The effect of breastfeeding on mean body mass index throughout life: a quantitative review of published and unpublished observational evidence[1–3]

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ABSTRACT

Background: Evidence from observational studies has suggested that breastfeeding may reduce the prevalence of obesity in later life.

Objective: The objective was to examine whether initial breastfeeding is related to lower mean body mass index (BMI; in kg/m^2) throughout life.

Design: The study was a systematic review of published studies investigating the association between infant feeding and a measure of obesity or adiposity in later life, which was supplemented with data from unpublished sources. Analyses were based on the mean differences in BMI between those subjects who were initially breastfed and those who were formula-fed (expressed as breastfed minus bottle-fed), which were pooled by using fixed-effects models throughout.

Results: From 70 eligible studies, 36 mean differences in BMI (from 355 301 subjects) between those breastfed and those formula-fed (reported as exclusive feeding in 20 studies) were obtained. Breastfeeding was associated with a slightly lower mean BMI than was formula feeding (−0.04; 95% CI: −0.05, −0.02). The mean difference in BMIs appeared larger in 15 small studies of <1000 subjects (−0.19; 95% CI: −0.31, −0.08) and smaller in larger studies of ≥1000 subjects (−0.03; 95% CI: −0.05, −0.02). An Egger test was statistically significant ($P = 0.002$). Adjustment for socioeconomic status, maternal smoking in pregnancy, and maternal BMI in 11 studies abolished the effect (−0.10; 95% CI: −0.14, −0.06 before adjustment; −0.01; 95% CI: −0.05, 0.03 after adjustment).

Conclusions: Mean BMI is lower among breastfed subjects. However, the difference is small and is likely to be strongly influenced by publication bias and confounding factors. Promotion of breastfeeding, although important for other reasons, is not likely to reduce mean BMI. *Am J Clin Nutr* 2005;82:1298–307.

KEY WORDS Infant feeding, body mass index, systematic review

INTRODUCTION

The recent increases in levels of adiposity and obesity in children and adults represent a major public health crisis in both the developed and developing worlds (1, 2). Hence, interest is increasing in public health interventions to reduce the burden of obesity. It has been suggested that initial breastfeeding may reduce the prevalence of obesity in later life, but the results of individual studies have differed, showing either protective (3) or null (4, 5) effects. Recent systematic reviews of published observational studies have suggested that breastfeeding is associated with a lower prevalence of obesity (6–8). However, these results may be subject to publication bias and confounding.

Although earlier studies focused mainly on whether breastfeeding reduces the prevalence of obesity, it is also important to establish whether it reduces average levels of adiposity, which is most commonly measured with the use of body mass index (BMI; in kg/m^2). This is important because the risks of cardiovascular disease and type 2 diabetes associated with obesity are graded and are increased at the mean BMIs occurring in many adult populations, not only at exceptionally high BMIs (9, 10).

Few studies have published data on the relation of infant feeding to mean BMI; as is the case for obesity prevalence, the results have been conflicting, showing both protective (11) and null (5) effects. We therefore reviewed the published literature and obtained data from previously unpublished sources to quantify the association between infant feeding and mean BMIs in later life. To standardize the presentation of results and minimize the extent of publication and reporting bias, we have systematically requested a series of estimates of mean BMIs from the authors of individual studies. The request for data also allowed for exploration of the effect of adjustment for confounding factors identified in an earlier review as important (6).

METHODS

Systematic review process

Published data sources

Eligible studies were those that examined the influence of infant feeding on obesity throughout life from 6 wk after birth and

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TABLE 1
Studies that provided data for inclusion in the meta-analysis[1]

								Differences adjusted for				
	Design	Source	Source of information on feeding	Year born, age measured[2]	Breast fed, formula-fed	Any exclusive breastfeeding or formula feeding	Duration of any breastfeeding	Age	Age and SES	Age and maternal BMI	Age and maternal smoking	Age, SES, and maternal BMI and smoking
Study					*n*							
Agostoni et al (24)	PC	Birth in San Paolo Hospital maternity ward (Italy)	In infancy	Not stated, 1	60, 55	Yes	7 mo (4–14 mo)	−0.20 ± 0.27[3]	−0.03 ± 0.28	—	—	—
Armstrong and Reilly (42)	HC	Child Health Surveillance Programme of Scottish children (UK)	In infancy	1995–1996, 3	8928, 23 938	Yes	6 wk	−0.04 ± 0.02	−0.05 ± 0.02	—	—	—
Baranowski et al (43)	CS	Studies of Children's Activity and Nutrition (TX)	Parental interview in infancy	1981–1993, 2	66, 173	Yes	7 mo (3 to <12 mo)	−0.81 ± 0.28	—	—	—	—
Bergmann et al (11)	PC	German Multicenter Atopy Study	In infancy	1990, 11	600, 69	Not stated	>2 mo	−0.20 ± 0.13	−0.18 ± 0.13	−0.15 ± 0.14	−0.16 ± 0.13	−0.10 ± 0.13
Butte et al (25)	PC	Infants recruited at the Children's Nutrition Research Center (Houston, TX)	In infancy	Not stated, 2	38, 34	Yes	335 d	−0.21 ± 0.34	−0.11 ± 0.36	−0.24 ± 0.37	—	—
Bynner (14)	PC	British Cohort Study	In infancy	1970, 23	736, 3609	No	≥3 mo	−0.44 ± 0.16	−0.22 ± 0.16	−0.22 ± 0.16	−0.27 ± 0.16	0.18 ± 0.16
de Bruin et al (26)	PC	Infants recruited at the Sophia Children's Hospital (Netherlands)	In infancy	1991–1992, 2	19, 17	Yes	≥4 mo	−0.59 ± 0.39	—	—	—	—
Fall et al (31, 46)	HC	Adults born in Hertfordshire (UK)	Birth records	1920–1980, 64	856, 69	Yes	Not known	0.24 ± 0.50	0.21 ± 0.50	—	—	—
Frye and Heinrich (47)	PC	The Bitterfeld Study consisting of 3 school surveys (Germany)	PQ	1979–1993, 10	762, 1956	Yes	20 wk	−0.08 ± 0.13	−0.06 ± 0.14	—	—	—
Gillman et al (28)	CS	Growing Up Today Study (offspring of the Nurses' Health Study II) (USA)	PQ	1981–1987, 12	4714, 1579	Yes	11 mo	−0.44 ± 0.09	−0.40 ± 0.09	−0.21 ± 0.09	−0.40 ± 0.09	−0.15 ± 0.09
Hediger et al (45)[4]	CS	The third National Health and Nutrition Examination Survey (NHANES III) (USA)	PQ	1983–1991, 4	560, 1498	Yes	16 mo	−0.34 ± 0.12	−0.30 ± 0.13	−0.34 ± 0.12	−0.39 ± 0.13	−0.34 ± 0.13
Langnäse et al (23)	PC	Kiel Obesity Prevention Study (Germany)	In infancy	1988–1996, 6	1750, 717	Yes	10 mo	−0.36 ± 0.10	−0.03 ± 0.12	−0.12 ± 0.10	−0.22 ± 0.12	0.20 ± 0.12
Leeson et al (29)	CS	Birth in a maternity hospital (Cambridge, UK)	Maternal recall	1969–1975, 24	182, 120	Yes	4 mo	0.03 ± 0.51	0.07 ± 0.51	—	—	—
Li et al (4)	CS	Offspring of the 1958 Birth Cohort (UK)	PQ	1973–1987, 8	1066, 961	No; breast-feeding at all	6 mo (≥ 3 mo)	−0.10 ± 0.06	−0.10 ± 0.06	−0.07 ± 0.06	−0.20 ± 0.11	−0.15 ± 0.11
Liese et al (48)	CS	Part of the International Study of Asthma and Allergy in Childhood (2 German cities)	PQ	1985–1987, 10	1754, 354	No: exclusively breastfed vs. mixed	3 mo	−0.81 ± 0.16	−0.73 ± 0.16	—	—	—
Maffeis et al (49)	CS	Recruited from schools in six areas of northeast Italy	PQ at 4–12 y	1976–1984, 10	864, 499	No: breastfed group mixed fed	3 mo	0.20 ± 0.08	—	—	—	—
Martin et al (21)	PC	Males born in Caerphilly (UK)	Questionnaire in adulthood	1918–1939, 52	1140, 416	No: ever breastfed	Not stated	0.37 ± 0.20	0.37 ± 0.20	—	—	—
Martin et al (50)	PC	The Boyd Orr cohort (UK)	Questionnaire in adulthood	1918–1939, 70	272, 90	No: ever breastfed	9 mo	0.11 ± 0.53	0.10 ± 0.53	—	—	—
Martin et al (19)	PC	Avon Longitudinal Study of Parents and Children (UK)	In infancy	1991–1992, 8	2082, 950	Yes	Not stated	−0.31 ± 0.17	−0.37 ± 0.18	−0.03 ± 0.18	—	—
Michaelsen (51)	PC	Copenhagen Cohort Study on Infant Nutrition and Growth (Denmark)	In infancy	1987–1988, 9	41, 62	No: bottle-fed mixed fed	9 mo	0.09 ± 0.38	0.13 ± 0.40	0.15 ± 0.38	0.17 ± 0.39	0.35 ± 0.39
O'Callaghan et al (52)	PC	Mater University Study of Pregnancy (Australia)	In infancy	1981–1984, 5	3488[5]	No: mixed fed vs. bottle-fed		0.02 ± 0.07	0.03 ± 0.07	0.08 ± 0.07	—	—

