cohort	1970	10 years	All	Breastfed for ≥ 3 months vs. Never breast fed	-0.16 (SE 0.38)	-0.21 (SE 0.33)
Brion, 2011 (*21*)	Cohort	1993	11 years	All	Breastfed ≥ 6 months vs. Breastfed < 1 month	-0.50 (SE 1.19)	-0.29 (SE 0.93)
Lawlor, 2005 (*37*)	Cross-sectional	Not stated	12 years	All	Exclusively breastfed vs. Not exclusively breastfed	-1.7 (SE 0.66)	Not stated
Singhal, 200 (*16*)	Randomized controlled trial	1982–1985	15 years	All	Allocated to banked breastmilk vs. Allocated to preterm formula	-2.7 (SE 1.52)	-3.2 (SE 1.31)
Owen, 2003 (*38*)	Cross-sectional	1982–1986	15 years	All	Exclusively breastfed for ≥ 3 months vs. Never breastfed	0.32 (SE 0.64)	-0.17 (SE 0.35)
Taittonen, 1996 (*39*)	Cohort	1962–1974	18 years	All	Breastfed > 3 months vs. Bottle fed	-5.48 (SE 1.14)	Not stated
Williams, 1992 (*32*)	Cohort	1972–1973	18 years	All	Exclusively breastfed (median 28 wk) vs. Bottle fed	-2.63 (SE 1.34)	-2.66 (SE 1.36)
Kolacek, 1993 (*40*)	Cohortr	1968–1969	21 years	All	Exclusively breastfed for ≥ 3 months vs. Never breastfed	0.00 (SE 1.96)	0.75 (SE 1.40)
Holmes, 2010 (*16*)	Cohort	1964-1968	22 years	All	Ever breastfed vs. Never breastfed	0.3 (SE 1.45)	1.5 (SE 1.17)
Leeson, 2001 (*41*)	Cross-sectional	1969-1975	24 years	All	Breastfed vs. Bottle fed	0.00 (SE 1.55)	-1.00 (0.94)
Martin, 2003 (*42*)	Cohort	1972–1974	25 years	All	Lowest vs. Highest quartile of dried formula consumption at age 3 months	-3.7 (SE 1.38)	-1.4 (SE 0.97)
Fall, 2011 (*19*)	Cohort	1969–1990	25 years	All	Ever breastfed vs. Never breastfed	-0.71 (SE 0.57)	-0.55 (SE 0.48)
Järvisalo, 2009 (*15*)	Cohort	1962–1977	31 years	M	Ever breastfed vs. Never breastfed	-1 (SE 1.77)	2 (SE 1.61)
				F	Ever breastfed vs. Never breastfed	-3 (SE 1.51)	-2 (SE 1.26)
Rudnicka, 2007 (*20*)	Cohort	1958	45 years	All	Breastfed > 1 months vs. Never breastfed	0.3 (SE 0.44)	0.15 (SE 0.30)
Ravelli, 2000 (*43*)	Cohort	1943–1947	51 years	All	Exclusively breastfed vs. Bottle fed	0.2 (SE 1.65)	0.9 (SE 1.08)
Martin, 2005 (*44,45*)	Cohort	1920–1938	52 years	Male	Breastfed vs. Bottle fed	-0.11 (SE 1.11)	-0.21 (SE 0.74)
Wadsworth, 1987 (*46*)	Cohort	1946	53 years	All	Exclusively breastfed for ≥ 3 months vs. Never breastfed	-0.94 (SE 0.97)	-0.32 (SE 0.37)
Fall, 1995 (*47*)	Cohort	1920–1930	66 years	Female	Exclusively breastfed vs. Bottle fed	-2.64 (SE 2.88)	-0.96 (SE 1.38)
Martin, 2005 (*45*)	Cohort	1918–1939	73 years	All	Breastfed vs. Bottle fed	-1.62 (SE 2.57)	-0.74 (SE 1.18)

TABLE 6.2

Breastfeeding and blood pressure in later life. Random-effects meta-analysis by subgroups.

Subgroup analysis	Systolic blood pressure			Diastolic blood pressure		
	Number of studies	Mean difference (95% confidence interval)	P-value	Number of studies	Mean difference (95% confidence interval)	P-value
By age group						
1 to 9 years	16	-0.98 (-1.55; -0.41)	0.001	13	-0.45 (-1.14; 0.24)	0.20
10 to 19 years	8	-1.71 (-3.00; -0.41)	0.01	6	-0.49 (-1.16; 0.19)	0.16
≥ 20 years	13	-0.54 (-1.16; 0.09)	0.09	13	-0.18 (-0.54; 0.18)	0.34
By study size						
< 300 participants	11	-2.22 (-3.24; -1.21)	< 0.001	10	-0.67 (-1.64; 0.29)	0.17
300–999 participants	15	-1.34 (-2.32; -0.37)	0.007	13	-0.41 (-1.35; 0.53)	0.39
≥ 1000 participants	11	-0.48 (-0.85; -0.12)	0.01	9	-0.26 (-0.50; -0.01)	0.04
By year of birth of subjects						
Before 1980	15	-1.07 (-1.93; -0.21)	0.02	13	-0.20 (-0.52. 0.12)	0.21
After 1980	21	-0.95 (-1.41; -0.48)	< 0.001	18	-0.50 (-1.05; 0.05)	0.08
By length of recall of breastfeeding						
< 3 years	21	-1.10 (-1.48; -0.73)	< 0.001	18	-0.54 (-0.87; -0.21)	0.001
≥ 3 years	16	-0.90 (-1.63; -0.17)	0.02	14	-0.22 (-0.76; 0.33)	0.44
By categorization of breastfeeding						
Ever breastfed	18	-0.74 (-1.13; -0.34)	< 0.001	17	-0.46 (-0.87; -0.04)	0.03
Breastfed for a given number of months	19	-1.15 (-1.82; -0.47)	0.001	15	-0.31 (-0.82; 0.21)	0.24
By control for confounding						
None	16	-1.53 (-2.51; -0.56)	0.002	13	-0.459 (-1.193; 0.274)	0.22
Adjusted for socioeconomic status	12	-0.92 (-1.71; -0.14)	0.02	12	-0.435 (-1.042; 0.173)	0.16
Adjusted for socioeconomic and demographics variables	9	-0.80 (-1.38; -0.21)	0.008	7	-0.258 (-0.624; 0.108)	0.17
Study setting						
High-income country	32	-1.02 (-1.49; -0.54)	< 0.001	28	-0.41 (-0.79; -0.04)	0.03
Middle / Low income country	5	-1.06 (-2.00; -0.12)	0.03	4	-0.27 (-1.00; 0.46)	0.47
Total	**37**	**-1.02 (-1.45; -0.59)**		**32**	**-0.37 (-0.71; -0.04)**	

Note: The total number of studies does not add to 37 for systolic blood pressure and 32 for diastolic blood pressure, due to missing information on year of birth of subjects (1 study).

FIGURE 6.1

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.

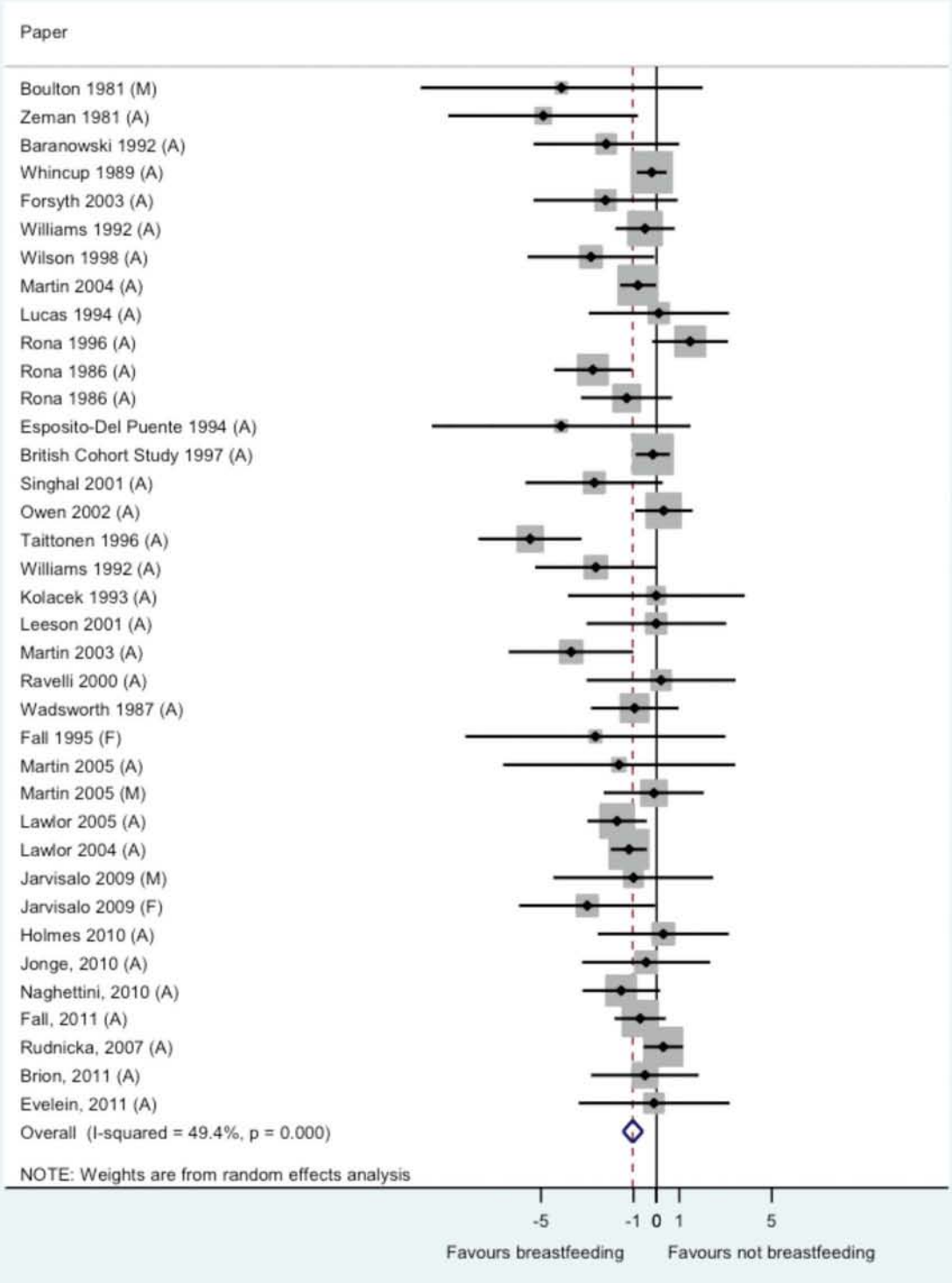


FIGURE 6.2

Mean difference in diastolic 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.

