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Breastfeeding and risk of overweight in childhood and beyond: a systematic review with emphasis on sibling-pair and intervention studies

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ABSTRACT

Background: Breastfeeding is associated with a lower risk of subsequent overweight or obesity, but it is uncertain whether this is a causal relation because most studies have not adequately reduced risk of bias due to confounding.

Objectives: The aim of this review was to examine whether *1*) ever compared with never consuming human milk and *2*) different durations of human milk consumption among infants fed human milk are related to later risk of overweight or obesity, with emphasis on sibling-pair and intervention studies.

Methods: The 2020 Dietary Guidelines Advisory Committee, together with the Nutrition Evidence Systematic Review team, conducted a systematic review of articles relevant to healthy full-term infants in countries with a high or very high level of human development. We searched PubMed, Embase, Cochrane, and CINAHL; dual-screened the results using predetermined criteria; extracted data from and assessed the risk of bias for each included study; qualitatively synthesized the evidence; developed conclusion statements; and graded the strength of the evidence.

Results: The review included 42 articles, including 6 cohorts with sibling-pair analyses and 1 randomized controlled trial of a breastfeeding promotion intervention. Moderate evidence suggested that ever, compared with never, consuming human milk is associated with a lower risk of overweight and obesity at ages 2 y and older, particularly if the duration of human milk consumption is >6 mo. However, residual confounding cannot be ruled out. Evidence was insufficient to determine the relation between the duration of any human milk consumption, among infants fed human milk, and overweight and/or obesity at age 2 y and older.

Conclusions: Further research, using strong study designs, is needed to disentangle the complex relation between infant feeding practices and the risk of subsequent overweight or obesity, as well as the biological and behavioral mechanisms if the relation is causal. *Am J Clin Nutr* 2021;114:1774–1790.

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Data described in the manuscript are publicly and freely available without restriction at https://nesr.usda.gov/sites/default/files/2020-07/B24%20human-milk-infant-formula-%20overweight-obesity%20-%20full%20SR.pdf.

Supplemental Tables 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: Add Health, National Longitudinal Study of Adolescent Health; HHS, US Department of Health and Human Services; NESR, Nutrition Evidence Systematic Review team at the USDA Center for Nutrition Policy and Promotion; NLSY79, National Longitudinal Survey on Youth 1979; PROBIT, Promotion of Breastfeeding Intervention Trial.

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Keywords: breastfeeding, human milk, overweight, obesity, infant, toddler, child, systematic review, sibling

Introduction

Birth to 24 mo of postnatal life is a critical phase of life for future health, and how and what infants are fed contributes to developmental programming (1). Breastfeeding provides health benefits for both the mother and the infant (2). Dissimilarities in growth trajectories have been documented in breastfed compared with formula-fed infants in the first year of life (3–5). Ever being breastfed has been associated with a 12–14% reduction in the risk of childhood obesity (6, 7), although associations are substantially attenuated in studies that have been able to control for important confounding factors (such as parental overweight, maternal socioeconomic status and physical activity), and in studies comparing siblings within the same family (8).

Every 5 y, a Federal Advisory Committee (9) reviews scientific evidence to make recommendations to the USDA and the US Department of Health and Human Services (HHS) before the USDA and HHS update the Dietary Guidelines for Americans. For the first time, the 2020–2025 Dietary Guidelines for Americans (10) includes dietary guidance for infants and toddlers from birth to 24 mo of age in response to the mandate from the Agricultural Act of 2014 (11). Accordingly, the 2020 Dietary Guidelines Advisory Committee reviewed the evidence about and provided recommendations for feeding this age group (12). Supported by the USDA Nutrition Evidence Systematic Review (NESR) scientists and librarians (nesr.usda.gov), the committee conducted several systematic reviews, including one on the relation between human milk consumption and subsequent overweight and obesity (13).

The full systematic review included numerous prospective observational studies. Such studies, however, are prone to bias due to confounding because infant feeding is strongly socially patterned (14, 15). Therefore, the committee gave special attention to studies that reduced this risk of bias by using more rigorous study designs, such as sibling-pair studies, which reduce confounding because siblings often share parental (i.e., genetic), familial, and environmental characteristics (15). When sibling pairs differ in infant feeding or in the outcome of interest, they are considered "discordant," and those differences yield insights into whether breastfeeding practices influence later overweight or obesity, assuming all other factors are equal. The committee also focused on the results of the sole randomized intervention trial that is relevant to this question, the Promotion of Breastfeeding Intervention Trial (PROBIT) in the Republic of Belarus (16–18). That trial evaluated the effects on multiple outcomes of a breastfeeding promotion program that led to a longer duration of breastfeeding in the intervention group compared with the control group.

The objective of this article is to describe the results of the sibling-pair and PROBIT studies within the context of the overall systematic review addressing the relation between breastfeeding and later overweight.

Methods

The committee used NESR's rigorous, protocol-driven method to conduct the full systematic review. The methods are described in detail in the scientific report of the committee (19) and in the systematic review documentation on the NESR website (13). An overview of the methods follows.

Development of the systematic review protocol

Committee members first developed a systematic review protocol that contained an analytic framework (**Figure 1**) and inclusion and exclusion criteria (13). The analytic framework described the population, interventions (for experimental studies) or exposures (for observational studies), comparators, and outcomes of interest for the systematic review. It also listed key confounders and how the committee defined key terms. The protocol and updates to the protocol were discussed by the committee in public meetings (20) and were posted at www.dietaryguidelines.gov for public comment and feedback and to ensure transparency to all stakeholders throughout the timeline of the committee's deliberations.

Population.

The population of interest was healthy full-term infants in countries with a high or very high level of human development (21). We examined evidence about healthy, full-term infants because the purpose of the Dietary Guidelines for Americans is to promote health and prevent disease, rather than to treat specialized populations, such as infants born preterm. We examined evidence from infants in countries with a high or very high level of human development (21) to allow for generalizability to US infants.

Interventions/exposures and comparators.

The full analytic framework included 6 comparisons of interventions/exposures compared with comparators, intended to align with the first feeding decisions caregivers make (Figure 1). In this article, we focus on the first 2 comparisons: *1*) ever compared with never consuming human milk and *2*) different durations of human milk consumption among infants fed human milk. Evidence for the other 4 comparisons [duration of exclusive human milk feeding prior to infant formula, extent of human milk feeding among infants fed both human milk and infant formula (mixed feeding), human milk fed by bottle compared with at the breast, and mixed feeding within a single feeding compared with not] was insufficient (13). We examined the consumption of mother's own milk fed at the breast or by bottle as well as infant formulas meeting US Food and Drug Administration (22) or Codex Alimentarius (23) food standards.

Outcomes.

The original protocol listed a wide range of outcomes related to growth, size, and body composition. The committee subsequently updated the protocol to focus on outcomes reflecting overweight and obesity at ages 2 y and older, given their public health importance. Other growth and size outcomes were not examined because differences in growth and size between breastfed and formula-fed infants have already been well documented, including by an expert panel convened by the US government (5).

