Critical review of the World Health Organization’s (WHO) 2007 report on ‘evidence of the long-term effects of breastfeeding: systematic reviews and meta-analysis’ with respect to obesity

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Summary

Obesity among children and adults has become a highly recognized public health concern and there is an increasing need to discover causes and evaluate preventative measures. One putatively causal influence on obesity is breastfeeding (BF). The World Health Organization (WHO) recently published a report (WR) on ‘Evidence of the Long-Term Effects of Breastfeeding: Systematic Reviews and Meta-Analysis’ and concluded ‘that the evidence suggests that breastfeeding may have a small protective effect [emphasis added] on the prevalence of obesity . . . [and] the effect of breastfeeding was not likely to be due to publication bias or confounding.’ Here we provide a critical overview of the WR’s section on BF and obesity by addressing eight questions: Q1: Is there sufficient evidence to conclude that BF is associated with lower rates of obesity in children? Q2: Is there sufficient evidence to conclude that BF is associated with lower rates of obesity among breastfed offspring once they reach adulthood? Q3: If there are such associations, what are their magnitudes in comparison with other putatively causal factors and with respect to the potential impact on individual or population levels of obesity? Q4: Is there sufficient evidence to conclude that BF causes a reduction in risk of obesity during childhood? Q5: Is there sufficient evidence to conclude that BF does not cause a reduction in risk of obesity during childhood? Q6: Is there sufficient evidence to conclude that BF causes a long-term reduction in risk of obesity that persists into adulthood? Q7: Is there sufficient evidence to conclude that BF does not cause a long-term reduction in risk of obesity that persists into adulthood? Q8: What further research might be done to address these questions? We conclude that, while BF may have benefits beyond any putative protection against obesity, and benefits of BF most likely outweigh any harms, any statement that a strong, clear or consistent body of evidence shows that BF causally reduces the risk of overweight or obesity is unwarranted at this time.

Keywords: Breastfeeding, infant formula feeding, meta-analysis, obesity.

Obesity reviews (2008) 9, 594–605

Introduction

Obesity’s prevalence has risen steadily in both adults and children for the past several decades and is recognized as a serious, unremitting public health concern by virtually every major body concerned with public health including the National Institutes of Health, the United States Department of Agriculture, Centers for Disease Control and Prevention, Food and Drug Administration and the World Health Organization (WHO). A primary reason
for public health concern is that obesity results in adverse conditions and diseases such as cardiovascular disease, stroke, type 2 diabetes mellitus and many forms of cancer. Apart from the established health problems linked to obesity, it is also economically costly to society, increases mortality rate and reduces quality of life and productivity. Obesity, in its severe forms, may truncate lifespan by as much as 5–20 years among young adults (1).

The causes of the population increase in obesity are only partially understood and almost certainly manifold (2). It seems that apart from generic conglomerations of factors labeled ‘genetics’, ‘environment’ and ‘energy balance’, no single factor explains more than a small proportion of inter-individual variance in adiposity. Thus, identification and subsequent intervention with many potentially modifiable factors that influence obesity development may be required to make profound and enduring changes to the population levels of obesity.

Breastfeeding (BF) is a putatively causal influence on obesity. A recent report from the WHO addressed this topic and concluded ‘that the evidence suggests that breastfeeding may have a small protective effect on the prevalence of obesity’. Yet, it is plausible that the WHO’s conclusion may not be consonant with the data available. In this review, a detailed analysis is provided of the obesity section of a WHO report entitled ‘Evidence of the Long-Term Effects of Breastfeeding: Systematic Reviews and Meta-Analysis’ (3). It has been proposed that BF (vs. not BF) causes a reduced risk of obesity in the breastfed offspring throughout life. In order to provide a detailed review, the following questions were addressed:

Q1: Is there sufficient evidence to conclude that BF is associated with lower rates of obesity in children?

Q2: Is there sufficient evidence to conclude that BF is associated with lower rates of obesity among breastfed offspring once they reach adulthood?

Q3: If there are such associations, what are their magnitudes in comparison with other putatively causal factors and with respect to the potential impact on individual or population levels of obesity?

Q4: Is there sufficient evidence to conclude that BF causes a reduction in risk of obesity during childhood?

Q5: Is there sufficient evidence to conclude that BF does not cause a reduction in risk of obesity during childhood?

Q6: Is there sufficient evidence to conclude that BF causes a long-term reduction in risk of obesity that persists into adulthood?

Q7: Is there sufficient evidence to conclude that BF does not cause a long-term reduction in risk of obesity that persists into adulthood?

Q8: What further research might be done to address these questions?