(*Continued*)

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TABLE 1 (*Continued*)

	Design	Source	Source of information on feeding	Year born, age measured[2]	Breast fed, formula-fed	Any exclusive breastfeeding or formula feeding	Duration of any breastfeeding	Differences adjusted for: Age	Age and SES	Age and maternal BMI	Age and maternal smoking	Age, SES, and maternal BMI and smoking
					n							
Owen et al (16)	CS	Ten Towns Heart Health Study (UK)	PQ at 5–7 y	1982–1986, 15	980, 947	Yes	7 mo (3 to 48 mo)	−0.18 ± 0.08	−0.12 ± 0.09	−0.17 ± 0.10	−0.12 ± 0.09	−0.04 ± 0.09
Parsons et al (5)	PC	1958 British Birth Cohort Study (UK)	PQ at 7 y	1958, 33	4153, 2891	No: wholly or partly breastfed	Unknown	−0.19 ± 0.06	−0.13 ± 0.06	−0.17 ± 0.07[6]	−0.17 ± 0.06	−0.10 ± 0.06[6]
Poulton and Williams (44)	PC	Dunedin Multidisciplinary Health and Development Study (New Zealand)	PQ at 3 y	1972–1973, 26	253, 405	Yes	28 wk	−0.28 ± 0.34	−0.34 ± 0.34	−0.22 ± 0.36	−0.27 ± 0.40	−0.14 ± 0.40
Rona et al (15)[7]	CS	National Study of Health and Growth (England and Scotland)	PQ at 9 y	1981–1990, 8	3776, 7078	Yes	4 mo (3–21 mo)	−0.01 ± 0.03	0.00 ± 0.03	0.01 ± 0.03	−0.05 ± 0.03	0.03 ± 0.03
Scaglioni et al (53)	PC	Birth at San Paolo Hospital (Italy)	In infancy	1990–1991, 5	101, 30	Yes	5 mo	0.04 ± 0.15	0.09 ± 0.16	0.10 ± 0.16	—	—
Sung et al (54)	CS	Primary schoolchildren (Hong Kong, China)	PQ	1988–1992, 11	72, 174	Yes	244 d	−1.69 ± 0.59	—	—	—	—
Toschke et al (55)	CS	Nationwide Anthropometric Survey of Children and Adolescents (Czech Republic)	PQ	1976–1985, 11	30 641, 3127	No: breastfed vs. mixed fed		−0.23 ± 0.05	−0.21 ± 0.05	−0.07 ± 0.05	—	—
Victora et al (22)	PC	Army recruits (Brazil)	In infancy	1982, 18	340, 177	No: predominantly breastfed	9 (3.5–49 mo)	0.05 ± 0.33	0.10 ± 0.33	−0.17 ± 0.36	—	—
von Kries et al (3)	CS	School entry health examination (Germany)	PQ	1991–1992, 5	5181, 4021	Yes	3–5 mo	−0.20 ± 0.04	−0.13 ± 0.04	—	—	—
Wadsworth et al (56)	PC	MRC National Survey of Health and Development (UK)	In infancy	1946, 53	1264[5]	Yes	9 mo	0.00 ± 0.27	0.05 ± 0.27	−0.03 ± 0.26	—	—
Whincup et al (17)	CS	Subjects recruited from 9 of 24 towns involved in the British Regional Heart Study (UK)	PQ at 5–8 y	1979–1983, 6	1224, 1791	Yes	7 mo (3–60 mo)	0.00 ± 0.03	−0.01 ± 0.03	—	—	—
Multiple studies												
Overall pooled estimate based on a fixed-effects model from 32 studies adjusted for age					135 769[5]			−0.08 (−0.10, 0.05)[8]	—	—	—	—
Overall pooled estimate based on fixed-effects models from 28 studies adjusted for age with and without adjustment for socioeconomic status					133 885[5]			−0.08 (−0.10, −0.06)	−0.06 (0.09, −0.04)	—	—	—
Overall pooled estimate based on fixed-effects models from 18 studies adjusted for age with and without adjustment for maternal BMI					80 717[5]			−0.11 (−0.14, −0.08)	—	−0.05 (−0.09, −0.02)	—	—
Overall pooled estimate based on fixed-effects models from 11 studies adjusted for age with and without adjustment for maternal smoking in pregnancy					38 445[5]			−0.10 (−0.14, −0.06)	—	—	−0.11 (−0.15, −0.07)	—
Overall pooled estimate based on fixed-effects models from 11 studies adjusted for age with and without adjustment for socioeconomic status, maternal BMI, and maternal smoking in pregnancy					38 445[5]			−0.10 (−0.14, −0.06)	—	—	—	−0.01 (−0.05, 0.03)