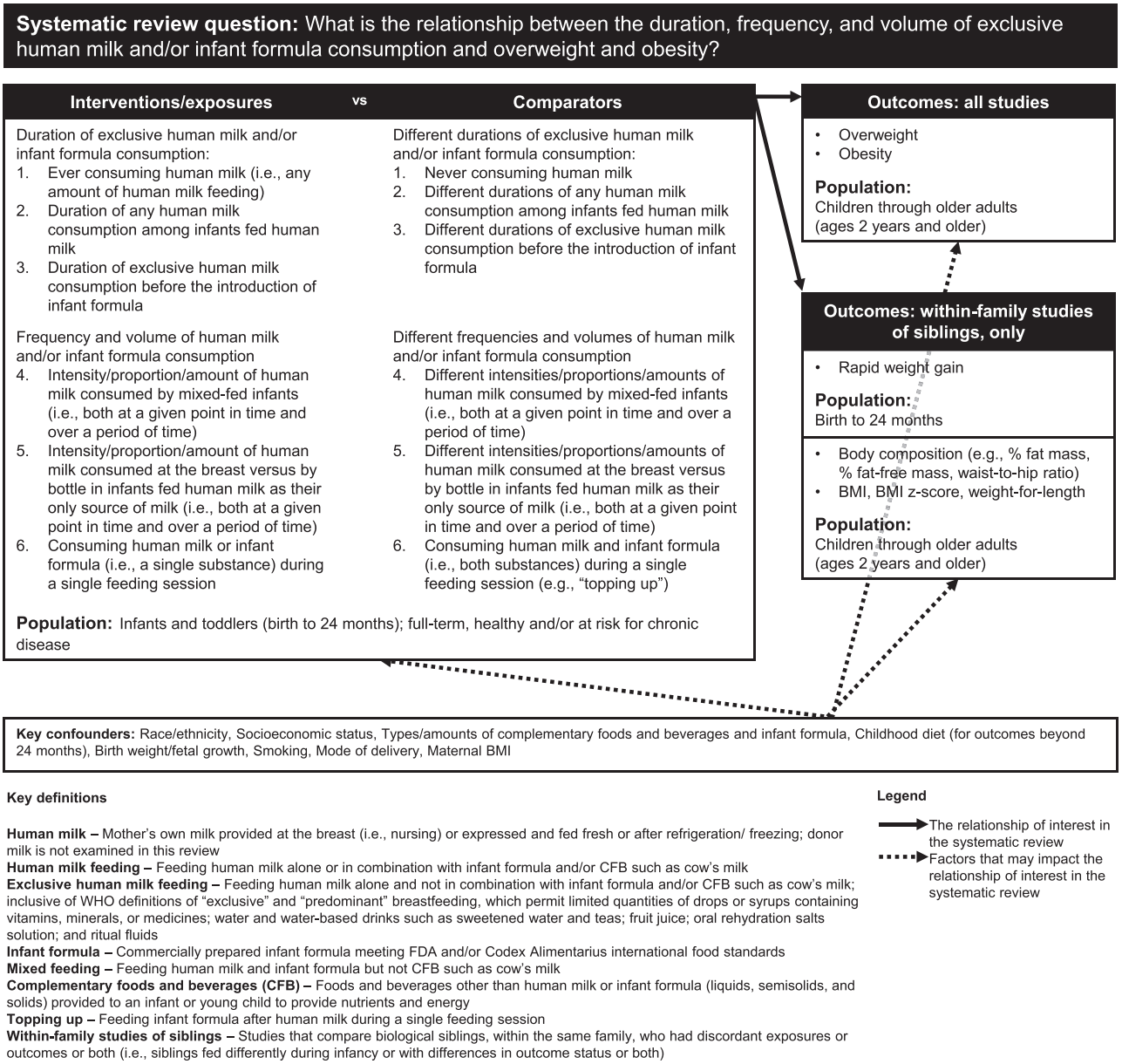

FIGURE 1 Analytic framework for the full systematic review (13). The analytic framework illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders considered in the systematic review.

Inclusion and exclusion criteria.

The systematic review included peer-reviewed articles published in English. The original protocol specified a publication date range from January 1980 to September 2019 when the literature search was conducted. We excluded articles published before 1980 because the Infant Formula Act of 1980 established nutrient requirements for commercial infant formulas in the United States, and thus health effects associated with formula consumption before 1980 might be different. For studies that did not assess sibling pairs, the updated protocol focused only on studies published after January 2011, because existing systematic reviews about infant feeding and later overweight and obesity include evidence from older studies (8). The committee included randomized and nonrandomized controlled trials, prospective and retrospective cohort studies, and nested case-control studies with at least 30 participants per study group, or a power analysis indicating sufficient statistical power to detect meaningful group differences. The updated protocol also specified that studies needed to account for at least one of the key confounders in the analytic framework to be eligible for inclusion.

For sibling-pair studies, the committee retained the original publication date range of January 1980 to September 2019 and also retained a broader list of outcomes that included rapid weight gain from birth to 24 months (as defined by study investigators), as well as BMI (in kg/m^2) and measures of body composition at ages 2 y and older. In addition, sibling-pair studies with a cross-sectional design were eligible for inclusion.