In each of the aforementioned questions, it is obesity in the offspring under consideration, not in the BF or non-BF mother. It is conceivable that BF has effects on obesity levels in the BF mother (4), but this is not the topic of this review.

Q1: Is there sufficient evidence to conclude that BF is associated with lower rates of obesity in children?

Overall evidence

In the WR, 33 studies were identified, yielding 39 estimated odds ratios (ORs) that express the odds of being obese given that one was BF divided by the odds of being obese given that one was not breastfed (BF), i.e.

\[
OR = \frac{P(O|BF)}{P(O|\neg BF)} / \left(1 - P(O|BF)\right), \text{ where } P(\text{A|B}) \text{ denotes the probability of A given B.}
\]

Thus, numbers less than 1.0 indicate that BF is associated with lower risk and lower odds of being obese. Of the 39 ORs for obesity reported in WR’s Table 3.1, 32 were on samples consisting only of people less than or equal to 18 years of age. Of these 32, 28 reported ORs less than 1.0 and four were greater than or equal to 1.0. All of the 32 ORs appear to be drawn from independent samples and we assume this to be the case. If we also assume that:

A. The studies included in the WR constitute a random sample of the relevant studies that hypothetically could have been included, and

B. There is no association between BF and obesity in childhood (i.e. the null hypothesis is true) in all of the populations from which the study samples were obtained, then the probability of obtaining no more than four studies with sample ORs greater than or equal to 1.0 can be obtained via the binomial distribution and is 0.0000097. Given this very low P value, it is reasonable to conclude that the data are inconsistent with assumptions A and B above. In turn, it is reasonable to conclude that either or both of the following are true:

(a) The studies included do not constitute a random sample of the relevant studies or reported results that hypothetically could have been included; or

(b) There is an association between BF and obesity in childhood (i.e. the null hypothesis is false) in at least one of the populations from which the study samples were obtained.
Can we assume the studies included in the WR constitute a random (or representative) sample of the relevant studies that hypothetically could have been included?

Publication bias (PB) is a relevant and likely factor that can cause the sample of studies included to not constitute a representative sample of the relevant studies that hypothetically could have been included. PB occurs when the probability of a study being published depends on the outcome of the study. Most frequently, PB involves statistically significant studies having a higher likelihood of being published than do studies with results that are not statistically significant. Methods are available to test for patterns in data that may be indicative of PB and WR authors applied some of these methods and obtained significant evidence for PB. Likewise, previous meta-analyses described in the WR indicated PB and WR’s fig. 3.1 shows this quite strikingly. Hence, the validity of assumption A above cannot be accepted; therefore, conclusion (a) seems reasonable and conclusion (b) becomes uncertain.

Is the extent of PB sufficient to potentially overturn the WR’s conclusion that there is an association between BF and obesity among children?

Given acceptance of conclusion (a), to justify acceptance of conclusion (b) would require there is reason to believe that, despite the PB that is strongly apparent, not all of the population ORs are equal to 1.0. WR authors wrote ‘In spite of the evidence of publication bias, a protective effect of breastfeeding was still observed among the larger studies (>1500 participants), suggesting that this association was not due to publication bias.’ The opinion that ‘this association was not due to publication bias’ may not be justified. In order to conclude that this statement is justified, a rule or mathematical justification would be needed to indicate that ‘When an association in a meta-analytic collection of studies is present in studies with samples of size X, then one can conclude it is not due to PB despite evidence for the presence of PB.’ To our knowledge, no such rule has been published. Moreover, even if such a rule did exist, it is unclear how large X must be. Again, inspection of the WR’s fig. 3.4 (reproduced here; referred to as Fig. 1 in this paper) shows the striking evidence for PB. As can be seen in fig. 3.4, as the standard error approaches zero (implying large samples and high statistical power), the estimated OR approaches 1.0, the null value, with no obvious evidence of having asymptoted. This suggests the possibility that the true OR may be 1.0 or very close to 1.0.

