Methods Appropriate for Studying the Relationship of Breast-feeding to Obesity\textsuperscript{1,2}

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Abstract

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Many factors support the plausibility of the hypothesis that breast-feeding protects against obesity. The hypothesized effects relate to breast-feeding behavior as well as to the biological components of human milk. For example, breast-feeding is thought to represent a responsive maternal feeding style that might influence development of appetite (3). At the same time, specific nutritional or hormonal factors in breast milk may influence the development of appetite or affect the level of dietary intake and, thus, obesity risk (4–6). The key question is whether there is a causal relation between mode of feeding and later obesity. Epidemiologic studies have yet to answer whether breast milk composition, breast-feeding behavior, or other associated behaviors are the factors responsible for observed associations between feeding and later obesity. The issue of causality cannot be resolved with observational studies, and randomization of individuals to feeding mode is not ethical. Because most of the evidence supporting an association of infant feeding to later overweight or obesity is based on observational studies, it is especially important to consider the strengths and weaknesses of observational study designs.

Recall bias and poor characterization of feeding exposures

Studies that use data collected prospectively during the period of breast-feeding or alternative feeding allow for accurate representation of the feeding exposures [for review see Owen et al. (7) and Dewey (8)]. In contrast, retrospective studies rely on recall of past feeding, often many years later, and are subject to recall bias. The main feeding-related exposures include initiation of breast-feeding or ever/never breast-fed and duration of exclusive/predominant or any breast-feeding. Recall bias may be evident not only in reporting duration but also ever/never breast-feeding. Jain et al. (9) provide a valuable discussion of the quality

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of breast-feeding measurement that can serve as a guideline for optimal characterization of breast-feeding exposures.

The discrepancies between prospectively collected and recalled feeding information can be illustrated using data from the Cebu (Philippines) Longitudinal Health and Nutrition Survey. During this community-based survey, mothers were interviewed every 2 mo from immediately after giving birth until their child was age 24 mo. At each visit, mothers were asked whether they were currently breast-feeding, and interviewers collected 24-h dietary recall data. If the mother had stopped breast-feeding or had introduced other foods or liquids, she was asked how long ago that had occurred. The cohort was next followed when the index child was age 8 y. Mothers then provided a complete reproductive history in which they reported feeding patterns for all of their children. After 8 y, 94% of 2157 women correctly recalled ever breast-feeding or not. A small percentage of women (4.1%) recalled that they had not breast-fed the index child, but our prospective records showed they had indeed breast-fed, and 1.9% said they had breast-fed, but prospective data were discordant. There were greater discrepancies in recall of breast-feeding duration. In recalling past feeding, mothers tended to report a longer duration of breast-feeding (mean difference of ~1 mo), and to lump estimated duration at specific ages (notably 12, 18, and 24 mo). Recall of duration of breast-feeding was more accurate for firstborn than for later-born children, suggesting another source of bias. This illustrates the potential to misclassify feeding exposures when using recalled breast-feeding data, particularly when data are collected many years later. Many large-scale surveys, such as the Demographic Health Surveys (10), rely on recalled feeding data. In general, recall bias may lead to inappropriate conclusions about the association of breast-feeding with obesity and other later health outcomes.

Appropriate characterization of feeding exposures may also be hindered by inability to quantify mixed feeding. The timing, amount, and quality of complementary foods may vary substantially between breast- and formula-fed infants in the same study and between studies. If this variation is not taken into account, differences that should be attributed to complementary foods may be mistakenly attributed to breast- or formula feeding.

Selection bias and inadequate control for confounding

Other limitations of epidemiologic studies have been acknowledged in several prior reviews and research articles (8,11,12). A key concern is that mothers who choose to breast-feed may also practice other health-promoting behaviors that influence the subsequent diet and physical activity of their child and thus weight gain and risk of obesity. Observational studies have not been able to fully sort out whether there is indeed a possible causal relation of breast-feeding and reduced risk of overweight or if any observed associations reflect shared underlying determinants of feeding and other healthy behaviors. Moreover, key underlying factors are unmeasured in most studies. Many studies control for maternal education, smoking, and some measure of socioeconomic status. However, specific maternal health-promoting behaviors that might more directly influence child growth are rarely quantified, partly because they are difficult to identify and measure. In addition, longitudinal data on child diet and physical activity beyond the period of breast-feeding are rarely collected or considered.

Even when data on potential confounders are available, comparisons across studies may be difficult because of differences in the pattern of confounding related to population-specific cultural norms. The poorest, least-educated rural women may breast-feed for the longest time in places such as the Philippines (13), whereas in high-income countries more-educated, affluent women breast-feed for longer periods of time (14,15). Social profiles of mothers who breast-feed may differ within populations over time as well (16,17). Similarly, breast milk substitutes have varied substantially in their composition over time (18). Individuals who are now adults in their 50s or 60s had quite different alternatives to breast milk compared with today’s breast-milk substitutes. Thus, the estimated effect of breast-feeding may be different in younger and older individuals because breast-feeding is compared with different alternatives.

Focus on main effects

Another important issue influencing the interpretation of these studies is their focus on main effects. Most analyses have been conducted without considering whether breast-feeding may associate differently with overweight according to mother and child characteristics. Some studies used stratified models and compared male and female infants; others looked at these relations in obese vs. nonobese mothers, or diabetic or nondiabetic mothers (19). There is evidence of differential effects of breast-feeding related to maternal and infant characteristics in some studies but not others. For example, although Mayer-Davis et al. (19) found similar effects for offspring of diabetic and nondiabetic and obese and nonobese mothers, another recent study found differential effects. The latter study assessed BMI and body composition in boys and girls (20), examining duration of breast-feeding by gender and maternal weight status. They found a protective effect of breast-feeding duration only in boys with an overweight mother. These studies suggest the importance of exploring potential benefits for at-risk subgroups (21).