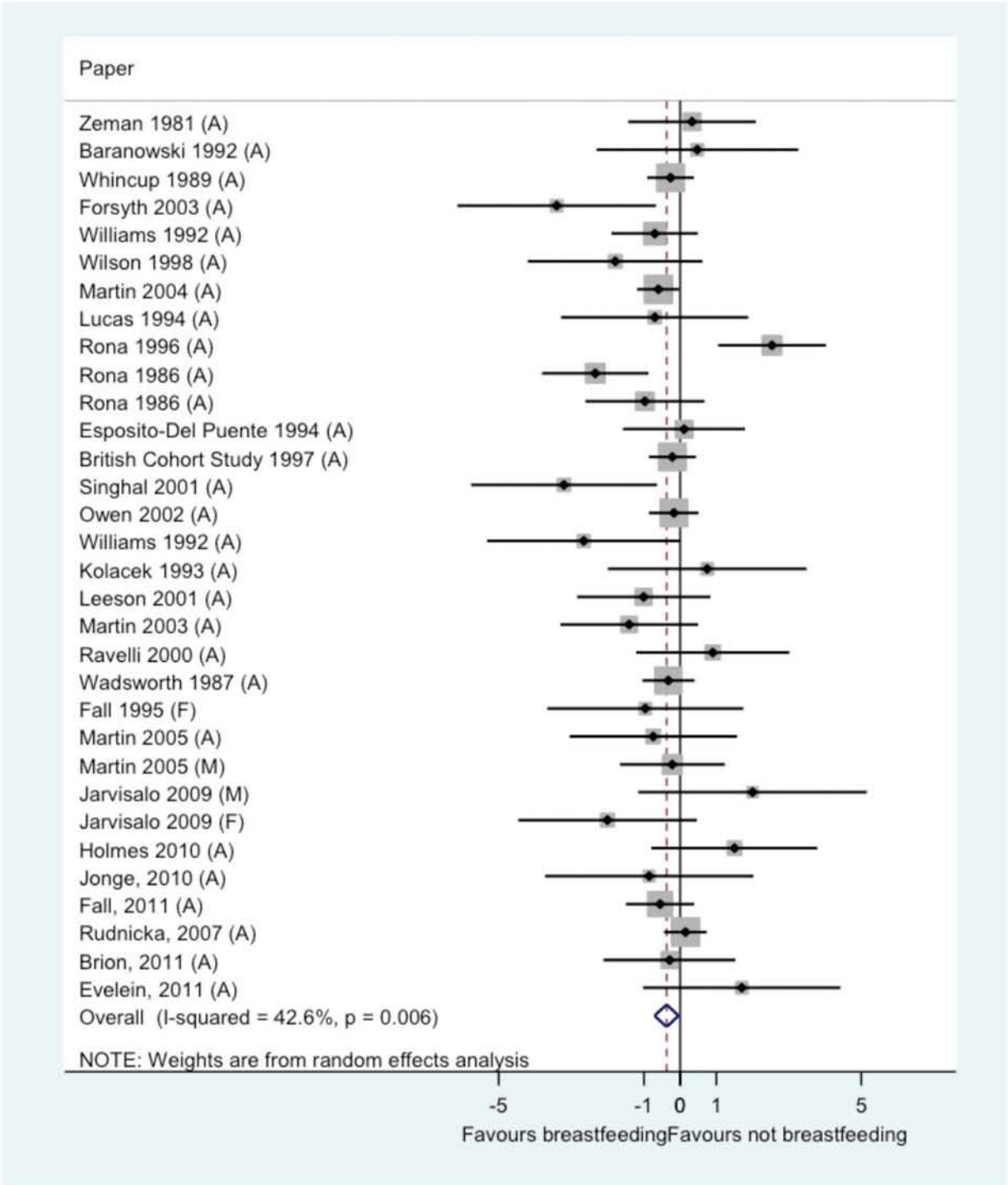


FIGURE 6.3

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

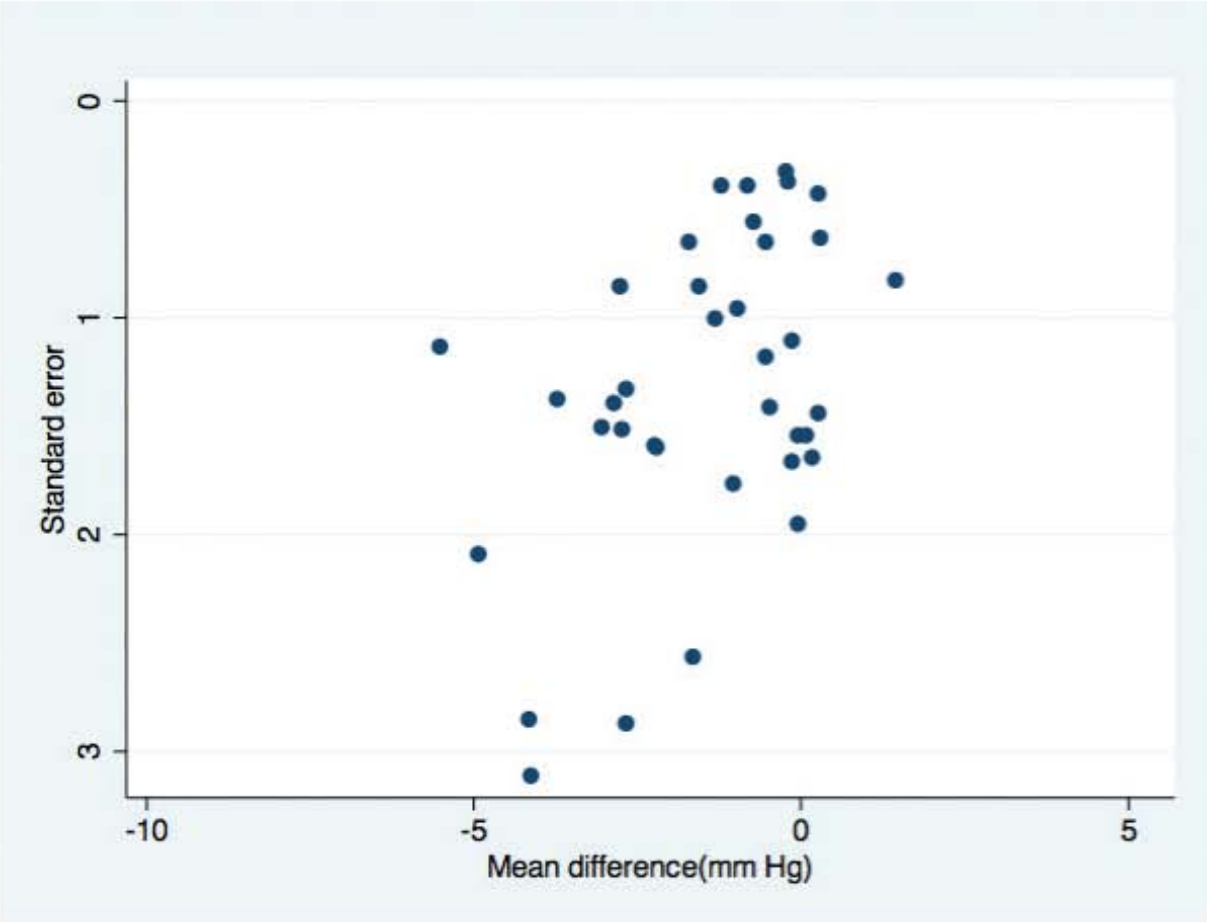
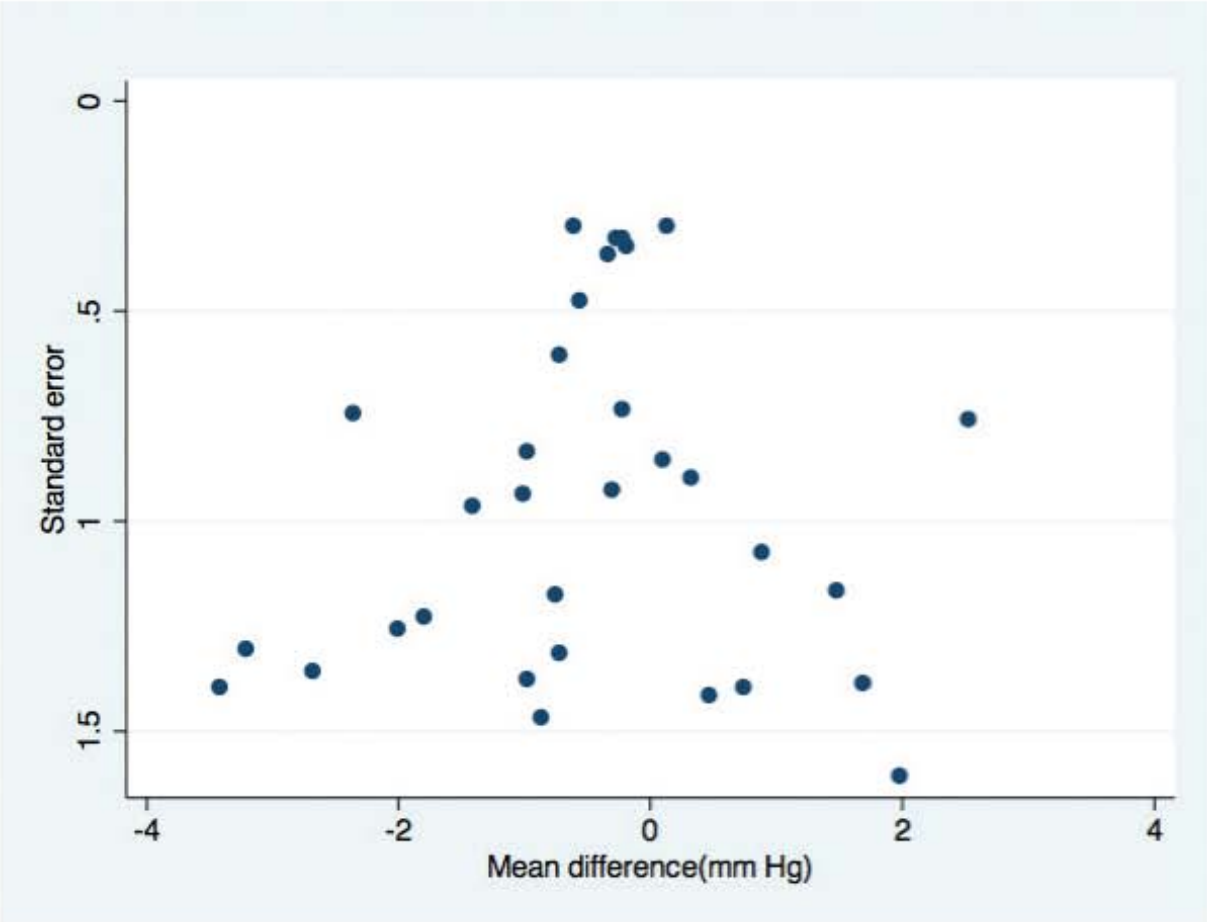


FIGURE 6.4

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



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··· CHAPTER 7 ···

Total cholesterol

Ischemic heart disease is the leading cause of death worldwide (*1*), and blood lipids levels constitute important risk factors (*2*). It has been suggested that the development of heart disease may be programmed by exposures in early life (*3*), including breastfeeding practices.