A different way to address this is to calculate a version of what has been referred to as a ‘fail-safe N’ (FSN) in the meta-analytic literature (5). The FSN is defined as the number of unpublished studies with null findings that would need to exist to overturn the significance of a meta-analytic finding. Returning to the binomial calculation above, it would take 13 unpublished studies with sample ORs greater than or equal to 1.0 for the binomial P value to no longer be significant (i.e. >0.05) if there are no other studies with ORs less than 1.0. How plausible is it for 13 or more unpublished studies with estimated ORs ≥ −1.0 to exist? One approach is to look at unpublished sources; WR authors did not describe any attempt of identifying or retrieving unpublished studies for the WR. Herein a quick search was conducted for unpublished data in OCLC FirstSearch Dissertation Database (1985–2007) and for meeting abstracts in Web of Science (1996–2007). The search for dissertations revealed seven hits (using obesity, BF, overweight). Further evaluation of these dissertations revealed that two were not applicable to the topic; two contained data indicating a relationship between BF and obesity (N. A. Sowan, 1996 and A. P. Graham, 2005); and two have actually been published as full manuscripts (6–8). Baker et al. (7) and Procter (8) were not published until 2007, which was after the WR was published; however, the dissertations were from 2003 and 2006, respectively, which could have been included in the WR.

Seven citations were found in a Web of Science search for meeting abstracts (1996–2007) that were relevant to BF and obesity among children (Table 1) – three of these showed an inverse association between BF and overweight/obesity in children; three showed no association between BF and overweight/obesity in children; and one was a review containing both inverse associations and no associations. Here it should be noted that we do not claim that these searches are exhaustive for every possible unpublished source. Even with this more thorough search it is difficult to determine the extent to which PB is biasing the estimated OR and whether, if PB were accounted for, the estimated OR would be different from the null value of 1.0. Based upon the identification of some potentially relevant
unpublished material with a cursory search and more so on the appearance of WR’s fig. 3.4 along with the WR authors’ own finding of significant PB, it is apparent that PB is a very real concern. While PB may not completely account for the apparent association, the possibility cannot be confidently ruled out and, if PB were accounted for it would likely substantially reduce the magnitude of the estimated association.

Concerns about selective inclusion or extraction of data
There are concerns about whether the data chosen for inclusion in the WR were fairly representative of the available information or were selected by some process that may have led to inflation of an apparent association. In particular, when studies reported more than one OR, it is not clear how the WR authors chose the OR to include in their analysis. Here are two examples to illustrate these points:

Poulton (9) presents data at multiple years of life including ages 21 and 26 years. The WR authors only used the data for age 21 in their consideration of adulthood. The estimated OR at age 21 was 0.79 as shown in the WR’s Table 3.1. This represents 21% lower odds of overweight with BF. In contrast, the estimated OR was 0.97 at 26 years leading to only an estimated 3% lower odds of overweight with BF. A second example pertains to the paper by Thorsdottir et al. (10). The WR’s meta-analysis only included male data, yet the abstract of Thorsdottir reported that ‘The duration of breast-feeding negatively correlated with body mass index (BMI) in 6-year-old boys (B = −0.19 ±/− 0.07, P = 0.011) but not in girls . . .’. These examples cause one to question the reliability and reasonableness of the data extraction process and suggest that an independent assessment of all data included in the WR is warranted.

Even if we accept that there is an association in some populations, do the data imply that there is an association in all populations studied?
No, As the WR authors noted ‘Because the great majority of the published studies were conducted in Western Europe and North America, we are not able to assess whether this association is present in low and middle-income settings.’ Moreover, they wrote ‘The forest plot shows that results were clearly heterogeneous.’ This implies that there are unexplained differences (explanatory contributing factors could include publication and reporting biases) in the population ORs being estimated in the different studies; therefore, it is plausible that in some populations the ORs may be greater than or equal to 1.0 implying no protective association with BF on obesity in those populations.

Conclusion with respect to Q1
In the overall sample of studies included in the WR’s meta-analysis, there is clear evidence that the average sample OR is less than 1.0. This indicates that, on average in these

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<th>Table 1 Meeting abstracts that reported on breastfeeding’s association to overweight or obesity in children and adolescents</th>
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<tr>
<td>Abstract (author, title, journal)</td>
</tr>
<tr>
<td>Scholten S, Gehring U, Brunekeef B, et al. Breastfeeding lowers overweight risk at 7 years through lower weight gain in first year of life. European Journal of Epidemiology 2006; 21(Suppl. S): 79.</td>
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</table>

BF, breastfeeding; BMI, body mass index.
samples, children who were BF were less likely to be obese than children who were not BF. That being said, it is less clear that this is an adequate representation of the overall population OR owing to strong PB. Moreover, the heterogeneity among studies suggests that even if the OR is less than 1.0 in some populations, it may not be in others.

Q2: Is there sufficient evidence to conclude that BF is associated with lower rates of obesity among breastfed offspring once they reach adulthood?