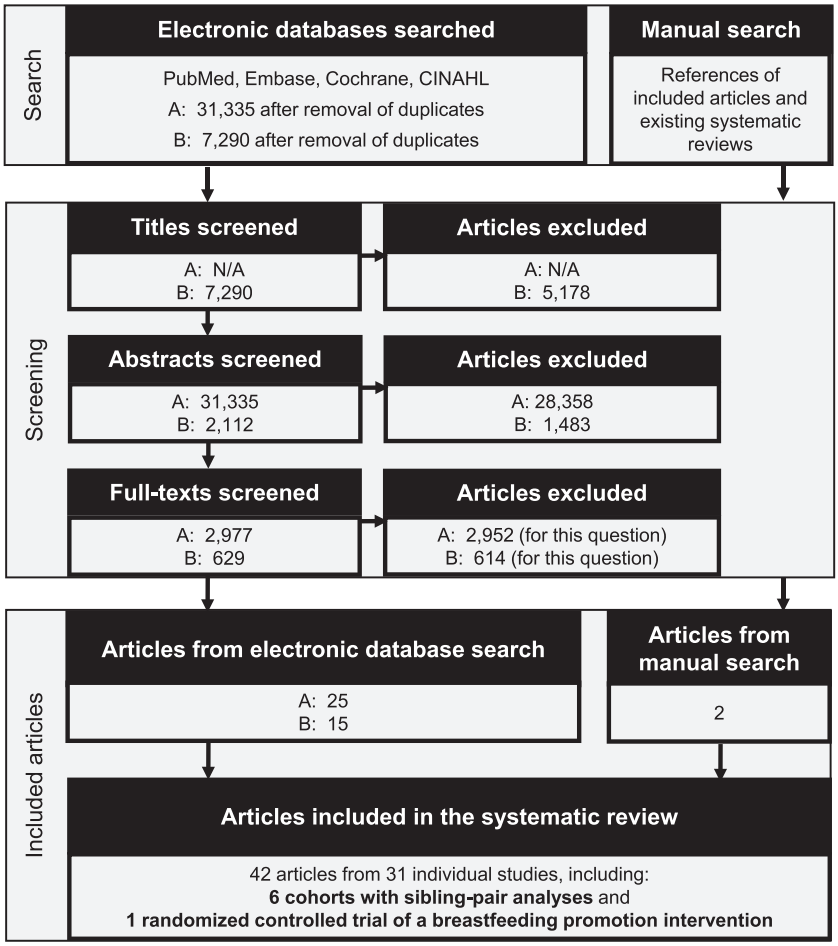

FIGURE 2 Literature search and screen flowchart. Two literature searches were used to identify articles. The first search (A) was conducted during the Pregnancy and Birth to 24 Months (P/B-24) Project to identify studies for a family of systematic reviews that examined human milk and infant formula consumption and several outcomes (https://nesr.usda.gov/infant-milk-feeding-practices-technical-expert-collaborative). Some of the intended reviews, including the review on overweight and obesity, were not completed before the end of the P/B-24 Project. The second search (B) was conducted during the work of the 2020 Dietary Guidelines Advisory Committee to identify studies published since the P/B-24 literature search.

Search process and screening of potentially relevant studies

A biomedical librarian from the NIH and systematic review librarians from NESR developed, peer-reviewed, and implemented the literature search to identify potentially relevant articles in PubMed, Embase, Cochrane, and CINAHL published from January 1980 to September 2019. Two NESR analysts used the inclusion and exclusion criteria to independently screen the titles, abstracts, and full texts of each search result in a stepwise manner with DistillerSR software (Evidence Partners). NESR analysts also manually reviewed the references of the included articles to identify articles to screen that were not retrieved by the literature search (**Figure 2**).

Data extraction and assessment of risk of bias

For each included article, 1 NESR analyst extracted data into DistillerSR and a second analyst verified the accuracy and completeness of the extracted data. The 2 analysts completed independent risk-of-bias assessments using study design–specific tools for each article (13, 19).

Synthesis and grading of the evidence

The committee conducted a qualitative synthesis of the evidence to develop conclusion statements that pertain to the entire body of evidence, which included the sibling-pair studies and PROBIT trial (13). To grade the strength of the evidence, the committee used NESR's grading criteria for consistency, precision, generalizability, directness, and risk of bias (19) (see **Supplemental Tables 1** and **2**). The evidence underlying each conclusion statement was graded as strong, moderate, limited, or grade not assignable by the committee. Evidence from sibling-pair studies and the PROBIT trial was synthesized separately, but we did not develop distinct conclusion statements for these categories of studies.

Results

Results of the full systematic review are available online (13). In the sections below, we present results of studies that included sibling-pair analyses (**Tables 1** and **2**) for the 2 key comparisons, ever compared with never consuming human milk and different

TABLE 1 Evidence examining the relation between ever, compared with never, consuming human milk and outcomes reflecting overweight and obesity at ages 2 y and older from studies with sibling-pair analyses[1]

Cohort	Article	Exposure[2]	Outcome[3]	Full-sample findings	Sibling-pair findings
Linked CENTURY Study (United States)	Hawkins et al. 2019 (24)	Initiated breastfeeding vs. did not initiate breastfeeding (reference) Birth years: 1987–2003	BMI *z* score at 2 y	β (95% CI): −0.06 (−0.09, −0.04) (n = 55,058)	β (95% CI): −0.04 (−0.10, 0.03) (n = 2260 siblings with discordant outcomes)
			BMI *z* score at 5 y	β (95% CI): −0.09 (–0.11, –0.07) (n = 43,893)	β (95% CI): −0.07 (−0.13, −0.01) (n = 3249 siblings with discordant outcomes)
			Obesity at 2 y	OR (95% CI): 0.80 (0.73, 0.87) (n = 55,058)	OR (95% CI): 0.97 (0.72, 1.32) (n = 2260 siblings with discordant outcomes)
			Obesity at 5 y	OR (95% CI): 0.77 (0.72, 0.83) (n = 43,893)	OR (95% CI): 0.94 (0.74, 1.20) (n = 3249 siblings with discordant outcomes)
Children of NLSY79 (United States)	Anderson et al. 2003 (25)	Ever breastfed vs. never breastfed (reference) Birth years: 1986–1996	Obesity vs. No obesity (reference) at 3–11 y	$\beta \pm$ SE: -0.018 ± 0.008[4] (n = 16,650 observations, probit model[5]) $\beta \pm$ SE: -0.016 ± 0.010 (n = 15,050 observations, instrumental variable model[5])	$\beta \pm$ SE: -0.021 ± 0.023 (n = 4471 observations in siblings at the same age, mean 6.6 y) $\beta \pm$ SE: 0.012 ± 0.017 (n = 7919 observations in siblings at the same point in time, mean 5.9 y for younger siblings and 9.2 y for older siblings)
	Colen and Ramey 2014 (26)	Ever breastfed vs. never breastfed (reference) Birth years: 1972–2006	BMI at 4–14 y	$\beta \pm$ SE: -0.449 ± 0.094; $P < 0.001$ (n = 8237)	$\beta \pm$ SE: -0.141 ± 0.188 (n = 1773 siblings with discordant exposures)
			Obesity at 4–14 y	$\beta \pm$ SE: -0.342 ± 0.066; $P < 0.001$ (n = 8237)	$\beta \pm$ SE: -0.173 ± 0.164 (n = 1773 siblings with discordant exposures)
Add Health (United States)	Evenhouse and Reilly 2005 (27)	Ever breastfed vs. never breastfed (reference) Birth years: 1976–1985	BMI at 10–18 y	$\beta \pm$ SE: -0.41 ± 0.07; $P < 0.10$ (n = 16,903)	$\beta \pm$ SE: 0.40 ± 0.33 (n = 576 siblings with discordant exposures)
			Overweight plus obesity at 10–18 y	OR $\pm$ SE from logit: 0.79 ± 0.03; $P < 0.10$ (n = 16,903)	OR $\pm$ SE from logit: 1.32 ± 0.21; $P < 0.10$ (n = 576 siblings with discordant exposures)
			Obesity at 10–18 y	OR $\pm$ SE from logit: 0.77 ± 0.04; $P < 0.10$ (n = 16,903)	OR $\pm$ SE from logit: 1.17 ± 0.25 (n = 576 siblings with discordant exposures)

(*Continued*)

TABLE 1 (*Continued*)

