The effect of breastfeeding on mean body mass index throughout life: a quantitative review of published and unpublished observational evidence

Christopher G Owen, Richard M Martin, Peter H Whincup, George Davey-Smith, Matthew W Gillman, and Derek G Cook

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/m²) 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between infant feeding and a measure of obesity or adiposity in later life, which was supplemented with data from unpublished sources.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 353 301 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/m²). 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...
<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Source</th>
<th>Source of information on feeding</th>
<th>Year born, age measured</th>
<th>Breast fed, formula fed</th>
<th>Any exclusive breastfeeding or formula feeding</th>
<th>Duration of any breastfeeding</th>
<th>Differences adjusted for</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agostoni et al (24)</td>
<td>PC</td>
<td>Birth in San Paolo Hospital maternity ward (Italy)</td>
<td>In infancy</td>
<td>Not stated, 1</td>
<td>60, 55</td>
<td>Yes</td>
<td>7 mo (4–14 mo)</td>
<td>−0.20 ± 0.27</td>
</tr>
<tr>
<td>Armstrong and Reilly (42)</td>
<td>HC</td>
<td>Child Health Surveillance Programme of Scottish children (UK)</td>
<td>In infancy</td>
<td>1995–1996, 3</td>
<td>8928, 23 938</td>
<td>Yes</td>
<td>6 wk</td>
<td>−0.04 ± 0.02</td>
</tr>
<tr>
<td>Baranowski et al (43)</td>
<td>CS</td>
<td>Studies of Children’s Activity and Nutrition in infancy</td>
<td>Parental interview</td>
<td>1981–1993, 2</td>
<td>66, 173</td>
<td>Yes</td>
<td>7 mo (3 to &lt;12 mo)</td>
<td>−0.81 ± 0.28</td>
</tr>
<tr>
<td>Bergmann et al (11)</td>
<td>PC</td>
<td>German Multicenter Antryp Study</td>
<td>In infancy</td>
<td>1990, 11</td>
<td>600, 69</td>
<td>Not stated</td>
<td>&gt;2 mo</td>
<td>−0.20 ± 0.13</td>
</tr>
<tr>
<td>Butte et al (25)</td>
<td>PC</td>
<td>Infants recruited at the Children’s Nutrition Research Center (Houston, TX)</td>
<td>In infancy</td>
<td>Not stated, 2</td>
<td>38, 34</td>
<td>Yes</td>
<td>35 d</td>
<td>−0.21 ± 0.34</td>
</tr>
<tr>
<td>Bynner (14)</td>
<td>PC</td>
<td>British Cohort Study</td>
<td>In infancy</td>
<td>1970, 23</td>
<td>736, 3609</td>
<td>No</td>
<td>≥ 3 mo</td>
<td>−0.44 ± 0.16</td>
</tr>
<tr>
<td>de Brun et al (26)</td>
<td>PC</td>
<td>Infants recruited at the Sophia Children’s Hospital (Netherlands)</td>
<td>In infancy</td>
<td>1991–1992, 2</td>
<td>19, 17</td>
<td>Yes</td>
<td>≤ 4 mo</td>
<td>−0.59 ± 0.39</td>
</tr>
<tr>
<td>Full et al (31, 46)</td>
<td>HC</td>
<td>Adults born in Herefordshire (UK)</td>
<td>Birth records</td>
<td>1920–1980, 64</td>
<td>856, 69</td>
<td>Yes</td>
<td>Not known</td>
<td>0.24 ± 0.50</td>
</tr>
<tr>
<td>Frye and Heinrich (47)</td>
<td>PC</td>
<td>The Bitterfeld Study consisting of 3 school surveys (Germany)</td>
<td>PQ</td>