Of the 39 ORs for obesity reported in the WR’s Table 3.1, seven were on samples consisting only of people greater than 18 years of age. Of these seven, six reported ORs less than 1.0 and the other OR was greater than 1.0. All of the ORs appear to be drawn from independent samples and we assume this to be the case. Again, if it is also assumed that:

A. The studies included in the WR constitute a random sample of the relevant studies that hypothetically could have been included, and

B. There is no association between BF and obesity in childhood (i.e. the null hypothesis is true) in all populations from which the study samples were obtained

then the probability of obtaining no more than only one study with a sample OR greater than or equal to 1.0 can be obtained via the binomial distribution and is 0.0625. This is not significant at the conventional 0.05 alpha (type 1 error rate) level. Given this relatively high P value, it is not reasonable to conclude that the data are inconsistent with assumptions A and B above. Our primitive analysis is consistent with the overall non-significant association observed in studies with offspring over 19 years of age as estimated in the WR’s meta-analysis1 (see WR Table 3.2). Thus, for Q2, it is quite straightforward to draw the conclusion that there is not sufficient evidence to conclude that BF is associated with lower rates of obesity among breastfed offspring once they reach adulthood. This is supported by the results of a new large study (11) reported since completion of the WR, where the results indicated that BF duration, including exclusive BF, was not associated with being overweight or obese in adulthood. A recent meta-analysis (12) concluded that ‘Overall, there is an association between a history of breastfeeding and a reduction in the risk of being overweight or obese in adolescence and adult life. [But] one should be cautious in interpreting all these associations because of the possibility of residual confounding’. This

1The simple ‘vote-counting’ method we have used is generally not as powerful as a meta-analysis based on averaging effect size estimates and we use it here for expository purposes and as a very simple ‘check’ on the more sophisticated meta-analysis conducted in the WR. The fact that both agree on the overall determination of significance is reassuring.

Q3: If there are such associations, what are their magnitudes in comparison with other putatively causal factors and with respect to potential impact on individual or population levels of obesity?

On page 40 and Table 6.1 of the WR, an attempt was made to place the magnitude of associations into perspective. This approach taken by the WR may be inappropriate and likely to engender misapprehensions in some consumers of the WR for several reasons. First, the text and table inappropriately use the word ‘effect’ in place of ‘association’ (13), potentially creating the misunderstanding that cause and effect have been demonstrated (see Inappropriate use of language implying cause and effect below). Second, no account is taken of the likelihood that PB, which the authors have identified as being present, is causing the association’s magnitude to be overestimated. Third, in WR’s Table 6.1, the WR authors compare the association of BF with that of recommendations for diet and exercise. There are at least two reasons why this comparison is specious:

1. As Kavvoura et al. (14) noted after an empirical analysis, ‘Published epidemiological investigations almost universally highlight significant associations between risk factors and outcomes. For continuous risk factors, investigators selectively present contrasts between more extreme groups, when relative risks are inherently lower.’ Thus, the BF-obesity association estimate is often estimated by comparing extreme ends of the spectrum of BF that, even were the association indicative of causality, would not be a fair representation of the likely effects of realistically achievable changes in BF.

2. Moreover, the WR authors themselves seem prepared to disavow their Table 6.1 with good reason. ‘This Table is intended for illustrative purposes only. It should be interpreted with caution because it includes a comparison of the effect of actual interventions – none of them with perfect compliance levels – with the gross difference of the effect between breastfed and non-breastfed subjects, which corresponds to an intervention with 100% compliance.’ While the WR authors recognized and acknowledged the specious nature of this comparison, this acknowledgement does not make the comparison less specious. Therefore, the comparison in Table 6.1 is inherently misleading and should not have been presented to readers.

If the WR authors wished to place the association of BF and obesity into perspective, the appropriate comparison would have been estimates of the association of other
putatively modifiable causal factors with obesity. We produced such a comparison by conducting a quick search of the literature to identify a few studies that assessed the association of some putatively modifiable factor with childhood overweight or obesity and expressed the association as an OR (Fig. 2 and Table 2).

Odds ratios were scaled such that numbers above 1.0 indicate a greater odds of overweight or obesity with higher numbers indicating greater strength of association. In all cases, if ORs were reported for multiple categories of exposure in the paper, then ORs that compared the two most extreme categories were chosen. The papers selected from this literature search do not represent the results of a comprehensive or systematic search of the literature, but do provide a different sense of the literature than does the WR’s Table 6.1. Therefore, the magnitude of the association between BF and obesity in the WR is difficult to put into perspective because (a) it is unclear that there is any effect or association; (b) it is difficult to account for the PB that appears to be causing an overestimation of the magnitude of association and (c) it is unclear which are appropriate association comparisons against which to compare

![Figure 2](image-url)

**Figure 2** Studies that assessed the association of some putatively modifiable factor with childhood overweight or obesity and expressed the association as an OR. Table 2 includes a list of the specific studies shown.