Cohort	Article	Exposure[2]	Outcome[3]	Full-sample findings	Sibling-pair findings
	Nelson et al. 2005 (28)	Ever breastfed vs. never breastfed (reference) Birth years: 1976–1985	Overweight plus obesity at 12–21 y	OR (95% CI): 0.90 (0.76, 1.05) ($n = 5929$ males) OR (95% CI): 0.83 (0.72, 0.95) ($n = 6069$ females)	OR (95% CI) that the sibling without overweigh/obesity was ever breastfed and the sibling with overweight/obesity was never breastfed vs. both siblings had overweight/obesity and were never breastfed (reference): 0.52 (0.22, 1.24) OR (95% CI) that the sibling without overweight/obesity was ever breastfed and the sibling with overweight/obesity was never breastfed vs. both siblings had no overweight/obesity and were never breastfed (reference): 1.22 (0.64, 2.32) OR (95% CI) that the sibling with overweight/obesity was ever breastfed and the sibling without overweight/obesity was never breastfed vs. both siblings had overweight/obesity and were never breastfed (reference): 2.03 (0.64, 6.43) OR (95% CI) that the sibling with overweight/obesity was ever breastfed and the sibling without overweight/obesity was never breastfed vs. both siblings had no overweight/obesity and were never breastfed (reference): 1.27 (0.65, 2.50) ($n = 224$ siblings with discordant exposures and outcomes)
			BMI z score difference at 12–21 y	Not reported	$\beta \pm$ SE when the lighter sibling was breastfed: -0.004 ± 0.11 $\beta \pm$ SE when the heavier sibling was breastfed: -0.09 ± 0.11 ($n = 224$ siblings with discordant exposures and outcomes)
CDS (United States)	Metzger and McDade 2009 (29)	Ever breastfed vs. never breastfed (reference) Birth years: 1984–1993	BMI z score at 9–19 y	Mean ± SE: -0.150 ± 0.065; $P < 0.05$ ($n = 2591$)	Mean ± SE: -0.397 ± 0.176; $P < 0.05$ ($n = 976$ siblings = 488 sibling pairs including 59 pairs with discordant exposures)

(*Continued*)

TABLE 1 (*Continued*)

Cohort	Article	Exposure[2]	Outcome[3]	Full-sample findings	Sibling-pair findings
			BMI >50th percentile vs. <50th percentile (reference) at 9–19 y	Not reported	OR: ~1.00[6] (ordinary least squares model[7]) OR: ~1.30 (fixed-effects model) (n = 30–44 siblings with discordant exposures and outcomes)
			Overweight plus obesity vs. no overweight or obesity (reference) at 9–19 y	Not reported	OR: ~0.60; $P < 0.01$ (ordinary least squares model) OR: ~0.40; $P < 0.05$ (fixed-effects model) (n = 30–44 siblings with discordant exposures and outcomes)
			Obesity vs. no obesity (reference) at 9–19 y	Not reported	OR: ~0.70 (ordinary least squares model) OR: ~0.20; $P < 0.01$ (fixed-effects model) (n = 30–44 siblings with discordant exposures and outcomes)

[1]Results are significant if a P-value < 0.05 is shown or the 95% CI does not include 1; otherwise they are not significant. Add Health, National Longitudinal Study of Adolescent Health; CDS, Child Development Supplement of the Panel Study of Income Dynamics; NLSY79, National Longitudinal Survey on Youth 1979 Cohort.

[2]Exposure that addresses ever compared with never consuming human milk or vice versa.

[3]All of the studies in this table used the CDC growth reference for BMI *z* scores, BMI percentiles, overweight plus obesity (BMI ≥85th percentile), and obesity (BMI ≥95th percentile)

[4]Anderson et al. (25) did not explicitly state that this finding was statistically significant, but the text of the article implied that it was.

[5]Probit models are a standard type of regression model that estimate the probability of a dichotomous outcome. A limitation of this modeling approach is that one cannot account for unobserved confounding that may bias the relation of interest. Instrumental variables estimation is an econometric approach that attempts to account for unobserved confounding. In this approach, a third variable, or "instrument" that is related to the exposure but is not related to the probability of the outcome, is used in the regression models as a substitute for the actual exposure.

[6]Approximated odds ratios taken from a bar graph.

[7]The authors used a least squares model for the sibling sample and a fixed-effects model for the sibling difference model. The fixed-effects model uses differences between siblings as the dependent and independent variables in an ordinary least squares or logistic regression, so that characteristics shared by siblings are differenced out of the model.

TABLE 2 Evidence examining the relation between the duration of any human milk consumption, among infants fed human milk, and outcomes reflecting overweight and obesity at ages 2 y and older from studies with sibling-pair analyses[1]

Cohort	Article	Exposure[2]	Outcome[3]	Full-sample findings	Sibling-pair findings
Children of NLSY79 (United States)	Colen and Ramey 2014 (26)	Breastfeeding duration (wk) Birth years: 1972–2006	BMI at 4–14 y	$\beta \pm$ SE: -0.007 ± 0.002; $P < 0.01$ ($n = 8237$)	$\beta \pm$ SE $= 0.005 \pm 0.003$ ($n = 1773$ siblings with discordant exposures)
			Obesity at 4–14 y	$\beta \pm$ SE: -0.007 ± 0.002; $P < 0.01$ ($n = 8237$)	$\beta \pm$ SE $= 0.001 \pm 0.004$ ($n = 1773$ siblings with discordant exposures)
Add Health (United States)	Evenhouse and Reilly 2005 (27)	Breastfeeding duration (mo; quasi-continuous using midpoints of the ranges 0–3, 3–6, 6–9, 9–12, 12–24, and >24 mo) Birth years: 1976–1985	BMI at 10–18 y	$\beta \pm$ SE: -0.03 ± 0.006; $P < 0.10$ ($n = 7417$)	$\beta \pm$ SE $= 0.01 \pm 0.03$ ($n = 470$ siblings with discordant exposures)
			Overweight plus obesity at 10–18 y	OR $\pm$ SE from logit: 0.98 ± 0.00; $P < 0.10$ ($n = 7417$)	OR $\pm$ SE from logit: 1.01 ± 0.01 ($n = 470$ siblings with discordant exposures)
			Obesity at 10–18 y	OR $\pm$ SE from logit: 0.98 ± 0.01; $P < 0.10$ ($n = 7417$)	OR $\pm$ SE from logit: 1.00 ± 0.02 ($n = 470$ siblings with discordant exposures)
GUTS (United States)	Gillman et al. 2006 (30)	Breastfeeding duration, per 3.7 mo (the mean difference in breastfeeding duration for discordant siblings) Birth years: 1982–1987	Overweight plus obesity at 9–14 y	OR (95% CI): 0.88 (0.82, 0.94) when adjusted for the same confounders as the discordant sibling analysis OR (95% CI): 0.94 (0.88, 1.00) when also adjusted for maternal BMI and smoking, as well as household income ($n = 5614$ siblings)	(below)
		Breastfeeding longer vs. shorter (reference) than the mean duration of the participant's sibship	Overweight plus obesity at 9–14 y	(above)	OR (95% CI): 0.92 (0.76, 1.11) ($n = 2372$ siblings with discordant exposures)
Helsinki Birth Cohort (Finland)	O'Tierney et al. 2009 (31)	Trend across the breastfeeding duration categories <2, 3–4, 5–7, and ≥8 mo Birth years: 1934–1944	BMI based on self-reported height and weight at ~62 y	Not reported	Mean $\pm$ SD: 26.6 ± 4.3 (<2 mo), 26.3 ± 4.3 (3–4 mo), 26.2 ± 4.2 (5–7 mo), 26.5 ± 4.0 (≥8 mo); $P = 0.80$ linear, 0.90 quadratic ($n = 831$ siblings with discordant exposures)