[1] Studies are ordered alphabetically. HC, historical cohort; PC, prospective cohort; CS, cross-sectional; PQ, parental questionnaire ≥ 3 y after delivery; UK, United Kingdom. BMI measured in kg/m^2.
[2] $\bar{x}$ (all values except ranges); age shown in years.
[3] $\bar{x}$ ± SE (all such values).
[4,7] Besides adjustment for parental rather than maternal BMI, mean differences adjusted for: [4]ethnicity, [7]geographical origin.
[5] Total number only.
[6] Adjusted for parental BMI instead of maternal BMI.
[8] 95% CI in parentheses (all such values).

that were identified in a recent systematic review of MEDLINE (1966 to September 2003) and EMBASE (1980 to September 2003) databases; these studies were supplemented with studies identified through manual searches and other studies previously known by the authors (6). Observational studies of cross-sectional and longitudinal design were included; case-control studies (that could not provide reliable data for comparisons based on mean BMI) were excluded. In brief, 3603 publications were identified. From abstract review, 97 publications were retrieved for more detailed evaluation. Fifty-eight of these studies comparing any measure of adiposity or obesity between those who were initially breastfed and those who were formula-fed were all considered for inclusion, including data from one national cohort and from offspring of this cohort (4, 5). The search strategy was repeated on a weekly basis from October 2003 until November 2004 using the automated OVID alert system; 2 further publications were identified (12, 13). One reviewer (RMM) completed and continues to maintain the literature search. In total, 60 published studies (385 765 subjects) of the association between infant feeding and a measure of adiposity or obesity in later life were considered for inclusion.

Unpublished data sources

Unpublished data were obtained from another national cohort (14), a national survey (15), other cohort and cross-sectional studies with data on early life exposures and measures of adiposity or obesity in later life (16–23). These represent 10 studies (with 28 985 subjects) in addition to the 60 studies previously identified, for a total of 70 studies with 414 750 subjects.

Outcome measurement

Although studies in infants and young children used measures of body size based on weight-for-length (24, 25) or weight (24–26), or both, mean differences in BMI were sought and were considered an appropriate measure of weight-for-height in this age group (≥3 mo old). Mean differences were extracted from the published literature where available. There was considerable variation in the presentation of results, with most studies reporting odds ratios (ORs) for obesity (using a variety of definitions) in preference to reporting mean differences in BMI. Mean BMI differences between breastfed and formula-fed infants were reported from only 10 (14%) of the 70 studies (5, 11, 12, 23, 27–32). To obtain further data and to standardize the format of the results, the reviewers devised a data request form. Attempts were made to obtain additional data from authors of all of the eligible studies. However, further information could not be obtained for 8 historical studies (published in the 1970s and 1980s) because contact addresses of study authors could not be found (33–40). None of these historic studies published mean differences in BMI; 3 published ORs (35, 38, 39) that have been included in a recent review (6). Requests for data were made to corresponding authors or Principal Investigators (or both) of 62 remaining studies, and individual data from 2 national studies were requested from the UK Data Archive. Hence, requests were made to 64 of the 70 eligible studies (91%). Where outcomes were measured at various ages throughout the lifecourse, the oldest age at ascertainment of BMI was included in the meta-analysis.

Assessment of infant feeding exposure

Authors were asked whether initial infant feeding status was ascertained from records or maternal recall at the time of infant feeding or from recall some years after birth. Information was extracted from the published literature when it was not possible to obtain data form the authors directly. Authors were asked to report the median duration of exclusive breastfeeding, exclusive bottle feeding, or mixed feeding [defined as breastfeeding and bottle (ie, formula) feeding]; the number of subjects; and the mean (±SEM) BMI in each feeding group, for males and females separately. The World Health Organization defines exclusive breastfeeding as breastfeeding while giving no other food or liquid—not even water—for the first 4 mo (and, if possible, for the first 6 mo) of life (41). Whereas we asked for BMI data for exclusive feeders, few studies report this definition. Hence, the exclusiveness of infant feeding is based on the classification given in individual study reports or where applicable reported directly by the author (**Table 1**). Bottle feeders were assumed to have been fed formula milk, not human milk, throughout.

Adjustment for confounding

Measures of the socioeconomic status (SES) of infants and children ($\bar{x}$ age: < 16 y) were based on the SES of the head-of-household parent; in adults, they were based or the subject's own SES. Authors were asked to specify whether SES was based on occupation, salary, or education or on all 3 variables. Data on the type of formula feed, year of birth, mean age, and minimum and maximum age of participants were also requested. Mean differences in BMI between those breast and bottle-fed (defined as breastfed – bottle-fed) were sought (1) without adjustment (to verify the reported means), (2) with adjustment for age only, (3) with adjustment for age and each of either SES, maternal BMI, or maternal smoking in pregnancy, or (4) with adjustment for age and SES, maternal BMI, and maternal smoking in pregnancy combined. Authors were invited to provide an anonymized data set if they were unable to carry out the analyses requested.

Statistical analysis

To carry out the meta-analyses, we used the mean difference in BMI between those initially breastfed and those formula-fed and the SE of the difference from each study, with the adjustments listed above. Separate analyses for males and females and for the sexes combined (also adjusted for sex) were conducted. Fixed effect models are reported throughout, because these reflect only the random error within each study and are less affected by publication bias (whereas small studies tend to publish larger estimates). Heterogeneity of the mean differences in BMI between studies was examined by using chi-square tests. Small-study bias was assessed by using funnel plots, Begg tests, and Egger tests (57–59). Meta-regression, which offers a conservative test of the effect of certain exposures on outcome (assessed at the study level), was used to examine the influence of the following factors (defined a priori) by using a test for trend: study size (<500, 500–2500, or > 2500 breastfed and formula-fed subjects), quintiles of age at outcome measurement (infants and young children, child aged < 5 y, children aged ≥ 5–8 y, older children and adolescents aged > 8–16 y, and adults > 16 y), year of birth (including whether born before or after 1980). The effect of the method of ascertainment of infant feeding status (whether contemporary or recalled over a period of ≥3 y) was also examined. Meta-regression and sensitivity analyses (which excluded studies with particular characteristics) were also used to examine the influence of exclusive feeding, duration of breastfeeding (in