<td>1979–1993, 10</td>
<td>762, 1956</td>
<td>Yes</td>
<td>20 wk</td>
<td>−0.08 ± 0.13</td>
</tr>
<tr>
<td>Gillman et al (28)</td>
<td>CS</td>
<td>Growing Up Today Study (offspring of the Names’ Health Study II (USA)</td>
<td>PQ</td>
<td>1981–1987, 12</td>
<td>4714, 1579</td>
<td>Yes</td>
<td>11 mo</td>
<td>−0.44 ± 0.09</td>
</tr>
<tr>
<td>Hetherington et al (45)</td>
<td>CS</td>
<td>The third National Health and Nutrition Examination Survey (NHANES III) (USA)</td>
<td>PQ</td>
<td>1983–1991, 4</td>
<td>560, 1498</td>
<td>Yes</td>
<td>16 mo</td>
<td>−0.34 ± 0.12</td>
</tr>
<tr>
<td>Langnase et al (23)</td>
<td>PC</td>
<td>Keel Obesity Prevention Study (Germany)</td>
<td>In infancy</td>
<td>1988–1996, 6</td>
<td>1750, 717</td>
<td>Yes</td>
<td>10 mo</td>
<td>−0.36 ± 0.10</td>
</tr>
<tr>
<td>Leeson et al (29)</td>
<td>CS</td>
<td>Birth in a maternity hospital (Cambridge, UK)</td>
<td>Maternal recall</td>
<td>1969–1975, 24</td>
<td>182, 120</td>
<td>Yes</td>
<td>4 mo</td>
<td>0.03 ± 0.51</td>
</tr>
<tr>
<td>Li et al (4)</td>
<td>CS</td>
<td>Offspring of the 1958 Birth Cohort (UK)</td>
<td>PQ</td>
<td>1973–1987, 8</td>
<td>1066, 961</td>
<td>No breastfeeding at all</td>
<td>6 mo (≥ 3 mo)</td>
<td>−0.10 ± 0.06</td>
</tr>
<tr>
<td>Läse et al (48)</td>
<td>CS</td>
<td>Part of the International Study of Asthma and Allergy in Childhood (2 German cities)</td>
<td>PQ</td>
<td>1985–1987, 10</td>
<td>1754, 354</td>
<td>No</td>
<td>exclusively breastfed vs. mixed</td>
<td>3 mo</td>
</tr>
<tr>
<td>Mafficis et al (49)</td>
<td>CS</td>
<td>Recruited from schools in six areas of northeast Italy</td>
<td>PQ at 4–12 y</td>
<td>1976–1984, 10</td>
<td>864, 499</td>
<td>No</td>
<td>breastfed vs. mixed</td>
<td>3 mo</td>
</tr>
<tr>
<td>Martin et al (21)</td>
<td>PC</td>
<td>Males born in Caerphilly (UK)</td>
<td>Questionnaire1998–1999, 52</td>
<td>1140, 416</td>
<td>No</td>
<td>ever breastfed</td>
<td>Not stated</td>
<td>0.37 ± 0.20</td>
</tr>
<tr>
<td>Martin et al (50)</td>
<td>PC</td>
<td>The Boyd Orr cohort (UK)</td>
<td>Questionnaire1988–1993, 70</td>
<td>272, 90</td>
<td>No</td>
<td>ever breastfed</td>
<td>9 mo</td>
<td>0.11 ± 0.53</td>
</tr>
<tr>
<td>Martin et al (19)</td>
<td>PC</td>
<td>Avon Longitudinal Study of Parents and Children (UK)</td>
<td>In infancy</td>
<td>1991–1992, 8</td>
<td>2082, 950</td>
<td>Yes</td>
<td>Not stated</td>
<td>−0.31 ± 0.17</td>
</tr>
<tr>
<td>Michauden (51)</td>
<td>PC</td>
<td>Copenhagen Cohort Study on Infant Nutrition and Growth (Denmark)</td>
<td>In infancy</td>
<td>1987–1988, 9</td>
<td>41, 62</td>
<td>No</td>
<td>bottle-fed vs. mixed</td>
<td>9 mo</td>
</tr>
<tr>
<td>O’Callaghan et al (52)</td>
<td>PC</td>
<td>Mater University Study of Pregnancy (Australia)</td>
<td>In infancy</td>
<td>1981–1984, 5</td>
<td>3488</td>
<td>No</td>
<td>mixed fed vs. bottle-fed</td>
<td>0.02 ± 0.07</td>
</tr>
</tbody>
</table>

**TABLE 1**

Studies that provided data for inclusion in the meta-analysis.