**Table 2** Manuscripts that assessed putatively modifiable factors associated with overweight or obesity in children and adolescents

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<tr>
<th>Manuscript</th>
<th>Modifiable factor related to childhood overweight or obesity</th>
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<tr>
<td>Adachi-Mejia AM, Longacre MR, Gibson JJ, Beach ML, Titus-Ernstoff LT, Dalton MA. Children with a TV in their bedroom at higher risk for being overweight. <em>Int J Obes (Lond)</em> 2007; 31: 644–651.</td>
<td>TV in the bedroom</td>
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the magnitude of the association and the WR authors inappropriately used clinical trial comparisons.

Q4: Is there sufficient evidence to conclude that BF causes a reduction in risk of obesity during childhood?

It is well established that correlation (or association) does not necessarily imply causation. Only randomized experiments allow us to draw near-unequivocal conclusions about causation.

Inappropriate use of language implying cause and effect

Although the WR authors acknowledge that they were studying associations that may or may not be indicative of cause and effect relations, they frequently and inappropriately used language that implied cause and effect. For example, on page 11, they wrote ‘the evidence suggests that breastfeeding has only a small protective effect [emphasis added] against excess weight.’ The well-trained reader will understand that the authors meant ‘the evidence suggests that breastfeeding has only a small association with less excess weight.’ However, if such statements are offered to the general public, media or regulators who may not have had the opportunity to read the full report, they may be inveigled to incorrectly conclude that cause and effect have been demonstrated.

Are there any randomized trials assessing the effect (if any) of BF on obesity?

There are very few randomized trials assessing the effect (if any) of BF on obesity during childhood. There is one report in which preterm babies were randomly assigned to receive banked breast milk or infant formula and later studied as adolescents. In this study there were no significant differences in body weight of the 216 participants at follow-up when they were 13–15 years old (15). It is not surprising that there are few reports as it is unlikely that such trials would be judged as ethical given the recognized benefits of BF and perhaps the unwillingness of many mothers to allow themselves and their children to be randomized in such a study. One paper has been published since the WR that described a cluster-randomized trial of a breastfeeding promotion intervention based on the WHO/UNICEF Baby-Friendly Hospital Initiative (16). Out of 17 046 infants originally enrolled, duplicate measurements of anthropometric variables and blood pressure were collected on 13 889 of these children at 6.5 years of age. The intervention did result in a substantially higher prevalence of BF at 3 months and for any BF throughout infancy; however, no significant intervention effects (and virtually no numerical differences) were observed on mean height, BMI, waist or hip circumference, triceps or subscapular skinfold thickness, or systolic or diastolic blood pressure. These findings indicate that while this intervention effectively promoted BF, the increased duration and exclusivity of BF did not reduce the measures of adiposity at 6.5 years of age in the experimental group (Fig. 3). Since this study was conducted in Belarus, Kramer et al. (16) concluded that ‘caution is therefore advised in generalizing our results to settings with a much higher prevalence of child obesity’.

Are there plausible confounders that have not been effectively accounted for in the extant observational studies?

In the absence of randomized trials, observational data can be used to draw weak and indirect inferences about causation. Before concluding that any association observed is evidence of causation, an association must first be observed; however, as discussed for Q1, even here doubts can be raised. Casting those doubts aside for the moment, it is important to ask whether any apparent association is evidence of causation or could be due to confounders that have not been effectively controlled.

As the WR noted, ‘Because nearly all studies included in the analyses are observational, it is not possible to completely rule out the possibility that these results may be partly explained by self-selection of breastfeeding mothers or by residual confounding.’ They further stated ‘Even if [known] confounding factors are controlled through multivariable analyses, there is a possibility of residual confounding. Inaccurate measurement of confounders, as well as incorrect specification of statistical models, may pre-
clude full adjustment for confounding and lead to estimates of the impact of breastfeeding that are biased.’

We agree with these statements by the WR regarding the possibility of confounding and the WR authors are to be commended for their cogency and forthrightness in acknowledging this limitation. Unfortunately, acknowledgment of a problem does not eliminate the problem. In their Executive Summary, WR authors wrote ‘Control for confounding, age at assessment, year of birth, and study design did not modify the effect of breastfeeding. Because a statistically significant protective effect was observed among those studies that controlled for socioeconomic status and parental anthropometry, as well as with >1500 participants, the effect of breastfeeding was not likely to be due to publication bias or confounding.’ The validity of their conclusion with respect to the lack of concern about confounding presupposes that: (a) those putative confounders that have been included in the analysis have been measured effectively; (b) those putative confounders that have been included in the analysis have been modeled appropriately in the analysis and (c) all relevant confounders have been identified and included in the analysis (17).