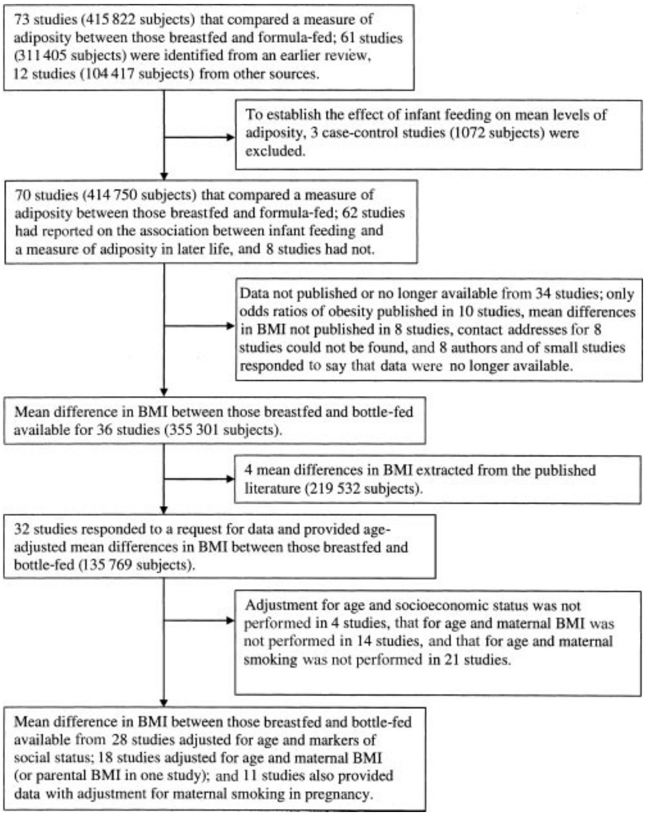

FIGURE 1. Flow diagram showing the number of studies included in and excluded from the meta-analysis.

those ever breastfed and those exclusively breastfed). Meta-regression tests were adjusted for study size.

To establish the likelihood of reporting bias, we compared pooled mean differences from studies that reported (either quantitatively or narratively; in the latter case, additional data obtained from the authors were used) on the direction of the association between infant feeding and any measure of adiposity found in the published literature with differences from those that did not publish on the association at all or those that published a mean difference in BMI (or both) and from those that did not publish a mean difference but provided an estimate in response to the request for data. In addition, we examined the effect of including data from 4 studies that did not provide data but when estimates could be derived from the published literature. Meta-regressions to examine reporting bias were not adjusted for study size.

RESULTS

From 70 eligible studies, we were able to extract 36 mean differences (355 301 subjects) in BMI between those who were breastfed and those who were formula-fed; of these differences, 32 were based on the responses of individual authors (135 769 subjects; **Figure 1** and Table 1), whereas 4 were obtained from the published literature (**Table 2**). Among the 36 mean differences, 7 were in infants and children aged < 5 y (including 1 study of infants with mean age 1 y; 24), 9 in children (aged ≥ 5–8 y), 9 in older children and adolescents (aged > 8–16 y), and 11 in adults aged > 16 y (Table 1). Twenty-four studies were based in Western Europe (including 13 from the United Kingdom), 1 in Eastern Europe, 7 in North America, 1 in South America, 2 in Australasia, and 1 in China. Twenty-three (64%) of 36 estimates related breastfeeding to a lower mean BMI in later life than was seen with formula feeding. There was evidence of heterogeneity between studies ($P < 0.001$). In a fixed-effects model including all 36 studies, subjects who were breastfed had lower BMI than did those who were formula-fed ($\bar{x}$ difference: −0.04; 95% CI: −0.05, −0.02; **Figure 2**). In the fixed-effects model, nearly two-thirds (65%) of the statistical weight was attributed to 2 large health surveys of American (32) and Scottish (42) children ($\bar{x}$ age: 3–4 y); exclusion of these studies increased the mean difference in BMI between those who were breastfed and those who were formula-fed (−0.09; 95% CI: −0.11, −0.06).

Influence of study size, publication, and reporting bias

Small studies tended to report larger mean differences in mean BMI between those who are breastfed and those who are bottle-fed, although the association was still present in larger studies. In 10 small studies (<500 participants), a mean difference of −0.12 (95% CI: −0.29, 0.04) was observed, whereas, in 13 studies of intermediate size (500–2500 participants) and in 13 large studies (>2500 participants), mean differences of −0.15 (95% CI: −0.21, −0.08) and −0.03 (95% CI: −0.04, −0.01), respectively, were observed. There were no statistically significant differences in the reporting of duration or exclusiveness of breastfeeding between groups of different sizes ($P > 0.4$). A test for trend between study size and mean difference in BMI was not statistically significant with or without adjustment for age ($P > 0.2$). Evidence of publication bias was difficult to perceive by a forest or funnel plot (Figure 2 and **Figure 3**). An Egger test for small-study bias was statistically significant ($P = 0.002$), but the Begg test for publication bias was not ($P = 0.97$).

The mean BMI difference in 31 published studies that reported (either narratively or quantitatively) on the direction of the association between infant feeding and adiposity (−0.04; 95% CI: −0.06, −0.02) did not differ significantly (P for difference = 0.58) from the combined estimate from the remaining 5 studies that did not report on the nature of the association (−0.02; 95% CI: −0.05, 0.02). Of the 32 studies that responded to our request for data, 6 had previously reported mean differences in BMI between infant feeding groups. The pooled mean difference in these studies appeared greater (−0.26; 95% CI: −0.34, −0.19) than the pooled estimate from the remaining 26 studies that had not previously reported mean BMIs (−0.06; 95% CI: −0.08, −0.04). Although this may show that studies with greater differences in mean BMI between infant feeding groups are more likely to report data than are those showing smaller differences, the difference between pooled estimates was not statistically significant ($P = 0.25$).

Influence of age at outcome and sex

The difference in mean BMI between infant feeding groups varied somewhat with age at outcome measurement. A mean difference of −0.01 (95% CI: −0.03, 0.01) in infants and children aged < 5 y, of −0.05 (95% CI: −0.08, −0.02) in children aged 5–9 y, of −0.19 (95% CI: −0.25, −0.13) in older children and adolescents, and of −0.11 (95% CI: −0.17, −0.04) in adults was observed. However, neither a test for overall age differences ($P = 0.28$) nor a test for trend across age groups (treating mean age as a continuous variable) were statistically significant ($P = 0.32$). Year of birth was unrelated to mean differences in BMI

TABLE 2
Studies in which mean differences were obtained from the published literature and used in a sensitivity analysis[1]

	Design	Source	Source of information on feeding	Year born, age measured[2]	Breastfed and formula-fed	Exclusivity of feeding	Definition of obesity used	Reported odds ratio	Adjustments	Difference in BMI between breastfed and formula-fed
Study					*n*					
Fomon et al (27)	PC	Infants from a maternity unit (USA)	In infancy	1971, 8	156, 276	No	None	—	—	0.11 ± 0.17[3]
Grummer-Strawn and Mei (32)	HC	The Special Supplemental Nutrition Program for Women, Infants, and Children; retrospective data from the Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System collected in a subsample (USA)	PQ at ≤ 2 y	1988–1992, 4	51 286, 126 018	Unclear[4]	BMI > 95th percentile adjusted for age	0.92 (0.90, 0.95)[5]	—	0.0 ± 0.01
Ravelli et al (30)	HC	Dutch Famine Birth Cohort Study	Postnatal medical records	1947, 48–53	520, 105	No	—	—	—	−0.4 ± 0.13
Rich-Edwards et al (12)	PC	The Nurses' Health Study (USA)	Questionnaire in adulthood	1921–1946, 59	15 242, 25 929	No	—	—	—	0.0 ± 0.05[6]
Multiple studies										
Overall pooled estimate (95% CI) based on a fixed-effects model from 4 studies that published a mean difference					67 204, 152 28					−0.00 (−0.02, 0.02)

[1] Studies are ordered alphabetically. HC, historical cohort; PC, prospective cohort; PQ, parental questionnaire ≥ 3 y after delivery. BMI is measured in kg/m^2.
[2] $\bar{x}$ (all values except ranges); age shown in years.
[3] $\bar{x}$ ± SE (all such values).
[4] Formula-fed group never breastfed; exclusivity of breastfeeding not stated.
[5] 95% CI in parentheses.
[6] Integer-only values for BMI were published.