(*Continued*)

TABLE 2 (*Continued*)

Cohort	Article	Exposure[2]	Outcome[3]	Full-sample findings	Sibling-pair findings
			BMI based on clinical measurement at ~62 y	Not reported	Mean ± SD: 29.5 ± 4.3 (<2 mo), 26.8 ± 5.2 (3–4 mo), 26.9 ± 4.2 (5–7 mo), 28.2 ± 4.9 (≥8 mo); $P = 0.80$ linear, 0.08 quadratic ($n = 129$ siblings with discordant exposures)
			Overweight based on self-reported height and weight at ~62 y	Not reported	Percent: 42.7 (<2 mo), 42.9 (3–4 mo), 41.2 (5–7 mo), 50.0 (≥8 mo); $P = 0.08$ linear, 0.50 quadratic ($n = 831$ siblings with discordant exposures)
			Percent fat mass at ~62 y	Not reported	Mean ± SD: 32.6 ± 9.7 (<2 mo), 27.6 ± 8.5 (3–4 mo), 28.4 ± 6.6 (5–7 mo), 30.8 ± 8.0 (≥8 mo); $P = 0.50$ linear, 0.03 quadratic ($n = 121$ siblings with discordant exposures)
		Breastfed <2 mo vs. 5–7 mo (reference)	BMI based on self-reported height and weight at ~62 y	Not reported	Mean difference (95% CI): 0.3 (–0.5, 1.1) ($n = 439$ siblings with discordant exposures)
			BMI based on clinical measurement at ~62 y	Not reported	Mean difference (95% CI): 2.3 (–0.1, 4.7) ($n = 60$ siblings with discordant exposures)
			Overweight based on self-reported height and weight at ~62 y	Not reported	Mean difference in percent (95% CI): 1.6 (–7.7, 11.0) ($n = 439$ siblings with discordant exposures)
			Percent fat mass at ~62 y	Not reported	Mean difference (95% CI): 3.9 (0.3, 7.4) ($n = 57$ siblings with discordant exposures)
		Breastfed 3–4 mo vs. 5–7 mo (reference)	BMI based on self-reported height and weight at ~62 y	Not reported	Mean difference (95% CI): 0.3 (–0.5, 1.1) ($n = 401$ siblings with discordant exposures)
			BMI based on clinical measurement at ~62 y	Not reported	Mean difference (95% CI): –0.4 (–2.7, 1.8) ($n = 68$ siblings with discordant exposures)

(*Continued*)

TABLE 2 (*Continued*)

Cohort	Article	Exposure[2]	Outcome[3]	Full-sample findings	Sibling-pair findings
			Overweight based on self-reported height and weight at ~62 y	Not reported	Mean difference in percent (95% CI): 1.9 (–8.0, 11.8) ($n = 401$ siblings with discordant exposures)
			Percent fat mass at ~62 y	Not reported	Mean difference (95% CI): 0.3 (–3.1, 3.7) ($n = 62$ siblings with discordant exposures)
		Breastfed ≥8 mo vs. 5–7 mo (reference)	BMI based on self-reported height and weight at ~62 y	Not reported	Mean difference (95% CI): 0.2 (–0.5, 1.0) ($n = 457$ siblings with discordant exposures)
			BMI based on clinical measurement at ~62 y	Not reported	Mean difference (95% CI): 1.2 (–0.9, 3.2) ($n = 77$ siblings with discordant exposures)
			Overweight based on self-reported height and weight at ~62 y	Not reported	Mean difference in percent (95% CI): 8.8 (–0.3, 18.0) ($n = 457$ siblings with discordant exposures)
			Percent fat mass at ~62 y	Not reported	Mean difference (95% CI): 1.3 (–1.7, 4.3) ($n = 74$ siblings with discordant exposures)

[1]Results are significant if a P-value < 0.05 is shown or the 95% CI does not include 1; otherwise they are not significant. Add Health, National Longitudinal Study of Adolescent Health; GUTS, Growing Up Today Study; NLSY79, National Longitudinal Survey on Youth 1979 Cohort.

[2]Exposure that addresses the duration of any human milk consumption among infants fed human milk.

[3]All of the US studies in this table used the CDC growth reference for overweight plus obesity (BMI ≥85th percentile) and obesity (BMI ≥95th percentile), and the study from Finland defined overweight as BMI 25–30 kg/m^2.

TABLE 3 Evidence examining the relation between the duration of any human milk consumption, among infants fed human milk, and overweight plus obesity and obesity at ages 2 y and older from the Promotion of Breastfeeding Intervention Trial[1]

Article	Participant age, y	Odds of overweight plus obesity[2] in the intervention vs. control group (reference), OR (95% CI)	Odds of obesity[3] in the intervention vs. control group (reference), OR (95% CI)
Kramer et al. 2007 (16)	6.5 (n = 13,889)	1.1 (0.8, 1.4)	1.2 (0.8, 1.6)
Martin et al. 2013 (18)	11.5 (n = 13,879)	1.18 (1.01, 1.39)	1.17 (0.97, 1.41)
Martin et al. 2017 (17)	16 (n = 13,557)	1.14 (1.02, 1.28)	1.09 (0.92, 1.29)

[1] In the Promotion of Breastfeeding Intervention Trial, the intervention group had a significantly longer duration of human milk consumption than the control group; all infants in the study were born in 1996–1997.
[2] BMI ≥85th percentile using CDC growth reference
[3] BMI ≥95th percentile using CDC growth reference.

durations of human milk consumption (among infants fed human milk). In the PROBIT intervention trial, all infants initiated breastfeeding, so results relevant to ever compared with never consuming human milk are not available. However, results from the PROBIT trial are relevant to the second comparison regarding the duration of human milk consumption and are thus presented in that section (**Table 3**). Although the search criteria specified articles published in English, none of the articles excluded due to language were sibling-pair or intervention studies.

Ever compared with never consuming human milk

Six articles, from 4 independent US cohorts, included sibling-pair analyses that examined outcomes associated with ever compared with never consuming human milk (24–29). All 6 studies used the CDC growth reference (32) to calculate BMI z scores or percentiles and defined overweight plus obesity as BMI ≥85th percentile and obesity as BMI ≥95th percentile.

Linked CENTURY study.

Hawkins et al. (24) analyzed data from the Linked CENTURY Study. The full sample included 55,058 children at 2 y and 43,893 children at 5 y, and the subsample of sibling pairs with discordant outcomes included 2260 children at 2 y and 3249 at 5 y. In the full sample, initiating, compared with not initiating, human milk feeding was associated with a significantly lower BMI z score at 2 and 5 y [β (95% CI): –0.06 (–0.09, –0.04) and –0.09 (–0.11, –0.07), respectively] and significantly lower odds of obesity at both 2 and 5 y [OR (95% CI): 0.80 (0.73, 0.87) and 0.77 (0.72, 0.83), respectively]. In the subsample of siblings with discordant outcomes, the inverse association between initiating human milk feeding and BMI z score was not significant at 2 y [β (95% CI): –0.04 (–0.10, 0.03)] but was significant at 5 y [β (95% CI): –0.07 (–0.13, –0.01)]. In addition, there was no association of initiating human milk feeding with obesity at 2 or 5 y; odds ratios were closer to the null [OR (95% CI): 0.97 (0.72, 1.32) and 0.94 (0.74, 1.20), respectively] than was observed for the full sample.