Were those putative confounders included in the analyses measured effectively?

No information was identified in the WR regarding the measurement of the confounders included in the obesity analyses. Moreover, many of the confounders that one might speculate about such as parental (not just maternal) body composition (not just BMI) can be quite difficult to measure in large-scale studies and are often measured inadequately. A study highlighting the complexity of the potential confounding relationships and identifying some specific potential confounders that should be addressed was reported by Baker et al. (6). Therein, infant weight gain was associated with maternal prepregnant BMI and with an interaction between the duration of BF and the timing of complementary food introduction. The authors concluded that future investigations of the effects of BF on infant weight gain should account for all of these factors. Similarly, socioeconomic status (SES), which should not be conflated with income, is also often measured poorly. SES has multiple aspects as the American Academy of Pediatrics’ Committee on Pediatric Research wrote ‘One aspect includes resources, such as education, income, and wealth and the other includes status or rank, a function of relative positions in a hierarchy, such as social class’ (18). Again, no information was provided in the WR to allow the reader to conclude whether those putative confounders that were included in the analyses were measured well.

Were those putative confounders included in the analyses modeled appropriately?

It is not enough to identify and effectively measure a confounder to eliminate its biasing influence. One must also model the correct functional form of the confounder in the analysis. Second, there are several specific putative confounders that are quite plausible that have not been included in the models. It is true that one can always speculate about some theoretically extant but unspecified confounder when observational data are analysed, yet should not let that dissuade from drawing tentative conclusions of causation when other available information is supportive and these theoretical confounders remain unspecifiable. For example, in Hill’s classic consideration of this question (20), born out of considering whether the association of smoking with lung cancer was causal, he notes that if an association is large and most or all other factors seem supportive, then it is reasonable to tentatively conclude that the association is indicative of causation. The reason is that it is more difficult to postulate an as yet unidentified confounding factor that has so large an influence that it can create the large observed association, yet has gone undetected. In contrast, among the large studies reviewed in the WR, the mean estimated OR is only 0.80. This is a small deviation from the null value of 1.0 and could quite plausibly be due to unspecified confounders and/or biases.

Were all relevant confounders identified and included in the analyses?

All relevant confounders were not clearly identified and included in the analysis. First, 16 of 39 ORs were estimated from models that included no control for any putative confounders. Second, there are several specific putative confounders that are quite plausible that have not been included in the models. It is true that one can always speculate about some theoretically extant but unspecified confounder if observational data are analysed, yet should not let that dissuade from drawing tentative conclusions of causation when other available information is supportive and these theoretical confounders remain unspecifiable. For example, in Hill’s classic consideration of this question (20), born out of considering whether the association of smoking with lung cancer was causal, he notes that if an association is large and most or all other factors seem supportive, then it is reasonable to tentatively conclude that the association is indicative of causation. The reason is that it is more difficult to postulate an as yet unidentified confounding factor that has so large an influence that it can create the large observed association, yet has gone undetected. In contrast, among the large studies reviewed in the WR, the mean estimated OR is only 0.80. This is a small deviation from the null value of 1.0 and could quite plausibly be due to unspecified confounders and/or biases.

There are several well-grounded putative confounders that have not been regularly and fully controlled or controlled at all. Perhaps chief among these is genotype, as it is well established that child and maternal genotypic influences will be correlated (21). Maternal genotype will influ-
ence maternal body composition just as child genotype will influence child body composition (22). Prepregnancy maternal body composition and probability of success at BF are correlated with higher BMI and adiposity being inversely related to successful BF (23–25) and prepregnancy maternal body composition has rarely been controlled for in studies of BF and obesity (6). One example of the importance of controlling for confounders was recently published. Procter et al. (8) showed that the protective association between BF and overweight in 4 year olds was no longer significant after controlling for confounders (child’s gender, race/ethnicity and birth weight; and the mother’s prepregnancy BMI). Moreover, if the maternal genes that influence body composition in the mother also influence BF in the mother other than by acting solely through an effect of maternal body composition on BF, then a correlation between BF and child body composition or obesity is created even in the absence of a causal effect and even if maternal body composition is controlled for statistically. Beyond these possibilities, are ones that may be more obvious and were acknowledged by the authors of the WR. They wrote:

Even within the same social group, mothers who breastfeed are likely to be more health-conscious than those who do not breastfeed. This may also lead them to promote other healthy habits among their children, including prevention of overweight, promotion of physical exercise and intellectual stimulation. This may be particularly true in high-income populations. Because these maternal attributes are difficult to measure, it is not possible to include them in the analyses as confounding factors. Nevertheless, this possibility should be taken into account when interpreting the study’s results (WR, p. 5).