(P = 0.32). In 32 studies that provided data by sex, the mean difference did not differ significantly between males (−0.06; 95% CI: −0.09, −0.03) and females (−0.09; 95% CI: −0.13, −0.06).

Influence of potential confounding factors

In 28 studies, it was possible to examine the effect of adjustment for SES (based on parental status in studies of infants and children or on individual status in studies of adults; Table 1 and **Table 3**). The age-adjusted difference in mean BMI was similar before and after adjustment for SES; considerable heterogeneity remained between study estimates (Table 3). Similarly, adjustment for maternal smoking in pregnancy (10 studies) had little effect on the mean difference observed (Table 3). In 18 studies, it was possible to examine the effect of adjustment for maternal BMI [parental BMI was used in one study (5)]. The age-adjusted mean difference was reduced from −0.11 to −0.05 after adjustment for maternal BMI (Table 3). A test for heterogeneity was of borderline statistical significance ($P < 0.001$ before adjustment; $P = 0.079$ after adjustment). The effect of combined adjustment for SES, maternal BMI, and maternal smoking during pregnancy could be examined in the 11 studies that provided data. The age-adjusted mean difference (−0.10; 95% CI: −0.14, −0.06) was effectively abolished after adjustment for these 3 factors (adjusted mean difference: −0.01; 95% CI: −0.05, 0.03). In 9 of the 11 individual studies, the pattern was similar—a negative effect before adjustment, which was either reduced in magnitude or became positive after adjustment for the 3 factors. A further study showed no change in mean BMI after adjustment, and another showed a slight increase after adjustment. Adjustment for these 3 factors appeared to explain some of the heterogeneity between estimates ($P < 0.001$ with adjustment for age; $P = 0.022$ with adjustment for age and the other 3 factors).

Influence of infant feeding exposure: ascertainment method, exclusivity, and duration

The mean difference in BMI between feeding groups was not significantly affected ($P = 0.58$) by whether infant feeding status was recorded in infancy (n = 16) or ascertained retrospectively by parental questionnaire (n = 20) administered ≥3 y after birth (43, 44). The difference in mean BMI appeared somewhat smaller between 20 studies in which initial feeding groups were definitely exclusive (−0.06; 95% CI: −0.09, −0.04) and 12 studies that did not report whether feeding was exclusive (−0.13; 95% CI: −0.18, −0.08). However, this difference was not statistically significant (P = 0.45).

Prolonged breastfeeding appeared to show a slightly greater protective effect on mean levels of adiposity than did breastfeeding for a shorter time. In 18 studies that reported on exclusive breastfeeding, the difference between the protective effect of breastfeeding and that of formula feeding was shown to be greatest in subjects who were breastfed for the longest time: in the 3 studies that reported exclusive breastfeeding for ≥8 mo (23, 25, 28), the mean difference was −0.39 (95% CI: −0.51, −0.26), whereas the mean difference for both tertiles of shorter breastfeeding was −0.05. In a meta-regression, each additional month of exclusive breastfeeding was associated with a decrease of 0.04

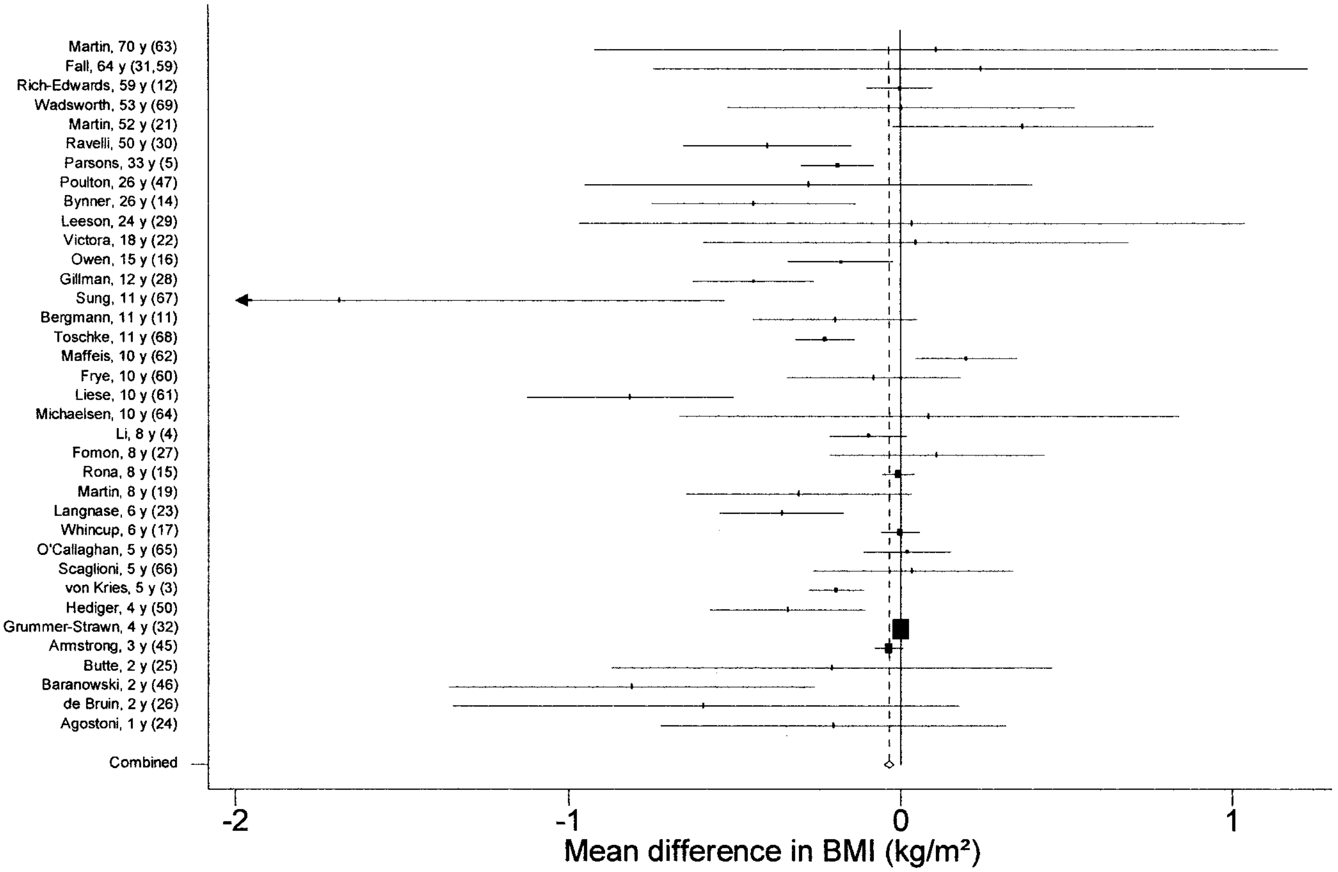

FIGURE 2. Mean (95% CI) difference in BMI between breastfed and bottle-fed participants in 36 studies (4 crude estimates, 32 adjusted for age). Box area of each study is proportional to the inverse of the variance, and horizontal lines show the 95% CI. The first author of each study is indicated on the *y*-axis, the mean age of that study's subjects (in y) is shown in ascending order, and the reference number is shown in parentheses. The pooled estimate, which is based on a fixed-effects model, is shown by a dashed vertical line; the diamond indicates the 95% CI.