Evidence from systematic reviews

A number of systematic reviews and meta-analyses have been published on the relation between breast-feeding and obesity (1,7,22). Dr. Butte, in a subsequent article (23), discusses these in more detail, but the highlights are presented here. Owen et al. (7) reported a pooled odds ratio (OR) for obesity in breast-fed subjects of 0.87 (95% CI: 0.85–0.89), that is, a 13% reduction in obesity associated with breast-feeding initiation. However, when controlled for confounding, this estimate was reduced (0.93, 95% CI: 0.88–0.99). The role of confounding, along with evidence of publication bias, led Owen et al. (7,11) to conclude that promotion of breast-feeding is not likely to reduce mean BMI in populations.

The World Health Organization monograph (1) evaluated prior systematic reviews and added additional analyses, including a meta-analysis. Estimated OR indicated a protective effect (OR = 0.78; 95% CI: 0.72–0.84) of ever having breast-fed on overweight and obesity. The more strongly protective effects were associated with younger age at measurement of the outcome. In contrast to the Owen review (11), WHO concluded that there was no effect of adjustment for confounders in those studies cited in the review and meta-analysis.

The strongest evidence to support a protective effect of breast-feeding comes from studies of dose-dependent relationships, summarized in a meta-analysis by Harder et al. (22). This study concluded that each additional month of breast-feeding was associated with a 6% reduction in the odds of overweight.

Alternate study designs

Several alternate study designs have been proposed to account for the limitations discussed previously. One involves community-level randomization to breast-feeding promotion (12). The strengths...
and weaknesses of this approach are discussed extensively by Dr. Kramer in this symposium (24).

The second strategy involves comparison of siblings. Several published sibling studies (25,26) relate infant feeding to later obesity, and a new sibling study is included in this symposium (27). Sibling designs are used in an attempt to control for unobserved maternal characteristics that may confound the breast-feeding/weight relation. These studies typically assume that siblings share common maternal factors. The design of most sibling studies rests on exploiting discordance in weight status or discordance in the initiation or duration of breast-feeding. The hypothesis is that the sibling with more breast-feeding exposure (exposed or unexposed, or breast-fed for a longer period of time) will have less body fat, a lower risk of obesity, or a lower BMI later in life. Sibling studies remain flawed in that they are unable to account for infant effects that may differ among siblings; i.e., 1 infant may be of low birth weight, whereas another is not. Alternatively, maternal characteristics may vary over time. For example, Dabelea et al. (28) found that siblings who had been exposed to maternal gestational diabetes or not had a different subsequent risk of developing type 2 diabetes. This study demonstrates that assumptions of a constant maternal environment over time may not be valid. In general, despite this limitation, sibling studies offer the main advantage of doing a better job of controlling for underlying maternal behavioral characteristics that may affect both infant feeding and other obesity risk factors.

Two published studies used sibling designs to explore the association of breast-feeding with risk of obesity in adolescence or young adulthood. The first used data from 11,998 participants, including 850 sibling pairs, in the National Longitudinal Study of Adolescent Health (25). Breast-feeding data were collected from parental report, and adolescent/young adult height and weight were measured to derive BMI. This study compared results from a classic cohort design with a sibling design. The cohort data were used to estimate the likelihood of overweight (age- and sex-specific BMI > 85th percentile of the NCHS/CDC 2000 reference) related to breast-feeding, adjusting for ethnicity, parental education, birth weight, maternal obesity, household income, age, pubertal status, and smoking (29). The sibling design examined differences in BMI Z-scores, hypothesizing that among pairs that were discordantly fed, the breast-fed sibling would be lighter and less likely to be overweight. The results show that, in the cohort, the odds of overweight associated with ever-breast-feeding are 0.83 (95% CI: 0.72–0.93) in girls, consistent with the meta-analysis from Owen et al. (7). In boys, the 10% reduction in the risk of later overweight was found to have a wide confidence interval (OR = 0.90; 95% CI: 0.76–1.05). The sibling analysis showed no evidence of a protective effect of breast-feeding. The siblings were a subgroup of the cohort and had similar characteristics. The null results in the sibling study suggest that the protective effects of breast-feeding found in the cohort study may be attributable to unobserved maternal characteristics related to both the choice to breast-feed and the development of weight status in offspring.

The second published sibling study is by Gillman et al. (26). This study involved a larger sample of nonwint sibling pairs, ages 9–14 y (n = 5614) with a larger number with discordant breast-feeding (n = 2372). Gillman et al. reported a protective effect of breast-feeding, with longer duration of breast-feeding associated with a lower odds of overweight (OR = 0.92; 95% CI: 0.76–1.11). In a dose-response analysis of participants irrespective of sibling status, they found that for every 3.7 mo increment in breast-feeding, the odds of overweight were reduced by ~6%.

Thus, sibling studies provide mixed evidence of a protective effect of breast-feeding on obesity.

Randomization of individual mothers to breast- or formula feeding is always an unethical study design, but informative alternatives exist. Additional sibling studies and studies that involve some degree of ethical randomization are needed. Prospective studies should include careful ascertainment and standard definitions of the duration of breast-feeding as well as the contribution of mixed feeding. Improved measurement of confounders is also needed. This includes other proximate determinants of weight and body composition, in particular patterns of diet and physical activity in children subsequent to the cessation of breast-feeding or formula feeding. Studies also need to include a broad range of maternal factors and to consider the potential roles of effect modifiers. Even in the absence of strong evidence for protection against obesity, breast-feeding requires continued promotion and support because of its other well-known protective effects for mothers and children.

Other articles in this supplement include references 23, 24, and 27.

### Literature Cited