Given this acknowledgement of not only the conceivability, but indeed the reality of important putative confounders going undetected, it is strange that the authors of the WR later concluded that ‘Because a statistically significant protective effect was observed among those studies that controlled for socioeconomic status and parental anthropometry . . . the effect of breastfeeding was not likely to be due to . . . confounding.’ This statement contradicts their lengthier acknowledgment quoted above.

Strong evidence that substantial confounding may be present

The WR authors, having acknowledged the potential for uncontrolled confounding, wrote: ‘In the absence of randomized studies, within-family analyses allow controlling for confounding by socioeconomic, maternal variables, as well as self-selection bias.’ They then describe two such analyses (26,27). In each study, siblings that experienced greater BF were compared with siblings that experienced lesser BF. Neither study found a statistically significant association of BF with offspring obesity or overweight levels. The WR authors did not cite a third such study (28) and it is unclear why since it was published within the time interval that met their inclusion criteria. This third study’s authors found that ‘ . . . after we take sibling differences and estimate the within-family model the between-family and within-family estimates have opposite signs, with the latter implying that the breastfed sibling is more likely to be overweight. This anomaly merits further investigation.’

These three studies are arguably the most informative studies in the literature. Although it must be acknowledged that within-family analyses too have flaws (possible differences in siblings’ energy needs, appetites and how a family handles each sibling) and are also observational and subject to confounding, the likelihood of confounding is expected to be radically reduced compared with the studies in the WR. The fact that none of these three studies found a statistically significant association in the predicted direction and that one found a statistically significant association in the opposite direction casts strong doubt on the conclusion that any association observed between BF and obesity is causal.

Flawed reasoning regarding the import of associations with overweight vs. obesity

The WR authors wrote: ‘Eight studies provided ORs for more than one outcome, such as overweight only (e.g. BMI 25–29.9), overweight plus obesity (e.g. BMI > 25) and obesity (e.g. BMI > 30). Six of these eight studies reported a more marked protective effect against obesity than against overweight only or overweight plus obesity. This suggests a causal effect of breastfeeding.’ They provide no explanation why the particular observation they have offered justifies the conclusion of causation and we know of no reason why it should. In contrast, for a trait such as BMI (kg/m²) in which the probability density function decreases monotonically after a certain point, the phenomenon they have observed is expected even in the absence of causation. That is, if there is a small association (whether that association is causal or not) between the central tendency (mean or median) of the distribution and some other factor (such as BF), the apparent strength of that association when expressed as an OR for a dichotomized version (e.g. overweight or obesity) of the original continuous variable (e.g. BMI) will be ever greater when one uses a higher cut-off point to define the dichotomy (29). Hence, we would expect the association with obesity to be stronger than that with overweight, regardless of causality.

Conclusion with respect to Q4

There is insufficient evidence to conclude that BF causes a reduction in risk of obesity during childhood for the following reasons:
1. Whether there is an association at all can be questioned (see Q1 Conclusion herein);

2. In the samples showing an association, the association is small and therefore plausibly explained by confounders or biases;

3. Plausible confounders that were not controlled for can be articulated;

4. The reasoning used by the WR authors to go from association to causation is unsupported; and most importantly

5. Three studies (26–28) that used an arguably far more effective way of controlling for confounding found no evidence of a protective association of BF with obesity; and

6. At least two randomized controlled trials (RCTs) (15,16) have been published that do not show an effect of BF on overweight or obesity in children and adolescents.

Q5: Is there sufficient evidence to conclude that BF does not cause a reduction in risk of obesity during childhood?

There is insufficient evidence to conclude that BF does not cause a reduction in risk of obesity during childhood. First, one can never ‘prove’ the null hypothesis (30). But even putting aside this philosophical point, the most compelling studies arguing for a lack of effect are the three within-family reports previously described (26–28) – here it should be noted that Segal & Allison (22) performed analysis on the National Longitudinal Study of Adolescent Health (1994 only) and Neale & Cardon (21) performed analysis on the National Longitudinal Study of Adolescent Health (1994–1996). As mentioned above, there are two randomized studies that did not show an effect of BF on obesity or overweight in children and adolescents (15,16). These studies, though strong in many ways, are not unassailable. Until and unless further strong data suggesting no effect are produced, the question about possible effects of BF on obesity in childhood should remain open.