Children of the National Longitudinal Survey on Youth 1979 cohort.

Two articles (25, 26) examined children and adolescents whose mothers were part of the National Longitudinal Survey on Youth 1979 (NLSY79) cohort. Anderson et al. (25) conducted analyses on a full sample (n = 16,650 observations using a probit model and n = 15,050 observations using an instrumental variable model) and on subsamples of sibling pairs measured at the same age (mean age of 6.6 y; n = 4471 observations) or at the same point in time (mean age, 5.9 and 9.2 y for the younger and older siblings, respectively; n = 7919 observations). In the full sample, children who were ever fed human milk had a ∼1.8% decrease in the likelihood of being obese at 3–11 y of age compared with children never fed human milk ($\beta \pm$ SE: –0.018 ± 0.008 and –0.016 ± 0.010, from probit and instrumental variable models, respectively; P values were not reported, but the instrumental variable model was described as nonsignificant). In both sibling-pair subsamples, human milk feeding was not significantly associated with the likelihood of being obese at 3–11 y of age ($\beta \pm$ SE: –0.021 ± 0.023 and 0.012 ± 0.017, respectively).

Colen and Ramey (26) conducted analyses on a full sample of 8237 participants and on a subsample of sibling pairs with discordant infant feeding (n = 1773 participants). In the full sample, ever compared with never consuming human milk was associated with a significantly lower BMI at 4–14 y of age ($\beta \pm$ SE: –0.449 ± 0.094; $P < 0.001$) and a significantly lower log odds of obesity ($\beta \pm$ SE: –0.342 ± 0.066; $P < 0.001$). Within the discordant-feeding sibling-pairs subsample, the associations were in the same direction but were not statistically significant (for BMI, $\beta \pm$ SE: –0.141 ± 0.188; for obesity, $\beta \pm$ SE: –0.173 ± 0.164).

National Longitudinal Study of Adolescent Health.

Two articles (27, 28) presented evidence from the National Longitudinal Study of Adolescent Health (Add Health), a nationally representative sample of 10- to 18-y-olds in 1994–1995 (baseline). At baseline, Evenhouse and Reilly (27) examined a full sample of 16,903 participants and a subsample of sibling pairs with discordant infant feeding (n = 576). In the full sample and the sibling-pairs subsample, ever compared with never consuming human milk was not significantly associated with BMI at 10–18 y of age ($\beta \pm$ SE: –0.41 ± 0.07, $P < 0.10$, and 0.40 ± 0.33, $P \geq 0.10$, respectively) or with the odds of overweight plus obesity (OR ± SE from logit: 0.79 ± 0.03 and 1.32 ± 0.21, respectively; $P < 0.10$ for both) or obesity (OR ± SE from logit: 0.77 ± 0.04, $P < 0.10$, and 1.17 ± 0.25, $P \geq 0.10$, respectively).

In a follow-up at 12–21 y of age, Nelson et al. (28) examined a full sample ($n = 5929$ males, 6069 females) and a subsample of siblings with discordant infant feeding and outcomes (i.e., in which the overweight sibling had been fed human milk and the nonoverweight sibling had not, and in which the overweight sibling had not been fed human milk and the nonoverweight sibling had; $n = 224$ discordant siblings). In the full sample, ever compared with never consuming human milk was associated with significantly lower odds of overweight plus obesity at 12–21 y of age among females [OR (95% CI): 0.83 (0.72, 0.95)] but not males [OR (95% CI): 0.90 (0.76, 1.05)]. Results for BMI z score were not presented for the full sample. The sibling-pair analyses did not show any significant associations between ever, compared with never, consuming human milk and overweight plus obesity or BMI z score at 12–21 y of age.

Child Development Supplement of the Panel Study of Income Dynamics.

Metzger and McDade (29) examined children and adolescents in the Child Development Supplement of the Panel Study of Income Dynamics cohort at 9–19 y of age, with 2591 in the full sample, 976 in a subsample of siblings (488 sibling pairs, including 59 pairs with discordant exposures), and 30–44 in another subsample of siblings with differences in both feeding and BMI status. In the full sample, ever compared with never consuming human milk was associated with a lower BMI z score (mean ± SE: –0.150 ± 0.065; $P < 0.05$). In the sibling subsample, ever compared with never consuming human milk was associated with a lower BMI z score (mean ± SE: –0.397 ± 0.176; $P < 0.05$). In the subsample of siblings with differences in both feeding and BMI status, ever compared with never consuming human milk was not significantly associated with the odds of having a BMI >50th percentile (OR: ~1.30 and ~1.00 from fixed-effects and ordinary least squares regression models, respectively) but was associated with a lower odds of overweight plus obesity (OR: ~0.40, $P < 0.05$ and ~0.60, $P < 0.01$, respectively, from fixed-effects and ordinary least squares regression models) as well as a lower odds of obesity (OR: ~0.20, $P < 0.01$ and OR ~0.70, $P \geq 0.05$, respectively, from fixed-effects and ordinary least squares regression models).

Duration of human milk consumption among infants fed human milk

Four articles, based on 3 US cohorts and 1 cohort in Finland, included sibling-pair analyses examining associations between the duration of human milk consumption and subsequent BMI, body fat percentage, or overweight and/or obesity status (26, 27, 30, 31). In addition, the PROBIT trial in the Republic of Belarus resulted in a different duration of human milk feeding between intervention and control groups and thus is also described below (16–18). The study from Finland defined overweight in adulthood as BMI 25–30, and all other studies defined overweight plus obesity as BMI ≥85th percentile and obesity as BMI ≥95th percentile, based on the CDC growth reference (32).

Children of NLSY79.

As reported in the previous section, Colen and Ramey (26) conducted analyses on a full sample of 8237 participants and on a subsample of sibling pairs with discordant infant feeding ($n = 1773$ participants). In the full sample, there were small but statistically significant inverse associations between weeks of human milk consumption and BMI ($\beta \pm$ SE: –0.007 ± 0.002; $P < 0.01$) as well as obesity ($\beta \pm$ SE: –0.007 ± 0.002; $P < 0.01$) at 4-14 y. In the sibling-pair subsample, these associations were not significant ($\beta \pm$ SE: 0.005 ± 0.003 for BMI; $\beta \pm$ SE: 0.001 ± 0.004 for obesity).

Add Health.

Evenhouse and Reilly (27) examined a full sample of 16,903 participants in Add Health (of whom 7417 were fed human milk) and a subsample of sibling pairs with discordant infant feeding (i.e., siblings fed human milk for different durations; $n = 470$). In the full sample and sibling-pair subsample, there were no significant associations between the duration of any human milk consumption and BMI, overweight plus obesity, or obesity at 10–18 y of age.