**Initial Breastfeeding and Body Mass Index**
### TABLE 1 (Continued)

<table>
<thead>
<tr>
<th>Design</th>
<th>Source</th>
<th>Year born, age measured</th>
<th>Source of information on feeding</th>
<th>Duration of any breastfeeding</th>
<th>Any exclusive breastfeeding or formula feeding</th>
<th>Age</th>
<th>Age and SES</th>
<th>Age and maternal BMI</th>
<th>Age and smoking</th>
<th>Age, SES, and maternal BMI and smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>CS</td>
<td>Ten Towns Heart Health Study (UK)</td>
<td>1982–1986, 15</td>
<td>PQ at 5–7 y</td>
<td>Yes</td>
<td>7 mo (3 to 48 mo)</td>
<td>0.18 ± 0.08</td>
<td>−0.12 ± 0.09</td>
<td>−0.17 ± 0.10</td>
<td>−0.12 ± 0.09</td>
<td>−0.04 ± 0.09</td>
</tr>
<tr>
<td>CS</td>
<td>British Birth Cohort Study (UK)</td>
<td>1958, 33</td>
<td>PQ at 7 y</td>
<td>No: wholly exclusively breastfed</td>
<td>Unknown</td>
<td>−0.19 ± 0.06</td>
<td>−0.13 ± 0.06</td>
<td>−0.17 ± 0.07&lt;sup&gt;5&lt;/sup&gt;</td>
<td>−0.17 ± 0.06</td>
<td>−0.10 ± 0.06&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>CS</td>
<td>Dunedin Multidisciplinary Health and Development Study (New Zealand)</td>
<td>1972–1973, 26</td>
<td>PQ at 3 y</td>
<td>Yes</td>
<td>28 wk</td>
<td>−0.28 ± 0.34</td>
<td>−0.34 ± 0.34</td>
<td>−0.22 ± 0.36</td>
<td>−0.27 ± 0.40</td>
<td>−0.14 ± 0.40</td>
</tr>
<tr>
<td>CS</td>
<td>National Study of Health and Growth (England and Scotland)</td>
<td>1981–1990, 8</td>
<td>PQ at 9 y</td>
<td>Yes</td>
<td>4 mo (3–21 mo)</td>
<td>0.08 ± 0.03</td>
<td>0.01 ± 0.03</td>
<td>0.01 ± 0.03</td>
<td>0.05 ± 0.03</td>
<td>0.03 ± 0.03</td>
</tr>
<tr>
<td>CS</td>
<td>Birth at San Paolo Hospital (Italy)</td>
<td>1990–1991, 5</td>
<td>In infancy</td>
<td>Yes</td>
<td>5 mo</td>
<td>0.04 ± 0.15</td>
<td>0.09 ± 0.16</td>
<td>0.10 ± 0.16</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CS</td>
<td>Primary schoolchildren (Hong Kong, China)</td>
<td>1988–1992, 11</td>
<td>PQ</td>
<td>No: breastfed</td>
<td>244 d</td>
<td>−1.69 ± 0.59</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CS</td>
<td>Nationwide Anthropometric Survey of Children and Adolescents (Czech Republic)</td>
<td>1976–1985, 11</td>
<td>PQ</td>
<td>No: breastfed vs. mixed fed</td>
<td>−0.23 ± 0.05</td>
<td>−0.21 ± 0.05</td>
<td>−0.07 ± 0.05</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>CS</td>
<td>Subjects recruited from 9 of 24 towns involved in the British Regional Heart Study (UK)</td>
<td>1979–1983, 6</td>
<td>PQ at 5–8 y</td>
<td>Yes</td>
<td>7 mo (3–60 mo)</td>
<td>0.03 ± 0.03</td>
<td>−0.01 ± 0.03</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

Multiple studies

Overall pooled estimate based on a fixed-effects model from 32 studies adjusted for age

Overall pooled estimate based on fixed-effects models from 28 studies adjusted for age with and without adjustment for socioeconomic status

Overall pooled estimate based on fixed-effects models from 18 studies adjusted for age with and without adjustment for maternal BMI

Overall pooled estimate based on fixed-effects models from 11 studies adjusted for age with and without adjustment for maternal smoking in pregnancy

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

<sup>1</sup> 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/m².