Q6: Is there sufficient evidence to conclude that BF causes a long-term reduction in risk of obesity that persists into adulthood?

There is clearly not sufficient evidence to support the proposition that BF causes a long-term reduction in risk of obesity that persists into adulthood. All of the same reasoning and evidence that led to the conclusion that inferring causation with respect to childhood obesity apply to adult obesity a fortiori, because with respect to adult obesity, there is not even statistically compelling evidence for the existence of an association.

Q7: Is there sufficient evidence to conclude that BF does not cause a long-term reduction in risk of obesity that persists into adulthood?

Here again, some openness must be retained in part because one can never prove the null hypothesis and in part because the overall association estimated in adults, even though not statistically significant, was in the predicted direction. If there is an association, it is likely to be quite small and may not reflect causality, but it would be premature to definitively conclude that there is no effect.

Q8: What further research might be done to address this issue?

There is value in conducting related research in model organisms to identify situations in which and mechanisms by which BF might reduce obesity and such research should be pursued. In humans, it seems that the primary needs are research that attempts to overcome concerns about bias in the estimation owing to: (a) theoretically controllable limitations in the statistical analyses and PB and (b) less easily controllable confounding by unmeasured variables.

Analytic limitations and PB

Perhaps the best way to overcome concerns about potential biases owing to theoretically controllable limitations in the statistical analyses and PB is to conduct a new analysis that identifies all available (or publicly available) raw data sets that meet certain criteria (e.g. minimum sample size), obtains those datasets, and subjects them to a common analytic protocol to the greatest extent possible. Such an analysis of raw data from multiple, very large, studies could likely reduce any concerns about PB and might provide a more convincing answer to the question about whether there is an association between PB and an unbiased estimate of the magnitude of the association.

Reducing confounding

Perhaps the best way to overcome concerns about potential biases owing to confounding is to use within-family designs as described in the above section Strong evidence that substantial confounding may be present. The WR rightly noted that the power in the studies conducted thus far were modest. It would be useful to identify multiple large datasets in which such within-family analyses could be conducted. This would arguably provide an opportunity for obtaining less biased estimates of causal effects of BF on obesity in humans. Finally, additional RCTs in which BF is promoted in an experimental group, but not in a control group as in Kramer et al. (16) may be valuable in deter-
mining the effects of such programmes on subsequent obesity. That being said, given that Kramer et al. (16) could not detect an effect with over 13,000 subjects and an apparently large effect on BF per se, suggests that interventions will have to have very large effects on BF if they are to have any detectable effects on adiposity and calls feasibility into question.

Conclusions
In conclusion, this review of the WR indicates that:

1. In the overall sample of studies included in the WR’s meta-analysis, there is clear evidence that on average, children in these samples who were breastfed as infants were less likely to be obese than were children who were not breastfed. That being said, there are significant concerns that biases have led to an overestimation of the magnitude of association.

2. There is no statistically convincing evidence that BF is associated with lower rates of obesity among breastfed offspring once they reach adulthood.

3. The magnitude of the association (as estimated by the WR authors) is modest in comparison with other putatively modifiable causal factors and was exaggerated by a spurious comparison the WR authors provided in their Table 6.1.

4. There is not sufficient evidence to conclude that BF causes a reduction in risk of obesity during childhood. The possibility of confounding is strong and supported by the stronger within-family studies which find no protective association of BF.

5. However, there is also not sufficient evidence to conclude that BF does not cause a reduction in risk of obesity during childhood.

6. There is not sufficient evidence to conclude that BF causes a long-term reduction in risk of obesity that persists into adulthood. Moreover, the lack of compelling evidence for an association with adult obesity, makes the likelihood of causation seem quite low.

7. However, again, it would be premature to conclude definitively that BF does not cause a long-term reduction in risk of obesity that persists into adulthood.

8. Further research seems warranted that: (a) conducts new analyses that identify all available (or publicly available) raw data sets that meet certain criteria (e.g., minimum sample size), obtains those datasets, and subjects them to a common analytic protocol to reduce publication bias concerns; (b) uses within-family designs to obtain less biased estimates of causal effects (if any) of BF on obesity or (c) conducts RCTs of BF promotion to determine effects on obesity.

Breastfeeding may have benefits beyond any putative protection against obesity. Although harmful effects are plausible (e.g., 28, 31, 32), our subjective opinion is that the benefits likely outweigh the harms for most people. That being said, any statement that a strong, clear and consistent body of evidence shows that BF causally reduces the risk of overweight or obesity is unwarranted at this time.

Conflict of Interest Statement
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References


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