Growing Up Today Study.

Gillman et al. (30) assessed the association between the duration of human milk consumption and overweight plus obesity at 9–14 y of age in a sample of children and adolescents in the US-based Growing Up Today Study cohort. The full sample included 5614 siblings from 2709 families, and the subsample of siblings with discordant infant feeding (i.e., siblings fed human milk for different durations) included 2372 children and adolescents. In the full sample, each additional 3.7-mo increase in the duration of any human milk consumption (which was the mean difference in duration for discordant siblings) was associated with significantly lower odds of overweight plus obesity at 9–14 y of age when applying the same statistical adjustments for confounders as in the discordant sibling analysis [i.e., age, sex, Tanner stage, menarcheal status for girls, birthweight, birth order, inactivity, physical activity, and energy intake; OR (95% CI): 0.88 (0.82, 0.94)]. When the model was also adjusted for maternal BMI and smoking, as well as household income, the magnitude of the association was slightly attenuated and the confidence interval included the null [OR (95% CI): 0.94 (0.88, 1.00)]. In the discordant sibling analysis, no significant association was detected between consuming human milk for a duration longer than the mean duration within each family, compared with a duration shorter than the mean family duration, and odds of overweight plus obesity at 9–14 y of age. The odds ratio was of similar magnitude to the odds ratios in the full sample, but the confidence interval was wider and included the null [OR (95% CI): 0.92 (0.76, 1.11)].

Helsinki Birth Cohort.

O'Tierney et al. (31) studied the Helsinki Birth Cohort from Finland. Offspring were born between 1934 and 1944. The study sample consisted of members of the cohort who were fed human milk, had a sibling in the cohort, and provided follow-up data in

the year 2000, along with their sibling. The outcomes of interest were BMI and overweight from self-reported data ($n = 831$) and BMI and percent body fat from clinical measurement ($n = 129$) at about 62 y of age. The analyses compared siblings fed human milk for different durations (<2, 3–4, 5–7, and ≥8 mo). Duration of human milk feeding was not associated with offspring BMI or prevalence of overweight. However, when BMI was based on measurements conducted in the clinic (i.e., rather than self-report), the quadratic trend approached significance ($P = 0.08$), suggesting a U-shaped association. Compared with a 5- to 7-mo duration of human milk feeding, BMI tended to be higher with durations of <2 mo (+2.3; 95% CI: –0.1, 4.7) and ≥8 mo (+1.2; 95% CI: –0.9, 3.2) but not with a duration of 3–4 mo (–0.4; 95% CI: –2.7, 1.8). There was a significant quadratic trend ($P = 0.03$) in the percent body fat of participants fed human milk for <2, 3–4, 5–7, and ≥8 mo, suggesting a similar type of U-shaped association between duration of breastfeeding and percent body fat.

PROBIT.

The PROBIT study conducted in the Republic of Belarus was a cluster randomized controlled trial of an intervention to promote prolonged duration and exclusivity of human milk feeding among mothers who chose to feed human milk. The study enrolled 17,046 infants at birth and followed 13,889 children to 6.5 y (16), 13,879 children to 11.5 y (18), and 13,557 adolescents to 16 y of age (17). The intervention group had higher rates of any human milk consumption measured at 3, 6, 9, and 12 mo of age compared with the control group (72.7% compared with 60.0% at 3 mo, 49.8% compared with 36.1% at 6 mo, 36.1% compared with 24.4% at 9 mo, and 19.7% compared with 11.4% at 12 mo). At 6.5 y of age, odds of overweight plus obesity or obesity did not differ by intervention group. At both 11.5 and 16 y of age, the intervention group had significantly higher odds of overweight plus obesity than the control group [OR (95% CI): 1.18 (1.01, 1.39) and 1.14 (1.02, 1.28), respectively]. For obesity, the confidence interval was wider and included the null [OR (95% CI): 1.17 (0.97, 1.41) and 1.09 (0.92, 1.29) at 11.5 and 16 y, respectively].

Discussion

This systematic review took a novel approach to the question of whether human milk feeding is related to subsequent risk of overweight or obesity by focusing on studies with lower risk of confounding (i.e., sibling-pair and intervention studies). It thus adds a new dimension to this important topic. The entire body of evidence, from all studies included in the review (12, 13), was considered when the committee developed conclusion statements. Because the conclusions differed for the 2 exposures examined, ever compared with never consuming human milk and different durations of human milk consumption among infants fed human milk, these 2 sets of evidence are discussed in separate sections below.

Ever compared with never consuming human milk

Based on evidence from 21 observational cohort studies published between 2011 and 2019, including the 4 sibling-pair studies described herein, the committee concluded that ever, compared with never, consuming human milk is associated with a lower risk of overweight and obesity at ages 2 y and older, particularly if the duration of human milk consumption is 6 mo or longer (13). This conclusion statement was graded as "moderate." The observational cohort studies were strongly consistent, with 14 of 21 studies showing a significantly lower risk of overweight and/or obesity in those who were ever fed human milk and another showing a marginal association in the same direction; several of the remaining studies may have lacked statistical power to detect an association. Five of the 7 studies that compared infants who consumed human milk for different durations with infants who never consumed human milk suggested that a longer duration of human milk consumption (e.g., ≥6 mo) is most protective. However, these 21 studies were limited by potential confounding because none of them controlled for all of the key confounders specified in the analytic framework. In particular, few studies accounted for complementary feeding practices and childhood diet, both of which are likely to be highly correlated with whether the child was fed human milk and may also influence the risk of overweight and obesity.

Sibling-pair studies greatly reduce the risk of bias introduced by confounding in observational studies because siblings share genetic, familial, and environmental risk factors. The sibling-pair analyses generally showed an attenuation of the significant associations that were found in full-sample analyses in those 4 studies, suggesting that confounding may explain a substantial proportion of the association between ever compared with never consuming human milk and subsequent overweight and obesity. Nevertheless, 1 of the sibling-pair analyses (29) did show a significant association between ever compared with never consuming human milk and lower odds of overweight plus obesity and obesity at 9–19 y of age. In another sibling-pair analysis (24), initiating human milk feeding was associated with a significantly lower BMI z score at 5 y of age, although not with risk of overweight or obesity. Sibling-pair studies are often limited by the smaller sample size available for such analyses, given that discordance between siblings is likely less common than concordance (15). The lower statistical power of such analyses makes it less likely to detect significant associations. Although risk of confounding is reduced in sibling-pair analyses, it is not eliminated entirely. For example, if a relation is found between infant feeding and child overweight, it is possible that the reason for discordance in infant feeding (e.g., cesarean section delivery or a change in family structure) is the actual causal factor predisposing to child overweight. Among these 4 studies, several other limitations also were of concern, including maternal recall of infant feeding 4–18 y after birth in 2 of the cohorts (27–29), self-report of weight and height (25, 26), and incomplete description of methods used to collect outcome data (27, 28). In addition, none of these studies included sibling-pair analyses that compared infants who consumed human milk for different durations with infants who never consumed human milk. Therefore, it is not possible to evaluate whether the trend described in the conclusion statement (i.e., that longer durations of human milk consumption may be important) is observed in sibling-pair analyses.