in mean BMI (95% CI: −0.06, −0.01; $P = 0.008$). The protective effect of exclusive breastfeeding for ≥8 mo was abolished in 2 studies (23, 28) after adjustment for SES, maternal BMI, and maternal smoking (from −0.4 to −0.02 after adjustment). Similar but weaker findings were observed when the duration of feeding was considered in subjects exclusively and subjects nonexclusively breastfed (data not presented).

DISCUSSION

This systematic review of 36 published and unpublished studies found lower mean BMIs in subjects who had been breastfed in infancy than in those who had been formula-fed. This small effect was halved by adjustment for maternal BMI in early life and abolished in a meta-analysis of 11 studies that simultaneously adjusted for 3 potentially important confounders—maternal BMI, maternal SES, and maternal smoking.

In our recent review of 28 published studies, in which we examined the influence of initial feeding on the odds of obesity in later life (6), the overall OR of obesity (mostly based on the 95th or 97th percentile of the BMI distribution) was 0.87 (95% CI: 0.85, 0.89). Assuming a normal distribution of BMI and a conservative estimate of 2 SD in BMIs (6, 60), this OR would be consistent with an overall mean difference in BMIs between infant feeding groups of −0.15 (95% CI: −0.18, −0.13). The higher mean difference estimated from the previous review—which was based entirely on published literature (6)—than the present estimated difference (−0.08; 95% CI: −0.10, −0.05; derived from both published and unpublished sources) may be explained by several factors. One potential explanation is publication bias. There was some evidence of small-study bias in the current review when we stratified the pooled analyses by study size and by using the Egger test (61), which is a more sensitive test for small-study bias than is the Begg test. These observations,

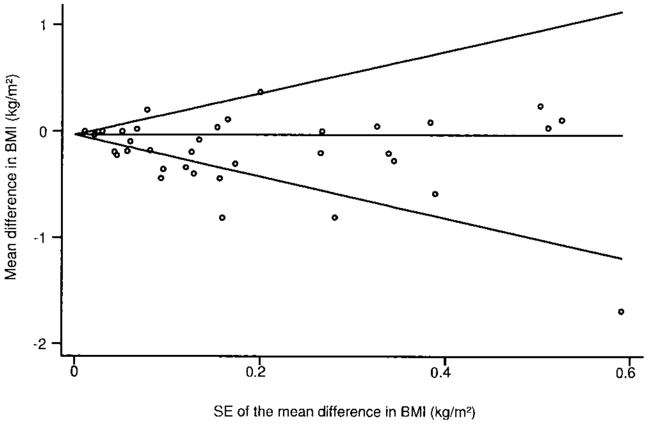

FIGURE 3. Begg's funnel plot (with pseudo 95% confidence limits) showing the mean (±SEM) difference in BMI.

TABLE 3
Pooled mean differences obtained by using fixed-effect models with various levels of adjustment[1]

		Difference in BMI (breastfed−bottle-fed) with various levels of adjustments					
			Adjusted for				
	No. of studies	Crude	Age	Age and SES	Age and maternal BMI	Age and maternal smoking in pregnancy	Age, SES, maternal smoking and maternal BMI
All studies	36	−0.04 (−0.06, −0.03)[2]	−0.04 (−0.05, −0.02)[3]	—	—	—	—
Chi-square test		250	173				
P		<0.001	<0.001				
Studies that responded	32	−0.09 (−0.11, −0.07)	−0.08 (−0.10, −0.05)	—	—	—	—
Chi-square test		206	140				
P		<0.001	<0.001				
With SES	28	−0.10 (−0.12, −0.07)	−0.08 (−0.10, −0.06)	−0.06 (−0.09, −0.04)	—	—	—
Chi-square test		191	111	74			
P		<0.001	<0.001	<0.001			
With maternal BMI	18	−0.14 (−0.18, −0.11)	−0.11 (−0.14, −0.08)	−0.08 (−0.11, −0.04)	−0.05 (−0.09, −0.02)	—	—
Chi-square test		120	62	44	26		
P		<0.001	<0.001	<0.001	0.079		
With SES, maternal BMI, and maternal smoking	11	−0.12 (−0.16, −0.08)	−0.10 (−0.14, −0.06)	−0.06 (−0.10, −0.02)	−0.06 (−0.10, −0.02)	−0.11 (−0.15, −0.07)	−0.01 (−0.05, 0.03)
Chi-square test		85	48	28	20	24	21
P		<0.001	<0.001	0.002	0.027	0.008	0.022

[1] BMI was measured in kg/m^2. SES, socioeconomic status.
[2] $\bar{x}$; 95% CI in parentheses (all such values).
[3] 32 of the 36 studies used adjustment for age.

combined with our sensitivity analyses of differences between published and unpublished estimates, suggest that publication bias is a potential concern in interpreting the published literature. An alternative explanation for the presence of stronger associations in small studies, ie, more precise exposure measurement, seems unlikely here; methods of ascertaining infant feeding did not differ systematically between smaller and larger studies and had little or no relation to outcome in a sensitivity analysis. It is also possible that breastfeeding is associated with a lower prevalence of obesity, but that it has no relation with mean BMI. Such a situation could occur if breastfeeding were associated not only with a lower prevalence of obesity but also with a lower prevalence of underweight, which would leave the mean BMI unchanged, as has been suggested by other investigators (32). Further examination of the association between infant feeding and underweight in later life is needed.

Although obtaining data directly from study authors allowed for standardization of data presentation by permitting examination of the influence of exposures such as prolonged breastfeeding, there was heterogeneity in mean differences in BMI across studies. This may well reflect the fact that participating studies were all observational and that variable degrees of confounding were present. Analysis based on 11 studies in which we able to obtain adjustment for 3 major confounders reduced the heterogeneity between study estimates. Adjustment for measures of size at birth may be important, especially because higher birth weight might be associated with formula feeding and with a higher BMI in later life (45, 62). However, a recent systematic review of a small number of studies with adjustment for size at birth failed to find any substantive effect of that variable on the magnitude of the associations between breastfeeding and the prevalence of obesity (6).