Biological plausibility

The high cholesterol content of breastmilk may have a long-term programming effect on blood cholesterol levels. Higher intakes of cholesterol in infancy down-regulate hepatic hydroxymethylglutaryl coenzyme A (HMG-CoA), reducing the synthesis of cholesterol (*4*). Animal studies have reported that early exposure to high levels of cholesterol is negatively associated with later cholesterol levels. Furthermore, Devlin et al (*5*) observed that HMG-CoA reductase was higher in formula-fed than in milk-fed piglets, whereas LDL receptor mRNA was independent of early diet. HMG-CoA is the rate-limiting enzyme in synthesis of cholesterol from acetate, and HMG-CoA reductase inhibitors (statins) have a cholesterol lowering effect (*6*).

Overview of the evidence

Our 2007 systematic review and meta-analysis assessed the long-term consequences of breastfeeding duration, with total cholesterol being one of the outcomes. In that review, subjects who had been breastfed presented lower total cholesterol in adulthood [mean difference: -0.18 mmol/L; 95% confidence interval: -0.30; -0.06 mmol/L)], whereas among children and adolescents no such association was observed. Publication bias was not present for studies assessing the long-term effect of breastfeeding on total cholesterol.

During the review process, we identified another meta-analysis that examined the effect of breastfeeding on blood cholesterol in adult life. Owen et al (*7*) systematically reviewed the evidence on the association between initial feeding (incidence of breastfeeding) and total cholesterol in adulthood (age > 16 years). Mean total cholesterol levels were slightly lower among subjects who were ever breastfed [mean difference: -0.04 mmol/L (95% confidence interval: -0.08; 0.00)].

Update of the 2007 meta-analysis

In the present update, the search strategy was the same as in the systematic review published in 2007. Below, we describe the additional eight studies that were identified in our new search.

Khan et al (*8*) evaluated subjects aged 11 to 14 years who had been followed in the first years of life as part of the Dundee Infant Feeding Study. Mean total cholesterol was similar among ever (mean 4.05 mmol/L) and never (mean 4.01 mmol/L) breastfed subjects.

Victora et al (*30*) evaluated subjects who have been followed up since birth in 1982, in Pelotas, a southern Brazilian city. At 18 years of age, mean total cholesterol was slightly higher among those male subjects who had been breastfed [mean difference 0.07 mmol/L (standard error: 0.06)].

Holmes et al (*9*) reported that breastfeeding was not related to blood cholesterol among subjects aged between 20 and 25 years who have been followed since adolescence. Information on breastfeeding was collected retrospectively at ages 12 and 15 years.

Williams et al (*33*) evaluated subjects who have been followed up since birth in 1972–73, in Dunedin, New Zealand. At 26 years of age, mean total cholesterol of women who had ever been breastfed was lower [mean difference -0.14 (standard error 0.08)] than that observed among the never breastfed women.

Järvisalo et al (*10*) assessed endothelial function and cardiovascular risk factors among subjects aged between 24 and 39 years who had been followed for 21 years. The manuscript provided crude estimates only, and total cholesterol was not associated with breastfeeding, in either sex.

In the Framingham Third Generation Study, Parikh et al (*11*) reported that breastfeeding was not associated with total cholesterol at mean age of 41 years.

Rudnicka et al (*12*) evaluated subjects who had been followed since birth in 1958, in England, Wales and Scotland (the British Birth Cohort). At 44–45 years of age, breastfeeding for > 1 month was not associated with total cholesterol.

Gunnarsdottir et al (*13*) also reported that breastfeeding was not associated with total cholesterol in adulthood, in a retrospective cohort in Iceland, information on infant feeding of 3614 subjects, who were born from 1914–1935, was gathered from midwives' birth records.

Our updated meta-analysis included 35 studies that provided 42 estimates on the effect of breastfeeding on total cholesterol (**Table 7.1**). **Figure 7.1** shows that there was marked heterogeneity among studies, with respect to the long-term effect of breastfeeding on total cholesterol. Indeed, the chi-square test for heterogeneity was statistically significant (p=0.004), and a random-effect model was used to pool the estimates. The mean difference was -0.01 mmol/L (95% confidence interval: -0.05; 0.02), suggesting no association between breastfeeding and total cholesterol levels.

In the 2007 meta-analysis, we observed that the effect of breastfeeding on mean cholesterol was modified by age at assessment, with significant protection restricted to adults. **Table 7.2** shows that in this updated meta-analysis, the effect modification by age was not so marked, and there was no significant interaction, nor was the benefit of breastfeeding among adults [mean difference: -0.03 (95% confidence interval: -0.08; 0.01)].

Other subgroup analyses were carried out. Length of recall ≥ 3 years resulted in larger, but non-significant differences [mean difference: -0.06 (95% confidence interval: -0.14; 0.02)]. On the other hand, control for confounding and for current body mass index did not modify the association between cholesterol and breastfeeding. In the meta-regression, age at assessment of blood cholesterol was the only variable whose inclusion in the model decreased heterogeneity among the studies, by 90.8%.

The funnel plot shows that small studies tended to report results in both directions, either negative or positive, suggesting no evidence of publication bias. Indeed, Egger's test was not statistically significant (p=0.49). Furthermore **Table 7.2** shows that the effect of breastfeeding on cholesterol was not related to study size.

When the analyses were restricted to the better designed studies (sample size of at least 700 individuals, including control of confounding factors), the pooled effect was equal to 0.00 mmol/L (95% CI -0.02;0.02).

Conclusion

In this updated meta-analysis, the beneficial effect of breastfeeding on total blood cholesterol in adulthood was smaller than that estimated by the earlier review. Compared to the original finding of -0.18 mmol/l in favor of breastfed subjects, the inclusion of new studies resulted in an estimate of -0.03 mmol/L (95% confidence interval: -0.08; 0.01). Because the confidence interval included the null effect, these results do not support a long-term programming effect of breastfeeding on blood lipids.

TABLE 7.1

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

Author, Year	Year of birth of subjects	Study design	Mean age at total cholesterol assessment	Gender	Comparison groups	Mean difference in total cholesterol (standard error) in mmol / L among breastfed subjects
Jooste, 1991 (*14*)	1981–1986	Cohort	1 year	All	Exclusively breastfed vs. Formula fed for the first 3 months	-0.07 (SE 0.09)
Mize, 1995 (*15*)	Not stated	Cohort	1 year	All	Ever breastfed vs. Never breastfed	0.35 (SE 0.21)
Friedman, 1975 (*16*)	Not stated	Cross-sectional	2 years	All	Breastfed vs. Bottle fed	0.02 (SE 0.19)
Ward, 1980 (*17*)	1974	Cross-sectional	2 years	All	Breastfed for ≥ 1 month vs. Bottle fed	0.25 (SE 0.13)
Freedman, 1992 (*18*)	Not stated	Cross-sectional	3 years	All	Ever breastfed vs. Bottle fed	0.03 (SE 0.02)
Routi, 1997 (*19*)	1990–1992	Cohort	3 years	All	Breastmilk only source of milk at 7 months vs. Formula only source of milk at 7 months	0.12 (SE 0.06)
Huttunen, 1983 (*20*)	1975	Cohort	5 years	All	Breastfed for ≥ 6 months and not receiving formula vs. Formula fed between 1 and 6 months	0.2 (SE 0.11)
Crawford, 1981 (*21*)	1969–1970	Cohort	6 years	All	Exclusively BF vs. Exclusively FF	-0.04 (SE 0.20)
Elaraby, 1985 (*22*)	Not stated	Cross-sectional	7 years	All	Breastfed for > 6 months vs. Bottle fed	-0.57 (SE 0.21)
Plancoulaine, 2000 (*23*)	1981–1987	Cross-sectional	8 years	M	Breastfed vs. Formula fed	-0.3 (SE 0.13)
				F	Breastfed vs. Formula fed	0 (SE 0.16)
Fomon, 1984 (*24*)	1966–1971	Cohort	8 years	M	Breastfed vs. Formula fed	-0.13 (SE 0.09)
				F	Breastfed vs. Formula fed	0.03 (SE 0.12)
Hodgson, 1976 (*25*)	1962–1965	Cohort	9 years	M	Exclusively breastfed vs. Formula fed for the first 3 months	0.54 (SE 0.34)
				F	Exclusively breastfed vs. Formula fed for the first 3 months	0.23 (SE 0.27)
Khan, 2009 (*8*)	1983–1986	Cohort	12 years	A	Breastfed vs. Not breastfed	0.04 (SE 0.12)
Hromodova, 1997 (*26*)	Not stated	Cohort	13 years	A	Breastfed vs. Formula fed	-0.09 (SE 0.27)
Owen, 2002 (*27*)	1982–1986	Cross-sectional	14 years	A	Exclusively breastfed vs Exclusively formula for the first 3 months	-0.02 (SE 0.04)
Singhal, 2004 (*28*)	1982–1985	RCT	14 years	A	Allocated to bank breastmilk vs. Allocated to preterm formula	-0.3 (SE 0.13)
Bergstrom, 1995 (*29*)	Not stated	Cross-sectional	15 years	A	Ever breastfed vs. Never breastfed	-0.03 (SE 0.10)

Author, Year	Year of birth of subjects	Study design	Mean age at total cholesterol assessment	Gender	Comparison groups	Mean difference in total cholesterol (standard error) in mmol / L among breastfed subjects
Friedman, 1975 (*16*)	Not stated	Cross-sectional	17 years	A	Breastfed vs. Bottle fed	0.03 (SE 0.25)
Victora, 2006 (*30*)	1982	Cohort	18 years	M	Ever breastfed vs. Never breastfed	0.07 (SE 0.06)
Kolacek, 1993 (*31*)	1968–1969	Cohort	20 years	M	Exclusively breastfed vs. Formula fed	-0.2 (SE 0.32)
				F	Exclusively breastfed vs. Formula fed	-0.2 (SE 0.31)
Holmes, 2010 (*9*)	1974–1978	Cohort	22 years	A	Breastfed vs. Not breastfed	0.2 (SE 0.13)
Leeson, 2001 (*32*)	1969-1975	Cross-sectional	24 years	A	Ever breastfed vs. Never breastfed	-0.18 (SE 0.11)
Williams, 2006 (*33*)	1972–1973	Cohort	26 years	F	Ever breastfed vs. Never breastfed	-0.14 (SE 0.08)
Järvisalo, 2009 (*10*)	1962–1977	Cohort	31 years	M	Breastfed vs. Formula fed	-0.2 (SE 0.15)
				F	Breastfed vs. Formula fed	-0.2 (SE 0.11)
Marmot, 1980 (*34*)	1946	Cohort	31 years	M	Exclusive breastfed for 5 month vs. Never breastfed	-0.1 (SE 0.25)
				F	Exclusive breastfed for 5 months vs. Never breastfed	-0.5 (SE 0.23)
Parikh, 2009 (*11*)	Not stated	Cohort	41 years	A	Breastfed vs. Not breastfed	-0.03 (SE 0.03)
Rudnicka, 2007 (*12*)	1958	Cohort	44 years	A	Breastfed > 1 month vs. Never breastfed	-0.01 (SE 0.02)
Ravelli, 2000 (*35*)	1943–1947	Cohort	50 years	A	Exclusively breastfed vs. Bottle-fed during stay in hospital	-0.16 (SE 0.11)
Lamont, 1998 (*36*)	1947	Cohort	50 years	A	Ever breastfed vs. Never breastfed	0.54 (SE 0.39)
Martin, 2005 (*37*)	1920–1934	Cohort	52 years	M	Breastfed vs. Bottle fed	0.04 (SE 0.07)
Gunnarsdottir, 2007 (*13*)	1914–1935	Cohort	55 years	M	Breastfed vs. Bottle fed	0 (SE 0.1)
				F	Breastfed vs. Bottle fed	0.1 (SE 0.13)
Huxley, 2004 (*38*)	1942–1944	Cohort	55 years	A	Ever breastfed vs. Never breastfed	0.33 (SE 0.46)
Fall, 1992 (*39*)	1920–1930	Cohort	65 years	M	Exclusively breastfed vs. Formula fed	-0.32 (SE 0.25)
Fall, 1995 (*40*)	1920–1930	Cohort	66 years	F	Exclusively breastfed vs. Formula fed	0.12 (SE 0.43)
Martin, 2005 (*41*)	1918–1939	Cohort	71 years	A	Breastfed vs. Bottle fed	0.12 (SE 0.14)