<sup>2</sup> <sup>5</sup> All values except ranges; age shown in years.

<sup>3</sup> ± SE (all such values).

<sup>4</sup> Besides adjustment for parental rather than maternal BMI, mean differences adjusted for: ethnicity, <sup>7</sup> geographical origin.

<sup>5</sup> Total number only.

<sup>6</sup> Adjusted for parental BMI instead of maternal BMI.

<sup>7</sup> 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 lifespan, 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 from 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 (≥ age: < 16 y) were based on the SES of the head-of-household parent; in adults, they were based on 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...
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 narratively or quantitatively; 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 that was not performed in 4 studies, and that for age and maternal BMI was not performed in 14 studies, and that for age and maternal smoking was not performed in 21 studies. 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 those who were formula-fed (β 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 (β 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.
(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

---

**Table 2**

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Source</th>
<th>Source of information on feeding</th>
<th>Year born, age measured</th>
<th>Mean difference</th>
<th>Exclusivity of feeding</th>
<th>Definition of obesity used</th>
<th>Adjustments</th>
<th>Difference in BMI between breastfed and formula-fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fomon et al (27)</td>
<td>PC</td>
<td>Infants from a maternity unit (USA)</td>
<td>In infancy</td>
<td>1971, 8</td>
<td>156, 276</td>
<td>No</td>
<td>None</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Grummer-Strawn and Mei (32)</td>
<td>HC</td>
<td>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)</td>
<td>PQ at ≤ 2 y</td>
<td>1988–1992, 4</td>
<td>51, 286, 126, 018</td>
<td>Unclear</td>
<td>BMI &gt; 95th percentile adjusted for age</td>
<td>—</td>
<td>0.92 (0.90, 0.95)</td>
</tr>
<tr>
<td>Ravelli et al (30)</td>
<td>HC</td>
<td>Dutch Famine Birth Cohort Study</td>
<td>Postnatal medical records</td>
<td>1947, 48–53</td>
<td>520, 105</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rich-Edwards et al (12)</td>
<td>PC</td>
<td>The Nurses’ Health Study (USA)</td>
<td>Questionnaire in adulthood</td>
<td>1921–1946, 59</td>
<td>15, 242, 25, 929</td>
<td>No</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Multiple studies</td>
<td>Overall pooled estimate (95% CI) based on a fixed-effects model from 4 studies that published a mean difference</td>
<td>67, 204, 152, 28</td>
<td>0.13</td>
<td>0.0 ± 0.02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Studies are ordered alphabetically. HC, historical cohort; PC, prospective cohort; PQ, parental questionnaire ≥3 y after delivery. BMI is measured in kg/m².
2 ± (all values except ranges); age shown in years.
3 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.
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 non-exclusively 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,
3 major confounders reduced the heterogeneity between study analyses based on 11 studies in which we were able to obtain adjustment for additional and that variable degrees of confounding were present. Analysis 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 were 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 size at birth (6).