The null effect observed after simultaneous adjustment for important confounders in 11 studies is of considerable interest and suggests that apparent protective effects of breastfeeding on adiposity may be explained by confounding. This finding is consistent with our earlier meta-analysis of ORs, which found that the protective effect of infant feeding on obesity was reduced from an OR of 0.86 to an OR of 0.93 in 6 studies that included adjustment for SES, parental BMI, and maternal smoking (6). However, to confirm this finding, further data are needed from studies that use simultaneous adjustment for important confounders. Randomized trials or studies in populations without social gradients in infant feeding (such as those from the developing world) may also be useful for confirming that observed effects are explained by residual confounding. However, experimental studies are generally impractical in this context, except in specific circumstances of preterm birth or randomized controlled trials of breastfeeding promotion (63, 64).

Although the overall and adjusted estimates of mean differences in BMI between breastfeeders and bottle feeders were modest, there was some evidence that prolonged breastfeeding was associated with a larger difference in BMI. It is possible that prolonged breastfeeding confers greater protection (and provides evidence of a dose-response relation), but the evidence from this review was weak, and further examination of this issue is needed. Some evidence indicates that the relation of breastfeeding to mean BMI differed with age and is stronger in adolescents. However, if the effect in adolescence is real, the relatively small difference in BMIs observed in adults (in whom the consequences of obesity are of greatest public health significance) implies that the long-term importance of breastfeeding is limited.

Although a protective effect of breastfeeding on levels of adiposity in later life is biologically plausible (3, 65, 66), our results suggest that, overall, breastfeeding is associated with at most a small effect on BMI in adolescence and adult life. Even if a protective effect of breastfeeding on BMI at the upper 95% confidence limit (ie, −0.2) in these age groups were observed, that would result in a reduction of ≈1% in the incidence of CHD and type 2 diabetes, according to earlier observational data that suggested that a decrease in BMI (from 21.9 to 20.0) was associated with a 10% reduction in coronary events and diabetes (9). Encouraging breastfeeding for the purpose of reducing mean BMIs cannot therefore be advocated on the basis of this review. However, it remains possible that breastfeeding provides some protection against obesity (6). In addition, breastfeeding has numerous other health benefits, including improved neural and psychosocial development (67, 68) and has the potential to protect against allergic disease (69) and lower blood cholesterol levels in later life (16).

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REFERENCES

1. James PT, Rigby N, Leach R. The obesity epidemic, metabolic syndrome and future prevention strategies. Eur J Cardiovasc Prev Rehabil 2004; 11:3–8.
2. de Onis M, Blossner M. Prevalence and trends of overweight among preschool children in developing countries. Am J Clin Nutr 2000;72: 1032–9.
3. Von Kries R, Koletzko B, Sauerwald T, et al. Breast feeding and obesity: cross sectional study. BMJ 1999;319:147–50.
4. Li L, Parsons TJ, Power C. Breast feeding and obesity in childhood: cross sectional study. BMJ 2003;327:904–5.
5. Parsons TJ, Power C, Manor O. Infant feeding and obesity through the lifecourse. Arch Dis Child 2003;88:793–4.
6. Owen CG, Martin RM, Whincup PH, Davey Smith G, Cook DG. Effect of infant feeding on the risk of obesity across the life course: a quantitative review of published evidence. Pediatrics 2005;115:1367–77.
7. Arenz S, Ruckerl R, Koletzko B, von Kries R. Breast-feeding and childhood obesity–a systematic review. Int J Obes Relat Metab Disord 2004; 28:1247–56.
8. Dewey KG. Is breastfeeding protective against child obesity? J Hum Lact 2003;19:9–18.
9. Shaper AG, Wannamethee SG, Walker M. Body weight: implications for the prevention of coronary heart disease, stroke, and diabetes mellitus in a cohort study of middle aged men. BMJ 1997;314:1311–7.
10. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961–9.
11. Bergmann KE, Bergmann RL, Von Kries R, et al. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. Int J Obes Relat Metab Disord 2003;27:162–72.
12. Rich-Edwards JW, Stampfer MJ, Manson JE, et al. Breastfeeding during infancy and the risk of cardiovascular disease in adulthood. Epidemiology 2004;15:550–6.
13. Bogen DL, Hanusa BH, Whitaker RC. The effect of breast-feeding with and without formula use on the risk of obesity at 4 years of age. Obes Res 2004;12:1527–35.
14. Bynner JM. 1970 British Cohort Study: twenty six-year follow-up, 1996 [computer file]. Colchester, Essex: UK Data Archive [distributor] 2003;SN 3833 (accessed 21 July 2003).
15. Rona RJ, Qureshi S, Chinn S. Factors related to total cholesterol and blood pressure in British 9 year olds. J Epidemiol Community Health 1996;50:512–8.
16. Owen CG, Whincup PH, Odoki K, Gilg JA, Cook DG. Infant feeding and blood cholesterol: a study in adolescents and a systematic review. Pediatrics 2002;110:597–608.
17. Whincup PH, Cook DG, Shaper AG. Early influences on blood pressure: a study of children aged 5–7 years. BMJ 1989;299:587–91.
18. Taittonen L, Nuutinen M, Turtinen J, Uhari M. Prenatal and postnatal factors in predicting later blood pressure among children: cardiovascular risk in young Finns. Pediatr Res 1996;40:627–32.
19. Martin RM, Ness AR, Gunnell D, Emmett P, Davey SG. Does breastfeeding in infancy lower blood pressure in childhood? The Avon Longitudinal Study of Parents and Children (ALSPAC). Circulation 2004; 109:1259–66.
20. Martin RM, Davey SG, Mangtani P, Tilling K, Frankel S, Gunnell D. Breastfeeding and cardiovascular mortality: the Boyd Orr cohort and a systematic review with meta-analysis. Eur Heart J 2004;25:778–86.
21. Martin RM, Ben-Shlomo Y, Gunnell D, Ellwood P, Yarnell JG, Davey SG. Breastfeeding and cardiovascular disease risk factors, incidence and