TABLE 7.2

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; 0.11)	0.63
10 to 19 years	7	-0.01 (-0.08; 0.06)	0.73
≥ 20 years	20	-0.03 (-0.08; 0.01)	0.16
By study size			
< 200 participants	16	0.02 (-0.12; 0.16)	0.76
200–699 participants	15	-0.06 (-0.14; 0.03)	0.18
≥ 700 participants	11	0.00 (-0.02; -0.02)	0.98
By year at birth			
Before 1980	26	-0.01 (-0.07; 0.04)	0.64
After 1980	8	-0.03 (-0.12; 0.06)	0.57
Birth cohort			
Yes	20	-0.01 (-0.07; 0.06)	0.84
No	22	-0.02 (-0.07; 0.02)	0.50
By length of recall of breastfeeding			
< 3 years	31	0.01 (-0.03; 0.05)	0.71
≥ 3 years	11	-0.06 (-0.14; 0.02)	0.12
By categorization of breastfeeding			
Ever breastfed	26	-0.01 (-0.05; 0.02)	0.48
Breastfed for a given number of months	2	-0.02 (-0.13; 0.08)	0.68
By control for confounders			
Yes	14	-0.01 (-0.05; 0.03)	0.61
No	28	-0.02 (-0.09; 0.06)	0.61
By control for current measure of body size			
Yes	9	-0.03 (-0.11; 0.05)	0.45
No	33	-0.01 (-0.06; 0.04)	0.71
Total	**42**	**-0.01 (-0.05; 0.02)**	

Note: The total number of studies does not always add to 42 due missing information on year of birth (8 studies), categorization of breastfeeding (14 studies)

FIGURE 7.1

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.

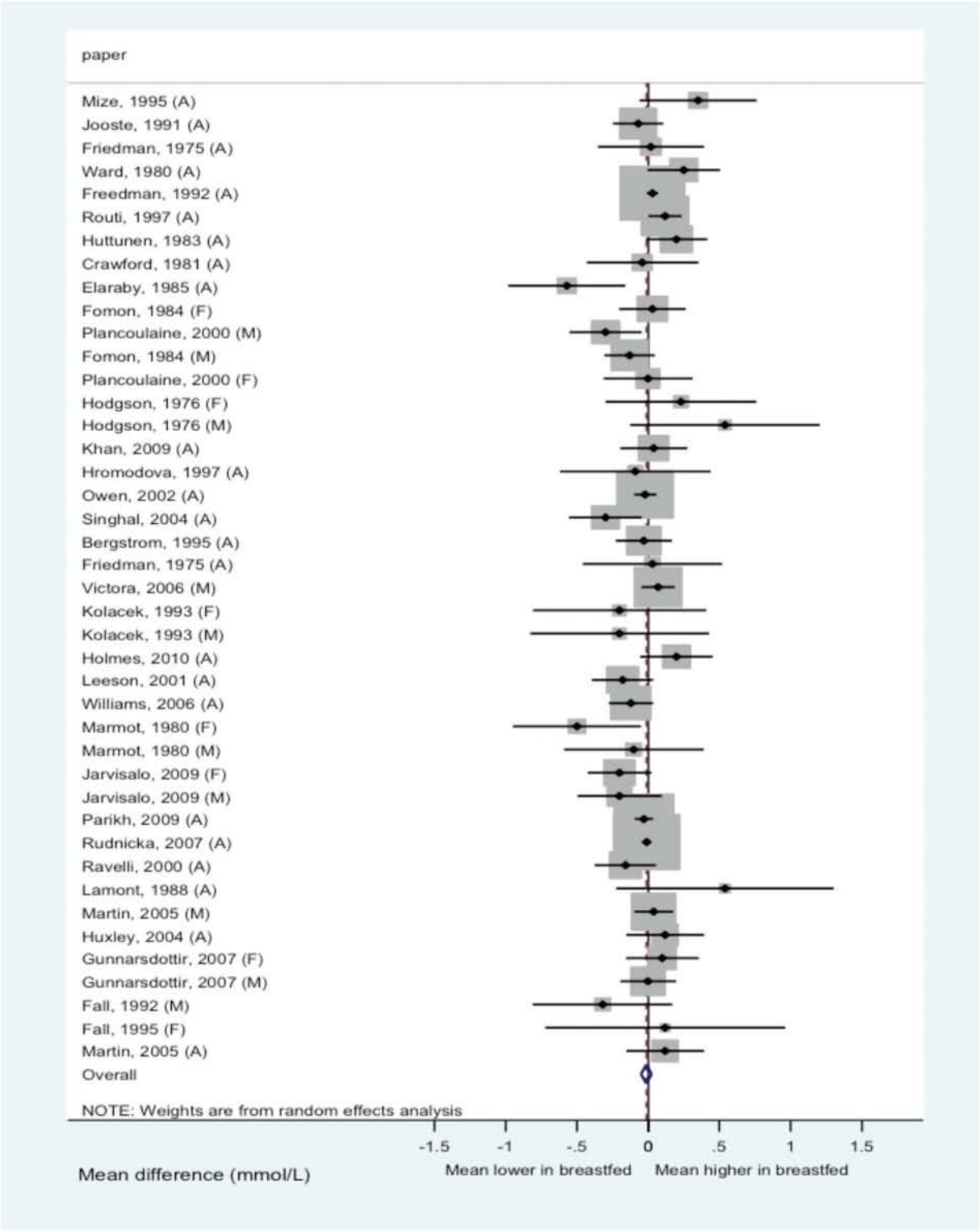
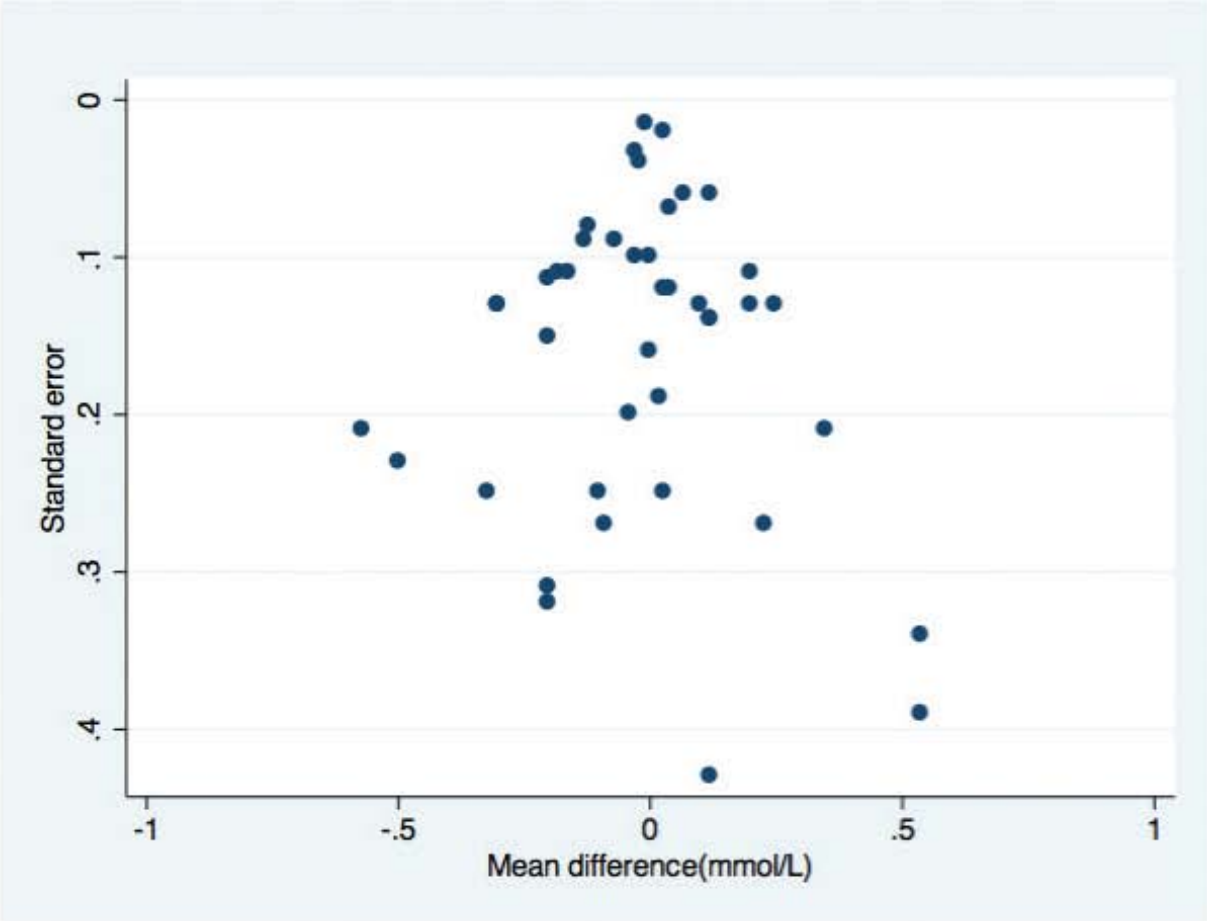


FIGURE 7.2

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



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··· CHAPTER 8 ···

Type-2 diabetes

Type-2 diabetes is the most common form of diabetes, being related to an increased risk of cardiovascular diseases (*1*). The incidence of type-2 diabetes has increased worldwide and it is also becoming more frequent among children and adolescents (*2*). The epidemic of type-2 diabetes has been partly attributed to an increase in obesity and a decrease in physical activity. There is also evidence that type-2 diabetes may be programmed by diet in early life (*3*).

Biological plausibility

At least three biological pathways have been proposed for explaining a protective effect of breastfeeding on type-2 diabetes.