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 were able to obtain adjustment for 3 major confounders reduced the heterogeneity between study

### TABLE 3

Pooled mean differences obtained by using fixed-effect models with various levels of adjustment

<table>
<thead>
<tr>
<th>Adjusted for</th>
<th>Difference in BMI (breastfed—bottle-fed) with various levels of adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of studies</td>
<td>Crude</td>
</tr>
<tr>
<td>All studies</td>
<td>36</td>
</tr>
<tr>
<td>Chi-square test</td>
<td>250</td>
</tr>
<tr>
<td>Studies that responded</td>
<td>32</td>
</tr>
<tr>
<td>Chi-square test</td>
<td>206</td>
</tr>
<tr>
<td>With SES</td>
<td>28</td>
</tr>
<tr>
<td>Chi-square test</td>
<td>191</td>
</tr>
<tr>
<td>With maternal BMI</td>
<td>18</td>
</tr>
<tr>
<td>Chi-square test</td>
<td>120</td>
</tr>
<tr>
<td>With SES, maternal BMI, and maternal smoking</td>
<td>11</td>
</tr>
<tr>
<td>Chi-square test</td>
<td>85</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

1. BMI was measured in kg/m². SES, socioeconomic status.
2. t: 95% CI in parentheses (all such values).
3. 32 of the 36 studies used adjustment for age.
Although the overall and adjusted estimates of mean differences in BMI at ages 3, 5, and 7 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 differences 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 cholesterol levels in later life (16).

We are grateful to the following investigators, who kindly provided data for our review: C Agostoni and S Scaglioni (San Paolo Hospital, University of Milan, Milan Italy); J Armstrong (Glasgow Caledonian University, Glasgow, Scotland); J Reilly (Royal Hospital for Sick Children, Glasgow, Scotland); T Baranowski, F Bradford, and N Butte (Baylor College of Medicine, Dallas, TX); K Bergmann (Epidemiology and Health Reporting, Health of Children and Adolescents, Berlin, Germany); N de Bruin (Sophia Children’s Hospital, University Hospital and Erasmus University, Rotterdam, Netherlands); C Fall (MRC Environmental Epidemiology Unit, University of Southampton, United Kingdom); L Schack-Nielsen, M Egge, and K Fleischer-Michaelaensen (The Royal Veterinary and Agricultural University, Frederiksberg, Denmark); S Rifas and G Colditz (Harvard Medical School, Boston, MA); M Hediger and W Sun (National Institute of Child Health and Human Development, NIH/DHHS, Bethesda, MD); J Heinrich (GSF Institute of Epidemiology, Neuherberg, Germany); A Liese (Arnold School of Public Health, University of South Carolina, Columbia, SC); S Weiland (University of Ulm, Ulm, Germany); M Maffeis (University of Verona, Verona, Italy); P Emmett, A Ness, and DA Lawlor (University of Bristol, Bristol, United Kingdom); M O’Callaghan (Mater Misericordiae Children’s Hospital, South Brisbane, Australia); C Leeson (John Radcliffe Hospital, Oxford, United Kingdom); A Lucas (Institute of Child Health, London, United Kingdom); P Tong and R Sung (The Chinese University of Hong Kong, The Prince of Wales Hospital, Hong Kong, China); A Toschke and R von Kries (Ludwig Maximilian University of Munich, Munich, Germany); B Horta and C Victora (Universidade Federal de Pelotas, Pelotas, Brazil); M Wadsworth and S Black (Royal Free and University College Medical School, London, United Kingdom); S Williams (Dunedin School of Medicine, University of Otago, Otago, New Zealand); DP Strachan (St George’s, University of London, London, United Kingdom); and K Langnase, S Danielzik, and M Muller (Christian-Albrechts-Universitat zu Kiel, Kiel, Germany). We acknowledge the original data creators, depositors, copyright holders, the funders of the Data Collections, and the UK Data Archive (University of Essex, Colchester, United Kingdom) for use of data from the 1970 British Cohort Study and the National Study of Health and Growth. They bear no responsibility for the analysis or interpretation of this data.

All authors contributed substantially to the conception and design of the study. RMM carried out the literature search, CGO sent the data request, coordinated the search for unpublished data sources, carried out statistical analysis, and drafted the manuscript. The manuscript was critiqued by all authors for intellectual content; CGO acts as guarantor (who accepts full responsibility for the integrity of the work as a whole). All authors had access to the data and approved the final version of the manuscript. None of the authors had any personal or financial conflicts of interest.

REFERENCES

65. Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B, Dewey KG. En-