mortality: the Caerphilly Study. J Epidemiol Community Health 2005; 59:121–9.
22. Victora CG, Barros F, Lima RC, Horta BL, Wells J. Anthropometry and body composition of 18 year old men according to duration of breast feeding: birth cohort study from Brazil. BMJ 2003;327:901.
23. Langnase K, Mast M, Danielzik S, Spethmann C, Muller MJ. Socioeconomic gradients in body weight of German children reverse direction between the ages of 2 and 6 years. J Nutr 2003;133:789–96.
24. Agostoni C, Riva E, Scaglioni S, Marangoni F, Radaelli G, Giovannini M. Dietary fats and cholesterol in italian infants and children. Am J Clin Nutr 2000;72:1384S–91S.
25. Butte NF, Wong WW, Hopkinson JM, Smith EO, Ellis KJ. Infant feeding mode affects early growth and body composition. Pediatrics 2000;106: 1355–66.
26. de Bruin NC, Degenhart HJ, Gal S, Westerterp KR, Stijnen T, Visser HK. Energy utilization and growth in breast-fed and formula-fed infants measured prospectively during the first year of life. Am J Clin Nutr 1998;67:885–96.
27. Fomon SJ, Rogers RR, Ziegler EE, Nelson SE, Thomas LN. Indices of fatness and serum cholesterol at age eight years in relation to feeding and growth during early infancy. Pediatr Res 1984;18:1233–8.
28. Gillman MW, Rifas-Shiman SL, Camargo CA Jr, et al. Risk of overweight among adolescents who were breastfed as infants. JAMA 2001; 285:2461–7.
29. Leeson CP, Kattenhorn M, Deanfield JE, Lucas A. Duration of breast feeding and arterial distensibility in early adult life: population based study. BMJ 2001;322:643–7.
30. Ravelli AC, van der Meulen JH, Osmond C, Barker DJ, Bleker OP. Infant feeding and adult glucose tolerance, lipid profile, blood pressure, and obesity. Arch Dis Child 2000;82:248–52.
31. Fall CH, Barker DJ, Osmond C, Winter PD, Clark PM, Hales CN. Relation of infant feeding to adult serum cholesterol concentration and death from ischaemic heart disease. BMJ 1992;304:801–5.
32. Grummer-Strawn LM, Mei Z. Does breastfeeding protect against pediatric overweight? Analysis of longitudinal data from the Centers for Disease Control and Prevention Pediatric Nutrition Surveillance System. Pediatrics 2004;113:e81–86.
33. Boulton J. Nutrition in childhood and its relationships to early somatic growth, body fat, blood pressure, and physical fitness. Acta Paediatr Scand Suppl 1981;284:1–85.
34. Charney E, Goodman HC, McBride M, Lyon B, Pratt R. Childhood antecedents of adult obesity. Do chubby infants become obese adults? N Engl J Med 1976;295:6–9.
35. Eid EE. Follow-up study of physical growth of children who had excessive weight gain in first six months of life. Br Med J 1970;2:74–6.
36. Hitchcock NE, Coy JF. The growth of healthy Australian infants in relation to infant feeding and social group. Med J Aust 1989;150:306–1.
37. Oakley JR. Differences in subcutaneous fat in breast- and formula-fed infants. Arch Dis Child 1977;52:79–80.
38. Richter J. Influence of duration of breast-feeding on body-weight-development. Arztl Jugendkd 1981;72:166–9.
39. Taitz LS. Infantile overnutrition among artificially fed infants in the Sheffield region. Br Med J 1971;1:315–6.
40. Wilkinson PW, Parkin JM, Pearlson J, Philips PR, Sykes P. Obesity in childhood: a community study in Newcastle upon Tyne. Lancet 1977; 1:350–2.
41. World Health Organization. Indicators for assessing breast-feeding practices. Division of Diarrhoeal and Acute Respiratory Disease Control. Report of an informal meeting. Geneva, Switzerland: World Health Organization, 1991.
42. Armstrong J, Reilly JJ. Breastfeeding and lowering the risk of childhood obesity. Lancet 2002;359:2003–4.
43. Baranowski T, Bryan GT, Rassin DK, Harrison JA, Henske JC. Ethnicity, infant-feeding practices, and childhood adiposity. J Dev Behav Pediatr 1990;11:234–9.
44. Poulton R, Williams S. Breastfeeding and risk of overweight. JAMA 2001;286:1449–50.
45. Hediger ML, Overpeck MD, Kuczmarski RJ, Ruan WJ. Association between infant breastfeeding and overweight in young children. JAMA 2001;285:2453–60.
46. Fall CH, Osmond C, Barker DJ, et al. Fetal and infant growth and cardiovascular risk factors in women. BMJ 1995;310:428–32.
47. Frye C, Heinrich J. Trends and predictors of overweight and obesity in East German children. Int J Obes Relat Metab Disord 2003;27:963–9.
48. Liese AD, Hirsch T, von Mutius E, Keil U, Leupold W, Weiland SK. Inverse association of overweight and breast feeding in 9 to 10-y-old children in Germany. Int J Obes Relat Metab Disord 2001;25:1644–50.
49. Maffeis C, Micciolo R, Must A, Zaffanello M, Pinelli L. Parental and perinatal factors associated with childhood obesity in north-east Italy. Int J Obes Relat Metab Disord 1994;18:301–5.
50. Martin RM, Davey Smith G, Mangtani P, Frankel S, Gunnell D. Association between breast feeding and growth: the Boyd-Orr cohort study. Arch Dis Child Fetal Neonatal Ed 2002;87:F193–201.
51. Michaelsen KF. Nutrition and growth during infancy. The Copenhagen Cohort Study. Acta Paediatr Suppl 1997;420:1–36.
52. O'Callaghan MJ, Williams GM, Andersen MJ, Bor W, Najman JM. Prediction of obesity in children at 5 years: a cohort study. J Paediatr Child Health 1997;33:311–6.
53. Scaglioni S, Agostoni C, Notaris RD, et al. Early macronutrient intake and overweight at five years of age. Int J Obes Relat Metab Disord 2000;24:777–81.
54. Sung RY, Tong PC, Yu CW, et al. High prevalence of insulin resistance and metabolic syndrome in overweight/obese preadolescent Hong Kong Chinese children aged 9–12 years. Diabetes Care 2003;26:250–1.
55. Toschke AM, Vignerova J, Lhotska L, Osancova K, Koletzko B, Von Kries R. Overweight and obesity in 6- to 14-year-old Czech children in 1991: protective effect of breast-feeding. J Pediatr 2002;141:764–9.
56. Wadsworth M, Marshall S, Hardy R, Paul A. Breast feeding and obesity. Relation may be accounted for by social factors. BMJ 1999;319:1576 (letter).
57. Light RJ, Pillemar DB. Summing up: the science of reviewing research. Cambridge, MA: Harvard University Press, 1984.
58. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.
59. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.
60. Chinn S. A simple method for converting an odds ratio to effect size for use in meta-analysis. Stat Med 2000;19:3127–31.
61. Egger M, Davey Smith G, Schneider M. Systematic reviews of observational studies. In: Egger M, Davey Smith G, Altman DG, eds. Systematic reviews in health care: meta-analysis in context. London, United Kingdom: BMJ Publishing Group, 2001:211–27.
62. Barker DJ, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. Lancet 1993;341:938–41.
63. Singhal A, Lucas A. Early origins of cardiovascular disease: is there a unifying hypothesis? Lancet 2004;363:1642–5.
64. Kramer MS, Guo T, Platt RW, et al. Breastfeeding and infant growth: biology or bias? Pediatrics 2002;110:343–7.
65. Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B, Dewey KG. Energy and protein intakes of breast-fed and formula-fed infants during the first year of life and their association with growth velocity: the DARLING Study. Am J Clin Nutr 1993;58:152–61.
66. Lucas A, Sarson DL, Blackburn AM, Adrian TE, Aynsley-Green A, Bloom SR. Breast vs bottle: endocrine responses are different with formula feeding. Lancet 1980;1:1267–9.
67. Makrides M, Neumann M, Simmer K, Pater J, Gibson R. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet 1995; 345:1463–8.
68. Fergusson DM, Woodward LJ. Breast feeding and later psychosocial adjustment. Paediatr Perinat Epidemiol 1999;13:144–57.
69. Lucas A, Brooke OG, Morley R, Cole TJ, Bamford MF. Early diet of preterm infants and development of allergic or atopic disease: randomised prospective study. BMJ 1990;300:837–40.

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