The presence of long-chain polyunsaturated fatty acids (LCPUFAs) in breastmilk, including docosahexanoic acid (DHA) and arachidonic acid (AA), has been proposed as a possible mechanism for the effect of breastfeeding on the incidence of type-2 diabetes. Breastfeeding increases LCPUFAs in skeletal muscle membrane, which in turn is inversely related to fasting glucose. Therefore, early changes in skeletal muscle membrane due to LCPUFAs saturation may protect against insulin resistance, β-cell failure, and type-2 diabetes (*4*).

Differences in insulin secretion according to infant feeding constitute another potential mechanism for the long-term programming of breastfeeding on glucose metabolism. Formula-fed infants have higher concentrations of insulin, which may lead to β-cell failure and type-2 diabetes (*5*).

It has also been suggested that breastfeeding protects against obesity, and this may constitute another pathway to type-2 diabetes (*6*). However, it is unlikely that this is an important pathway, because – as discussed in **Chapter 5** – current evidence suggests that breastfeeding has a small protective effect against overweight or obesity.

Overview of the evidence

In 2007, we carried out a systematic review and meta-analysis that assessed the long-term consequences of breastfeeding duration, in which type-2 diabetes was one of the outcomes. In that meta-analysis, breastfeeding presented a protective effect against type-2 diabetes (pooled odds ratio: 0.63; 95% CI: 0.45; 0.89).

During that review process, we identified a 2006 meta-analysis that examined the effect of breastfeeding on type-2 diabetes, and concentration of insulin and glucose. Owen et al (*3*) reported that breastfeeding was associated with a lower risk of type-2 diabetes (pooled odds ratio: 0.61; 95% CI: 0.44; 0.85).

Update of the 2007 meta-analysis

In the present update, the search strategy was the same as in the systematic review published in 2007. Three additional studies were identified, which are described below.

Mayer-Davis et al (*7*) carried a case-control study on type-2 diabetes including 10–21 year-old cases from six clinical sites across South Carolina and Colorado, using controls from primary care clinics in the same area. After adjustment for several confounders, the odds ratio for type-2 diabetes among those subjects who were ever breastfed was 0.43 (95% CI: 0.19; 0.99). Adjustment for current BMI z-score reduced the strength of the association (0.82 [95% CI; 0.30; 2.30]).

Parikh et al (*8*) evaluated the protective effect of breastfeeding for cardiovascular disease risk factors among subjects enrolled in the Framingham Third Generation cohort. The mean age of the studied population was 41 years, and diabetes was defined as fasting plasma glucose ≥126 mg/dL or treatment with either insulin or oral hypoglycemic agents. The odds ratio of diabetes among ever breastfed subjects was 0.40 (95% CI: 0.09; 1.70), after adjustment for several confounding variables.

Fall et al (*9*) analyzed data from the COHORTS collaboration (Consortium on Health Orientated Research in Transitional Societies) comprising birth-cohort studies in five low and middle income countries: Brazil, Guatemala, India, Philippines and South Africa. The adjusted analyses showed that diabetes (defined as a glucose concentration ≥ 7.0 mmol/l) was not related to ever breastfeeding [odds ratio: 1.25 (95% CI: 0.63; 2.51)]. It should be noted, however, that very few infants were never breastfed in these cohorts. Additional analyses showed a U-shaped association between breastfeeding duration and diabetes, with the lowest risk in the intermediate duration categories, but the association was not statistically significant.

Our updated meta-analysis included 10 studies (**Table 8.1**). **Figure 8.1** shows that there was heterogeneity among studies (p=0.02). In a random-effects model, subjects who were breastfed were less likely to present type 2-diabetes, with the pooled odds ratio equal to 0.66 (95% CI: 0.49; 0.89).

Table 8.2 shows that the protective effect of breastfeeding was higher among studies involving adolescents, compared to adults. The effect of breastfeeding was smaller in studies that adjusted for body mass index (pooled odds ratio: 0.79), suggesting that obesity may partly mediate the association. The small number of studies precluded the statistical assessment of the main sources of heterogeneity.

Interpretation of funnel plot is challenging, given the small number of studies. Nevertheless, **Figure 8.2** suggests that there is publication bias. In spite of one small study showing a higher risk of diabetes among breastfed subjects, small studies reporting moderate odds of diabetes for breastfed subjects seem to be missing.

Due to the small number of studies, it was not possible to select a sizeable subgroup with stronger designs. Two large studies (*8,9*) had samples greater than 500 subjects and controlled for confounding factors, but their odds ratios were very different, 1.25 and 0.40 respectively. The latter adjusted for current body weight as well as socioeconomic position, which may have underestimated the true protection. In light of such heterogeneity, no firm conclusions can be drawn from the two studies with the strongest designs.

Conclusion

The evidence suggests that breastfeeding may have a protective effect against type-2 diabetes, particularly among adolescents. Obesity/overweight seems to account for part of the association. Generalization from these findings is restricted by the small number of studies and the presence of significant heterogeneity among them.

TABLE 8.1

Breastfeeding and type-2 diabetes in later life: studies included in ascending order of subjects' age at which outcome was measured

Author, Year	Study design	Mean age at assessment	Gender	Categorization of breastfeeding	Odds ratio of type-2 diabetes among breastfed subjects
Young, 2002 (*10*)	Case-control	13 years	All	Breastfed ≥ 6 months vs. Breastfed < 6 months	0.36 (0.13; 0.99)
Mayer-Davis, 2008 (*7*)	Case-control	15 years	All	Ever breastfed vs. Never breastfed	0.82 (0.30; 2.30)
Evenhouse, 2005 (*11*)	Cross sectional	15 years	All	Ever breastfed vs. Never breastfed	0.40 (SE: 0.24)
Fall, 2011 (*9*)	Cohort	25 years	All	Ever breastfed vs. Never breastfed	1.25 (0.63; 2.51)
Petit, 1997 (*12*)	Cohort	25 years	All	Exclusively breastfed vs. exclusively bottle fed	0.41 (0.18; 0.93)
Rich-Edwards, 2004 (*13*)	Cohort	59 years	Female	Ever breastfed vs. Never breastfed	0.79 (0.74; 0.85)
Parikh, 2009 (*8*)	Cohort	41 years	All	Ever breastfed vs. Never breastfed	0.40 (0.09; 1.70)
Ravelli, 2000 (*14*)	Cohort	50 years	All	Exclusively breastfed vs. bottle-fed during stay in hospital	0.51 (0.3; 0.9)
Martin, 2005 (*15*)	Cross-sectional	52 years	Male	Ever breastfed vs. Never breastfed	2.89 (0.65; 12.83)
Martin, 2005 (16)	Cohort	71 years	All	Ever breastfed vs. Never breastfed	0.97 (0.41; 2.30)

TABLE 8.2

Breastfeeding and the risk of type-2 diabetes in later life: Random-effects meta-analyses of risk of type-2 diabetes by subgroup.

Subgroup analysis	Number of estimates	Pooled odds ratio and 95% confidence interval	P Value
By age group			
10 to 19 years	3	0.44 (0.30; 0.65)	< 0.001
≥ 20 years	7	0.76 (0.55; 1.04)	0.09
By study size			
< 500 participants	3	0.54 (0.29; 0.99)	0.04
≥ 500 participants	6	0.70 (0.47; 1.04)	0.08
By study design			
Cohort	6	0.73 (0.55; 0.96)	0.02
Cross-sectional or case-control	4	0.63 (0.30; 1.31)	0.22
By adjustment for BMI			
No	7	0.64 (0.44; 0.93)	0.02
Yes	3	0.79 (0.43; 1.44)	0.44
Total	**10**	**0.66 (0.49. 0.89)**	

FIGURE 8.1

Odds ratio and 95% confidence interval of having type-2 diabetes in different studies, comparing breastfed vs. non-breastfed subjects.

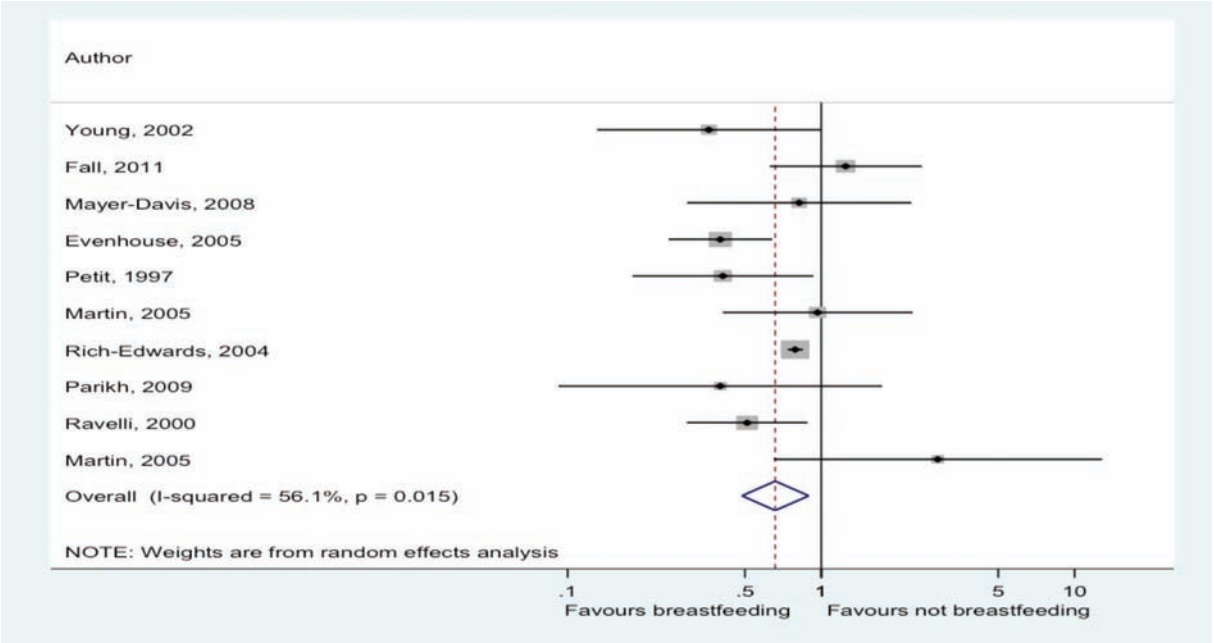
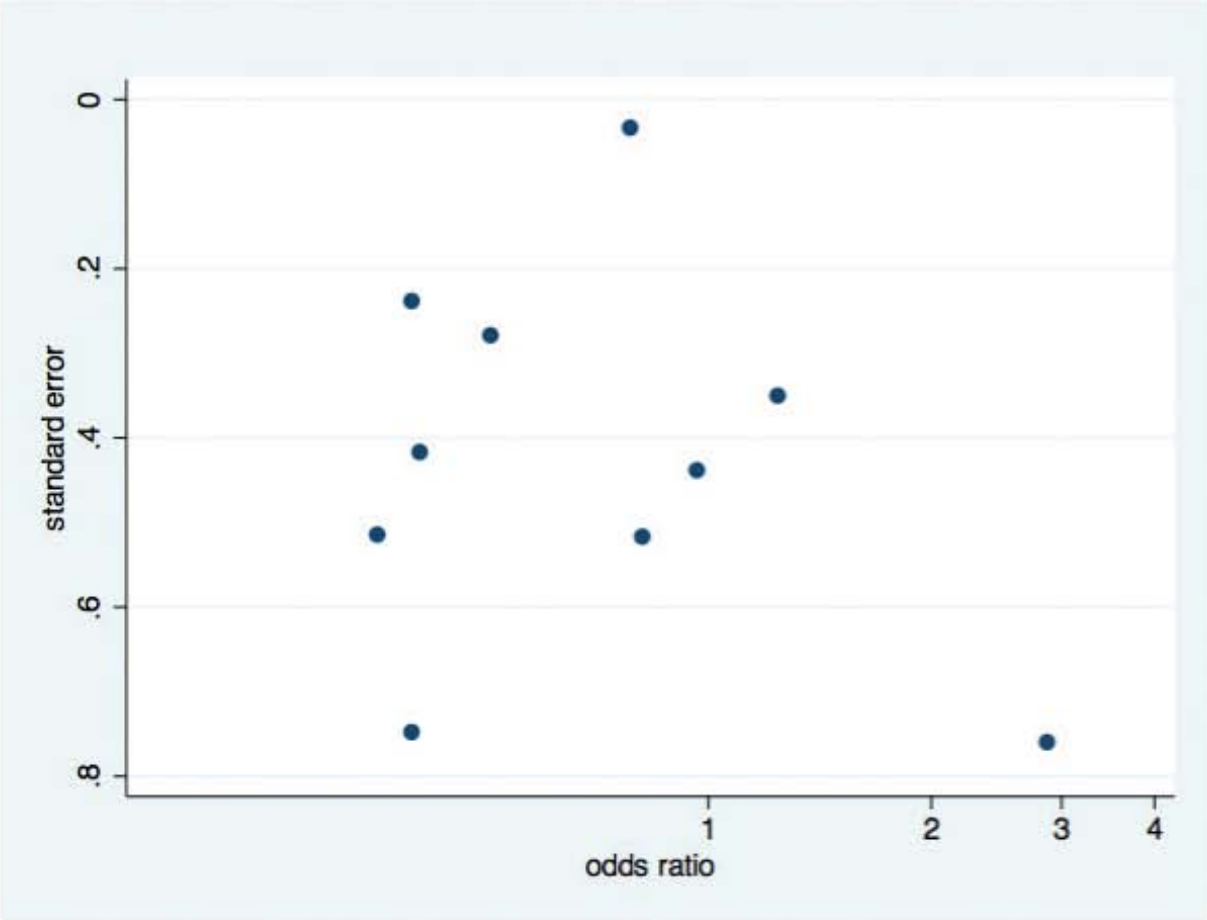


FIGURE 8.2
Funnel plot showing odds ratio for type-2 diabetes by standard error of odds ratio



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··· CHAPTER 9 ···

Performance in intelligence tests

The relationship between breastfeeding and child development has been studied since long ago. In 1929, Hoefer and Hardy (*1*) observed that breastfeeding was positively associated with intelligence among children aged from 7 to 13 years. In 1950, Douglas reported that duration of breastfeeding was inversely related to the age at which the child started walking (*2*). These early findings were followed by several studies reporting that breastfeeding was positively associated with child development (*3*).

Biological Plausibility

Some studies have proposed that the benefits of breastfeeding in terms of child development may be due to improved care rather than better nutrition (*4*). Nevertheless, there are several biological mechanisms that may account for a nutritional effect.

The presence of long-chain polyunsaturated fatty acids in breastmilk, including docosahexanoic acid (DHA) and arachidonic acid (AA), is a possible mechanism for its effect on development (*5*). AA and DHA, which are important for retinal and cortical brain development (*6,7*), accumulate in the brain and retina during the last trimester of pregnancy and the first months after birth (*8*). Breastfed infants have higher concentrations of these fatty acids (*9*). Indeed, Isaacs et al reported that breastfeeding was positively related to brain volume and – among male subjects – white matter was also related to breastfeeding (*10*), thus suggesting that breast milk promotes structural changes in the brain.

Genetic epidemiology techniques are starting to be employed to explore the role played by DHA metabolism in the association between breastfeeding and intelligence (*11*). By using genetic variants as proxies for DHA exposure, confounding is avoided, because the inheritance of one trait is independent of socio-behavioral variables or of other genetic traits. Particular attention has been given to the FADS2 gene which affects the metabolism of DHA (*12,13,14,15,16*). However, evidence on how the FADS2 genotype may modify the effect of breastfeeding on intelligence tests is still controversial (*17,18*).

Breastfeeding is also positively associated with maternal sensitivity and with bonding between mother and infant (*19*), which constitute an additional mechanism for the long-term effect of breastfeeding on cognition.

Specific methodological issues

General methodological issues have already been addressed in the Introduction. When assessing the association between infant feeding and later performance in intelligence tests, two methodological issues deserve special attention: self-selection bias and residual confounding.

At least in high-income societies, breastfeeding mothers are likely to be more health-conscious, and, therefore, to promote healthy habits and provide stimulation to their infants. For example, Der et al (*20*) observed that breastfeeding mothers were more likely to stimulate their infants. Because stimulation at home is positively related to performance in intelligence tests (*21,22*), studies assessing the long-term consequences of infant feeding on cognition should adjust their estimates for variables measuring home stimulation. Reinforcing the importance of such adjustment, it has been reported that the magnitude of the association between breastfeeding and cognition is reduced after adjustment for home stimulation (*20*).

Residual confounding by socioeconomic status should also be considered when interpreting the evidence on breastfeeding and intelligence. Because performance in intellectual tests is higher among wealthy and educated subjects (*23*), residual confounding may affect the assessment of causality in settings where breastfeeding is also directly associated with socioeconomic status. Even large studies accounting for several potential confounders may still be affected, if such confounders were not properly measured or were mis-specified in the regression model. Comparison of observational studies with different confounding structures may be used to assess this possibility.

Overview of the evidence

In 2007, we carried out a systematic review and meta-analysis that assessed the long-term consequences of breastfeeding duration. Performance in intelligence tests was one of the outcomes we assessed. We employed the following selection criteria:

- cognition had to be assessed using standard tests;
- estimates had to be adjusted for stimulation or interaction with the child.

In that meta-analysis, breastfeeding was associated with higher scores in intelligence tests (mean difference: 4.9 points; 95% CI: 2.97; 6.92).

Update of the 2007 meta-analysis

In this updated review, eight additional studies were identified, which are described below.

Der et al (*20*) studied the children of women enrolled in the US National Longitudinal Survey of Youth(NLSY79), which has been following a cohort of young people aged 14 to 22 since 1979. Children with birthweight < 2500g or gestational age < 35 weeks were excluded. Data on 5475 children was obtained and IQ was assessed through the Peabody individual achievement test. Adjustment for stimulation at home, maternal IQ, socioeconomic and demographic variables, and birthweight reduced the difference in performance in intelligence tests from 4.69 points (standard error: 0.38) to 0.52 (standard error: 0.36).

Gibson-Davis et al (*24*) studied 1645 children enrolled in the Fragile Families and Child Wellbeing Study, a cohort of mostly unmarried parents and their children from 20 cities in 15 North American states. Maternal and child cognition were assessed during the visit at 3 years using the Peabody Picture Vocabulary Test-III (PPVT-III). In the crude analysis the PPVT-III score was 6.6 points higher among those children who were breastfed. After controlling for maternal performance in PPVT-III, stimulation at home, socioeconomic and demographic variables the difference between breastfed and non-breastfed children fell to 1.72 points (standard error: 0.60).

Clark et al (*25*) followed a cohort of healthy full-term children born in urban communities near Santiago, Chile and had been enrolled in a trial on prevention of iron deficiency. At five years, 784 children were evaluated and cognition was assessed using the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R). Those who were breastfed for more than 8 months scored 1.0 point (95% confidence interval: -1.1; 3.1) higher than those breastfed < 2 months, after adjustment for home stimulation, maternal IQ, socioeconomic variables, and nutritional status at 12 months. For children who were breastfed for 2 to 8 months, the score was 1.3 points higher than that for children breastfed < 2 months.

Evenhouse et al (*26*) used data from 2743 sibling pairs enrolled in the National Longitudinal Study of Adolescent Health, United States, to assess the relationship between breastfeeding and cognition. Of these, 288 pairs comprised one ever breastfed and one never breastfed sibling. IQ was evaluated using the PPVT test. Ever breastfed siblings scored on average 1.68 percentile point (standard error 0.94) higher. Sibling comparisons are one of strategies that can be used to improve causal inference, by controlling for confounders as well as for self-selection bias (assuming that maternal characteristics are shared among siblings). On the other hand, heterogeneity in breastfeeding duration is smaller than that for unrelated subjects; therefore, precision of estimates is reduced.

Zhou et al (*4*) studied 302 children from a trial aimed at assessing the efficacy of iron supplementation in pregnancy. IQ was assessed at 4 years of age using the Stanford-Binet Intelligence Scale. After adjustment for home stimulation and socioeconomic status, the IQ of children who were breastfed for at least 6 months was 0.8 (standard error 1.29) points higher than the observed among children who were breastfed for less than 6 months.

Eickmann et al (*27*) studied a cohort of 205 children born in a poor area in the interior of Pernambuco (Northeast Brazil). At 12 months, child development was assessed using the Bayley Scales of Infant Development II. After control for confounding (home stimulation, socioeconomic status and haemoglobin level), the mean score was 3.0 (95% confidence interval: 0.48; 5.53) points higher among those children who were exclusively or predominantly breastfed at 1 month.

Whitehouse et al (*28*) used data from the follow-up of the Western Australian Pregnancy (Raine) Cohort to assess whether breastfeeding was related to performance in the PPVT-R test at 10 years of age. In the multivariable regression, children who were predominantly breastfed for > 6 months scored 4.04 points higher than those who never breastfed, after adjustment for maternal age at conception, maternal smoking during pregnancy, alcohol intake during pregnancy, maternal schooling, parity, socioeconomic status, and home stimulation

In this new meta-analysis, we included 13 studies with 14 estimates on the effect of breastfeeding on performance in intelligence tests. When interpreting these results it is important to note that different tests for intellectual performance were included (although all of these had a reference mean value of 100 with a standard deviation of 15). In addition, each comparison included two groups according to the duration of breastfeeding, but the cut-off points were different from study to study (in 6 studies, the comparison was never vs ever breastfed; in the remainder different duration of breastfeeding were used as cut-off). **Figure 9.1** shows that there was marked heterogeneity among the studies. Because this was statistically significant, a random-effect model was used to pool the estimates. In the pooled analysis, breastfed subjects presented higher performance in intelligence tests (mean difference: 3.45 points; 95% confidence interval: 1.92; 4.98).

Maternal IQ is positively associated with offspring cognition as well as with breastfeeding duration, at least in high-income societies where most studies were carried out (*29,30*). We assessed whether adjustment or matching by maternal intelligence was a source of heterogeneity among the study findings. Studies were considered as having controlled for maternal IQ if (a) they included maternal IQ in the multivariable analysis, (b) were randomized clinical trials or (c) discordant sibling pair analyses. **Figure 9.2** shows that there was marked heterogeneity among studies, with smaller effects in studies that controlled for maternal IQ. Adjustment for maternal IQ explained 77.3% of the heterogeneity among the studies; the pooled effect from studies with control of maternal IQ was equal to 2.19 (95% CI: 0.89; 3.50).

Further adjustment for other study characteristics (length of recall for breastfeeding information, age at measurement of outcome, type of categorization of breastfeeding duration, control of confounding factors other than maternal IQ, type of design) did not provide further explanation for heterogeneity. **Figure 9.3** shows that year of publication was also related to heterogeneity among studies, and the reported benefit of breastfeeding was lower for those studies published from 2006 onwards. Adjustment for year of publication explained 51.9% of the heterogeneity.

The funnel plot was clearly asymmetrical, and small studies reporting a negative effect of breastfeeding on cognition appear to be missing (**Figure 9.4**). Nevertheless, the overall effect of breastfeeding on intelligence cannot be explained by such bias. **Table 9.1** shows that the mean effect was similar among those studies with sample sizes < 500 (mean effect: 3.61; 95% confidence interval: 1.59; 5.63) and ≥ 500 subjects(mean effect: 3.25; 95% confidence interval: 1.09; 5.40). **Table 9.1** also shows that categorization of breastfeeding duration did not modify the association between breastfeeding duration and performance in intelligence tests. On the other hand, those studies that were carried in subjects < 10 years of age observed a higher mean difference than studies involving older subjects.

Relevant studies not included in the present review

Two randomized trials were identified. The first, by Lucas et al (*31*), compared preterm infants who were allocated to breastmilk or to formula. Because this study entailed a comparison of infants who received different types of milk, it was included in the meta-analysis. The second was the cluster randomized trial on promotion of breastfeeding by Kramer et al (*32*) in Belarus, in which 31 maternity hospitals and surrounding clinics were included (16 in the intervention and 15 in the comparison group). The proportion of infants exclusively breastfed at 3 and 6 months was higher among infants from the intervention group and performance in the Wechsler Abbreviated Scale of Intelligence at 6.5 years of age was also higher in the intervention group, with cluster-mean IQ differences of 7.5 points (95% confidence interval: 0.8; 14.3). These analyses were based on intent to treat and are very relevant to this review because of the randomized design. Nevertheless, the quantitative estimates could not be included in the meta-analyses because both groups – intervention and comparison – included breastfed and non-breastfed subjects.

As mentioned in the methodology section, residual confounding by socioeconomic status should be taken into account when interpreting the evidence on association between breastfeeding and intelligence. Brion et al33compared the association between breastfeeding and cognition in two cohorts, one from a high-income country (ALSPAC, UK) and another from a middle-income country (Pelotas, Brazil). In ALSPAC socioeconomic status was positively associated with breastfeeding duration, whereas in Pelotas there was no such association. In both settings, duration of breastfeeding was directly related to cognition. The authors concluded that the observed association is unlikely to

be explained by residual socioeconomic confounding. These two datasets were not included in the meta-analyses because there was no adjustment for home stimulation.

Conclusion

This meta-analysis suggests that breastfeeding is associated with increased performance in intelligence tests in childhood and adolescence, of 3.5 points on average. Maternal IQ is an important confounder, but it accounts for only part of this association – even among those studies that adjusted for maternal intelligence, breastfeeding was associated with an additional 2.19 IQ points. The two existing randomized trial on this issue also reported significant benefits of breastfeeding, suggesting that this association is causal.

On the other hand, the practical implications of a small increase in the performance in intelligence tests may be open to debate. Nevertheless, one Brazilian study suggests that breastfeeding is associated with achieved schooling in adolescents, in a population where breastfeeding duration does not present marked variability by socioeconomic position (*34*).

TABLE 9.1

Breastfeeding and mean difference in cognitive development scores and its 95% confidence interval between breastfed and non-breastfed subjects in different studies mean: Random-effects meta-analysis by subgroups

Subgroup analysis	Number of estimates	Mean difference (95% confidence interval)	P Value
By age group			
1 to 9 years	8	4.74 (2.41; 7.08)	< 0.001
10 to 19 years	4	2.50 (0.97; 4.03)	0.001
By study size			
< 500 participants	7	3.61 (1.59; 5.63)	< 0.001
≥ 500 participants	7	3.25 (1.09; 5.40)	0.003
By categorization of breastfeeding			
Ever breastfed	5	3.25 (0.91; 5.58)	0.006
Breastfed for a given number of months	9	3.52 (1.53; 5.51)	0.001
Total	**14**	**3.45 (1.92; 4.98)**	

Note: The total number of studies does not add to 14, due to missing information on age at assessment of intellectual performance (2 studies).

FIGURE 9.1

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.

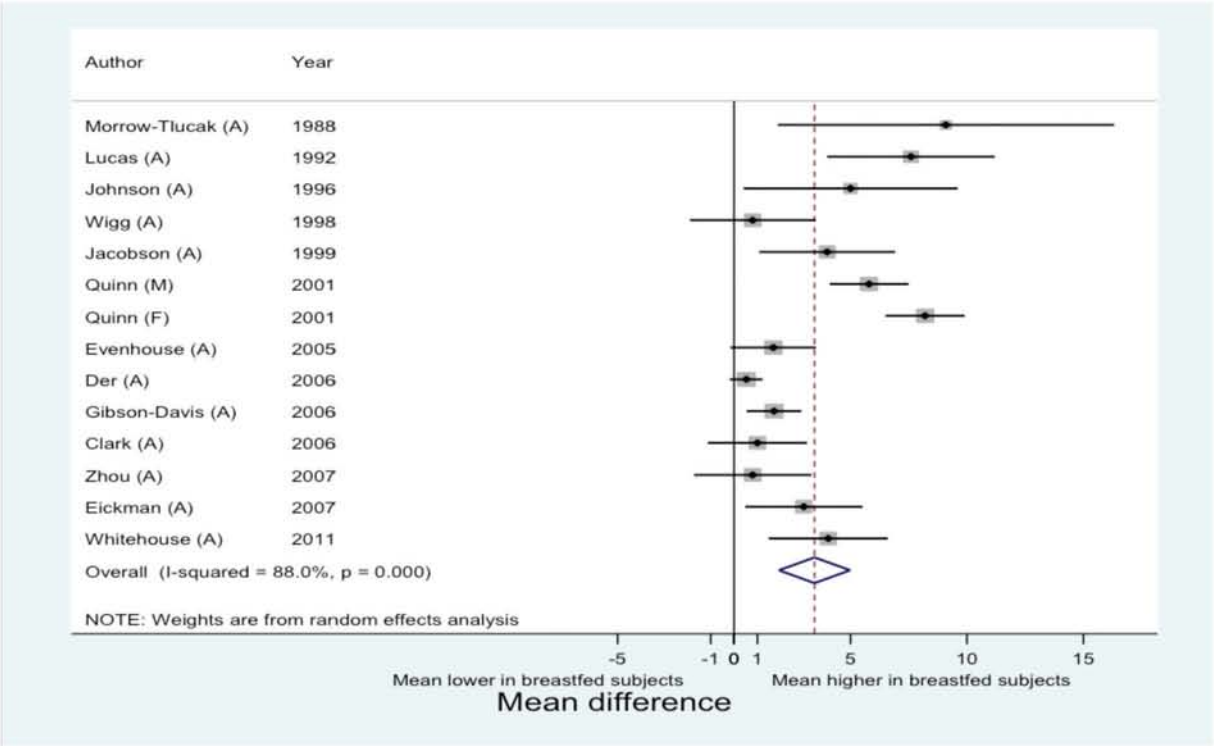


FIGURE 9.2

Mean difference in cognitive development scores and its 95% confidence interval between breastfed and non-breastfed subjects in different studies, stratified by adjustment for maternal IQ in analysis or in the study design

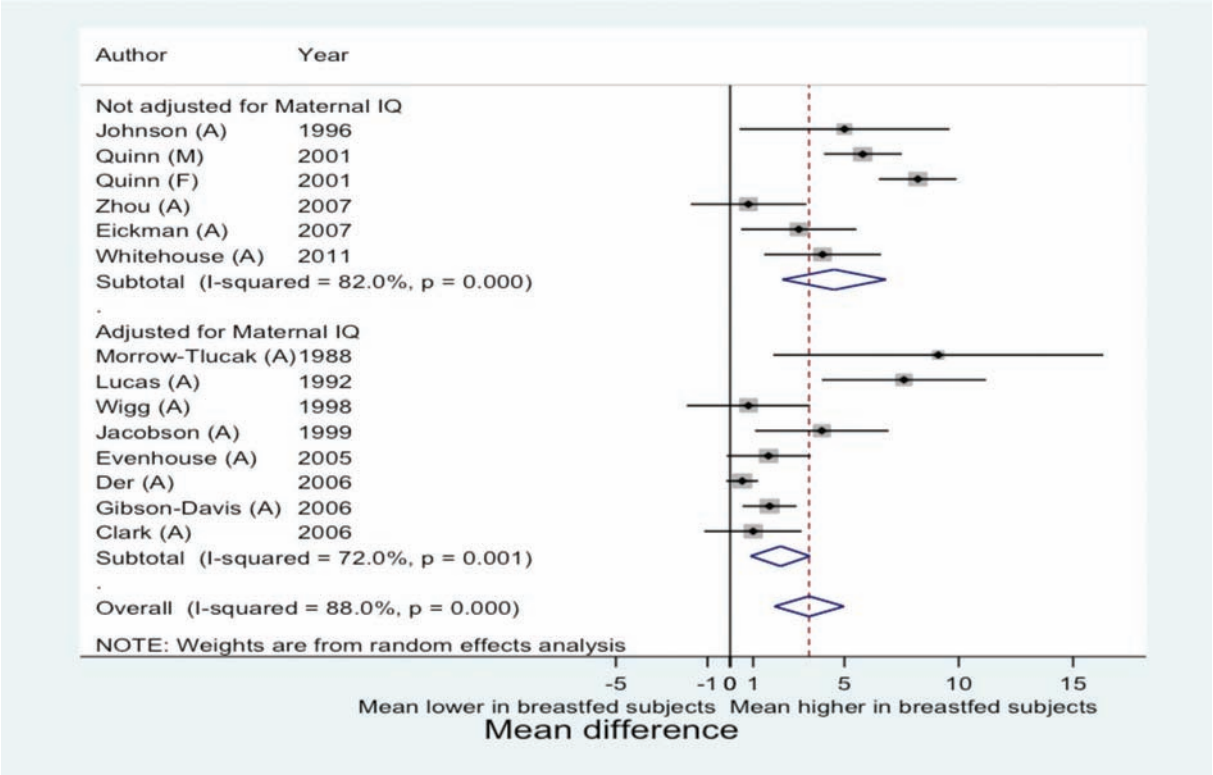


FIGURE 9.3

Mean difference in cognitive development scores and its 95% confidence interval between breastfed and non-breastfed subjects in different studies, stratified by year of publication

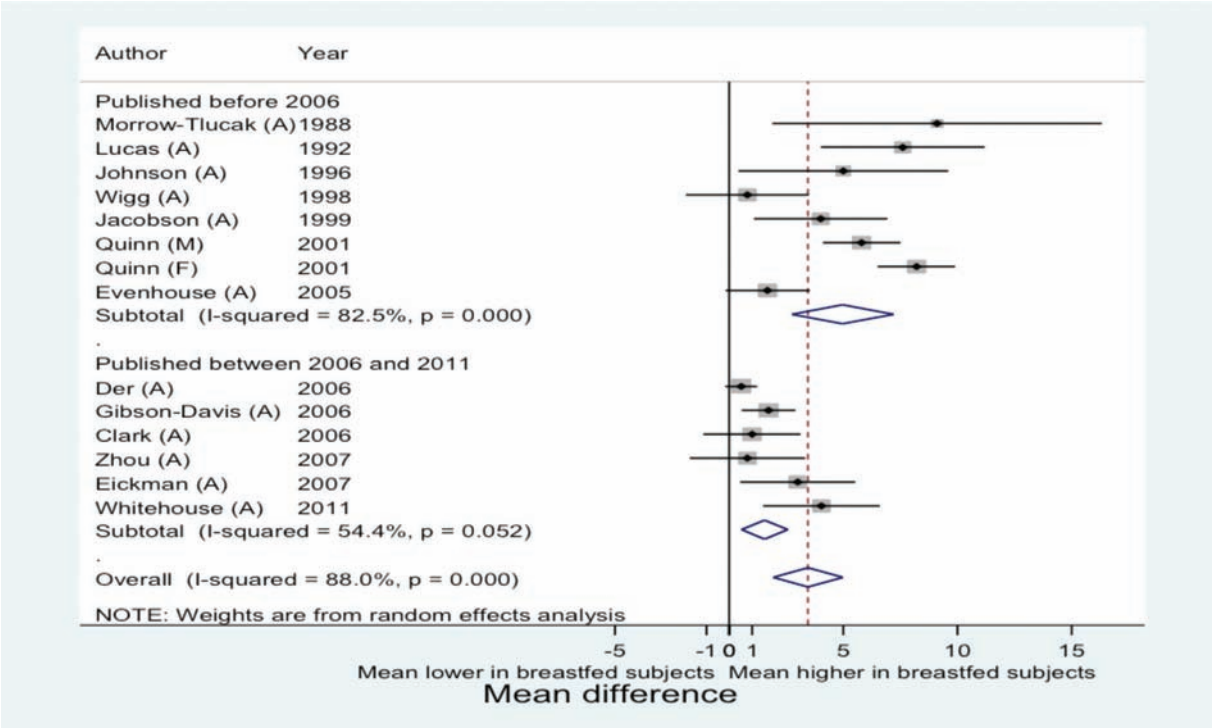
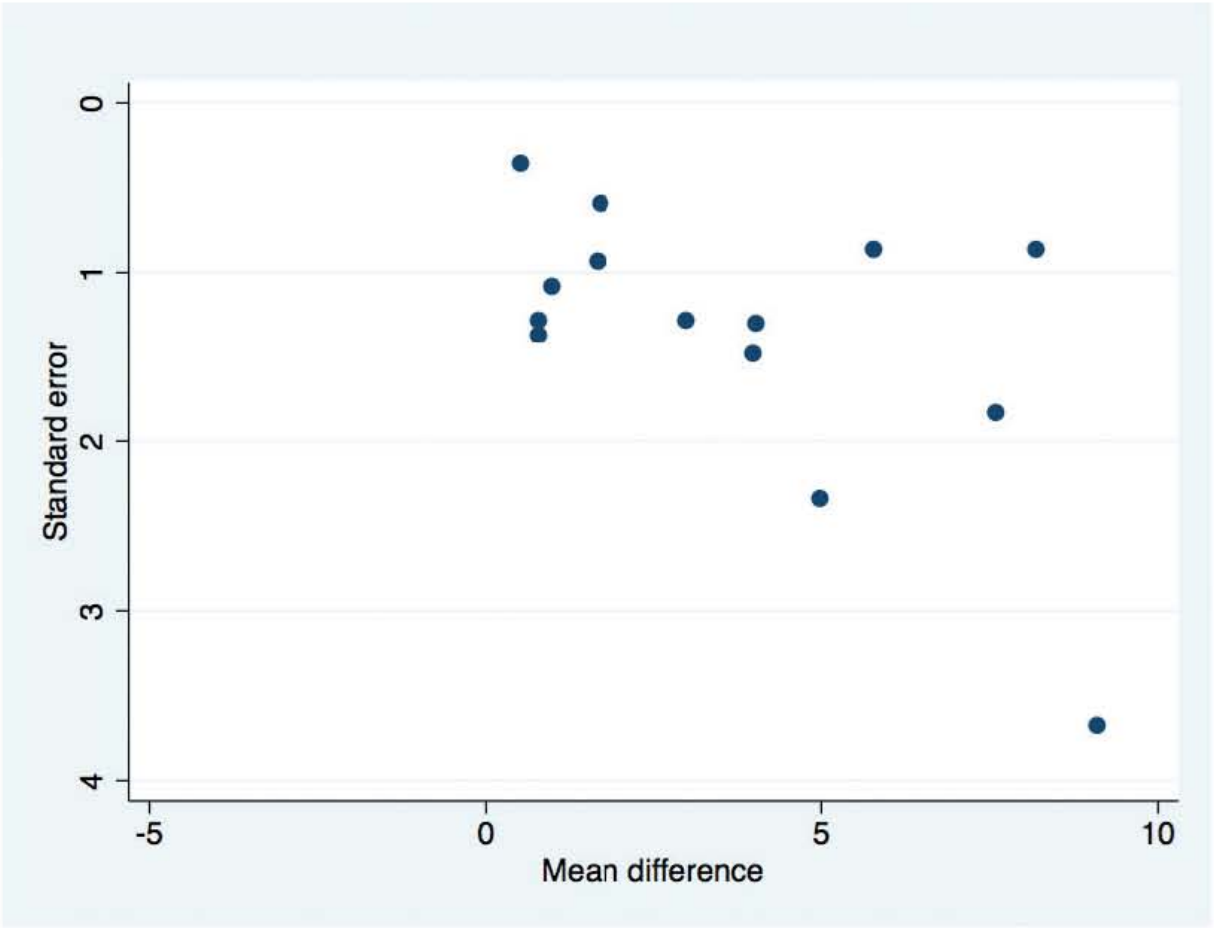


FIGURE 9.4

Funnel plot showing mean difference in performance in intelligence tests by standard error of mean difference



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··· CHAPTER 10 ···

Conclusions

Relative to the 2007 systematic review, the present analyses rely on a considerably larger evidence base, including 60 additional studies published in the last five years. Availability of additional data has also allowed more detailed breakdowns of the studies, and a better understanding of reasons for heterogeneity. **Table 10.1** summarizes the effect measures from the meta-analyses.

TABLE 10.1
Pooled effects for each outcome, from all studies and from those deemed to be of higher scientific quality

Outcome	Pooled effect (95% confidence interval)	
	All studies	High-quality studies[a]
Mean total blood cholesterol (mmol/L)	-0.01 (-0.05; 0.02)	0.00 (-0.02; 0.02)
Mean systolic blood pressure (mmHg)	-1.02 (-1.45; -0.59)	-0.71 (-1.24; -0.19)
Mean diastolic blood pressure (mmHg)	-0.37 (-0.71; -0.04)	-0.27 (-0.64; 0.09)
Odds ratio of type-2 diabetes	0.66 (0.49-0.89)	Not estimated
Odds ratio of overweight/obesity	0.76 (0.71; 0.81)	0.88 (0.83; 0.93)
Mean performance in intelligence test (points)	3.45 (1.92-4.98)	2.19 (0.89-3.50)

[a] High-quality studies include those with larger sample sizes and adjustment for confounding variables relevant to each outcome (see individual chapters for further details).

The meta-analyses of overweight/obesity, blood pressure, diabetes and intelligence suggest that benefits are larger for children and adolescents, and smallest among adults, suggesting a gradual dilution of the effect with time.

Because the meta-analyses are almost exclusively based on observational studies (see **Chapter 2**), the possibility of self-selection and residual confounding must be considered. Even when multiple studies show similar results, these studies may largely be subject to the same biases. In particular, most studies are derived from high-income settings where breastfeeding is more common among highly-educated, better-off mothers who are more health conscious, and whose offspring may be less likely to suffer from the negative outcomes covered in the present review. The fact that estimates from high-quality studies, with tighter control of confounding, are less marked than those from all studies suggests that this may be the case.

Interpretation of results from observational studies may be aided by also considering the findings of the only two randomized studies on the topic. The first is the follow up of English preterm infants allocated to breast or formula milk in early life, which showed a positive effect of breastfeeding on IQ, but no significant or sizeable effects on blood pressure or BMI (*1,2*). The second was the Belarus PROBIT trial whose mothers were allocated to breastfeeding promotion. These intent-to-treat analyses

compared an intervention group in which over 40% of subjects were exclusively breastfed at three months of age, with a control arm where only 6% were exclusively breastfed. Even though the true effects of breastfeeding may be underestimated, analyses at 7 years of age showed significant effects on IQ. No association was found with blood pressure or overweight/obesity. Results on cholesterol, diabetes or glucose levels are not available.

Interpreting the results of the present meta-analyses jointly with those of the two randomized trials, our conclusions are outlined below.

Total cholesterol. There was no effect in the overall meta-analyses. In the 2007 review, there was a significant effect among adults, which is no longer present in the updated analyses. The UK trial of preterm infants showed a small protective effect (*3*), while the Belarus trial did not report on this outcome. We conclude that breastfeeding does not seem to protect against total cholesterol levels.

Blood pressure. The pooled estimate from the high-quality studies indicates a small reduction of less than 1 mmHg in systolic pressure among breastfed subjects, and no significant protection in terms of diastolic pressure. Residual confounding may be an important problem. The Belarus and UK preterm trials found no effect of breastfeeding (*2,4*). We conclude that the protective effect of breastfeeding, if any, is too small to be of public health significance.

Diabetes. There was substantial protection in the pooled analyses, with a 34% reduction, but few studies are available and their results were considerably heterogeneous. Only two high-quality studies were identified, with conflicting results (one showing an increase and another a reduction among breastfed subjects). The randomized trials did not present any results on these outcomes. Our conclusion is that further studies are needed on this outcome.

Overweight-obesity. In the pooled analyses of all studies, breastfeeding was associated with a 24% reduction in overweight and/or obesity, but the reduction was only 12% in the high-quality studies. Residual confounding may be still affecting these results, because protection is not evident in studies from low and middle-income countries where the social patterning of breastfeeding is not clear cut. The Belarus trial did not find an association (*4*). We conclude that breastfeeding may provide some protection against overweight or obesity, but residual confounding cannot be ruled out.

Intelligence tests. Breastfeeding was associated with an increase in 3.5 points in normalized test scores in the pooled analyses of all studies, and 2.2 points when only the high-quality studies are included. The two randomized trials also found significant effects (*1,5*). We conclude that there is strong evidence of a causal effect of breastfeeding on IQ, although the magnitude of this effect seems to be modest.

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