Because of the risk of confounding in observational studies and the limitations of the sibling-pair studies, it is difficult to determine whether a causal relation exists between ever compared with never consuming human milk and risk of later

overweight or obesity. Other systematic reviews and meta-analyses on this topic have generally come to similar conclusions. For example, a systematic review of systematic reviews (8) concluded that breastfeeding is consistently associated with a reduction in the odds of overweight or obesity in childhood and adulthood, by about 13% in high-quality studies, but residual confounding could not be ruled out.

Duration of any human milk consumption among infants fed human milk

The committee concluded that the evidence was insufficient to determine the relation between the duration of any human milk consumption, among infants fed human milk, and overweight and/or obesity at age 2 y and older (13). This was based not on a lack of evidence (18 observational cohort studies, including 4 with sibling-pair analyses, and the PROBIT randomized controlled trial were included in the review) but rather on the inconsistency in the findings. Five studies showed significant inverse associations; 3 studies showed significant positive associations; 1 study reported significant associations, in opposite directions, at different ages; and 10 studies reported no significant associations between duration of human milk consumption and risk of overweight or obesity. Notably, all of the sibling-pair analyses showed no association, and the PROBIT trial found a higher risk of overweight or obesity in the intervention group compared with the control group. The relevance of the PROBIT trial to the US population has been questioned, given the much lower prevalence of child obesity in the Republic of Belarus at the time of the study relative to the US prevalence (17). Nonetheless, our conclusion is consistent with the systematic review of systematic reviews (8), which suggested that although breastfeeding of very short duration may be less protective than breastfeeding of longer duration with regard to subsequent overweight and obesity, residential confounding cannot be excluded.

Potential mechanisms and research needs

Despite the challenges of establishing a causal relation between human milk feeding exposures and risk of subsequent overweight or obesity, several lines of evidence suggest potential biological or behavioral mechanisms for such a relation (33). Rapid weight gain during infancy (particularly during the first 6 mo) is consistently related to subsequent risk of overweight or obesity (34–36), and rapid weight gain is more likely among formula-fed than among breastfed infants (35). Although the reasons for more rapid weight gain among formula-fed infants are not yet fully understood, infant self-regulation of energy intake may potentially differ between breastfed and formula-fed infants (37). In addition, higher protein intake among formula-fed infants drives hormonal differences that may stimulate greater weight gain and fat deposition (38), although the precise mechanisms are not yet clear, and this is an active area of investigation (39, 40). Randomized controlled trials of reduced protein formulas have demonstrated less rapid infant weight gain and reduced obesity at school age (41–45). The concentrations of free amino acids in human milk, when compared with infant formula, also may be important. For example, free glutamate, which is much higher in human milk than in conventional infant formulas, is a key signal for satiation. An experimental study comparing extensively hydrolyzed formula, with higher free glutamate content, with a standard infant formula reported a significant difference in early rapid weight gain between the groups (46).

Overfeeding of formula-fed infants also is a possibility, as feeding by bottle may make it more difficult for the infant to communicate satiety signals, and in some cases, the caregiver may urge the infant to finish the bottle so as to avoid wastage (47–49). The feeding dynamics of feeding at the breast may differ from those during bottle feeding. In a small pilot study using a within-subject approach (50), mothers were more sensitive to infant cues during breastfeeding, and the latency from feeding session midpoint to the first satiation cue was significantly longer when they were breastfeeding compared with when they were bottle feeding. Other investigators have reported that infants feeding directly from the breast exhibit more engagement and disengagement cues than do formula-fed infants (51). Differences in the dyadic approach of mothers and infants during feeding may have longer-term implications for programming of appetite regulation. At 3–6 y of age, children who were fed human milk in a bottle as infants were less likely to have high satiety responsiveness compared with directly breastfed children, after controlling for child age, child weight status, maternal race/ethnicity, and maternal education (48). All of the above studies were relatively small, however; thus, additional research on satiety signals and responsiveness is needed.

Future research studies on infant milk-feeding practices and health outcomes should be designed to reduce bias from confounding factors as much as possible. Sibling-pair studies are one example of this type of study design, but few such studies have been conducted, they tend to have much smaller sample sizes than do other types of observational studies, and causes of discordance in infant feeding between siblings complicate interpretation. Larger sibling-pair studies are needed that include consideration of reasons for discordance, and they need to examine siblings who differ in terms of the duration of human milk consumption (e.g., $<$6 mo, $\geq$6 mo), not just with respect to ever compared with never consuming human milk. Additional large randomized controlled trials of breastfeeding promotion, like the PROBIT trial (52), are also needed. If the trial achieves substantial differences in duration or exclusivity of breastfeeding between intervention groups, this provides an opportunity to examine effects on subsequent overweight or obesity (and many other outcomes).

Observational studies that make use of large data sets, especially those that follow participants longitudinally and, in particular, link children with siblings and parents, also would be useful for robustly assessing associations and providing more confidence in conclusions regarding potential causality. This could be achieved by linking surveillance systems that collect data about infant feeding and health outcomes (including overweight and obesity) and making use of emerging electronic medical record data. In general, observational studies need to take into account all of the key confounders in the analytical framework of this review, including aspects of the child's diet (complementary feeding and later dietary patterns). The use of instrumental variables, such as Mendelian randomization approaches that make use of genetic traits linked with breastfeeding, also could help minimize confounding (53). In both observational and intervention studies, researchers should consider effect

modification in their study design whenever possible (e.g., child sex, parental obesity, socioeconomic status, race or ethnicity, child diets, child activity levels) to examine the impact of infant feeding on these outcomes within key subgroups.

Given the high prevalence of mixed feeding in the United States and elsewhere, additional research is also needed to investigate how the patterns and proportions of human milk feeding across the day and night and within each feeding, in the context of mixed feeding, are related to health outcomes. Similarly, very little evidence is available on the consequences of feeding human milk by bottle compared with from the breast. The composition of human milk varies during the day and within a feeding, which may affect the infant's physiology (54); bottle feeding human milk may modify these patterns, as well as the feeding dynamics of breastfeeding and bottle-feeding mothers and their infants.

We conclude that further carefully designed research is needed to disentangle the complex relation between infant feeding practices and the risk of subsequent overweight or obesity, as well as the biological and behavioral mechanisms if the relation is causal. This review was designed to be relevant to healthy infants in countries with a high or very high level of human development and may not be generalizable to other situations. Further research in countries undergoing the nutrition transition, greater use of stronger study designs, and comparing results across studies with different types of limitations is required to advance our understanding. Despite uncertainty about the relation of human milk feeding to the prevention of subsequent overweight, there are still many reasons to promote breastfeeding with regard to other outcomes for both the mother (55) [e.g., reduced risk of breast, ovarian, and endometrial cancers (56, 57); hypertension and cardiovascular disease (58); nonalcoholic fatty liver disease (59); and type 2 diabetes (60)] and the child [e.g., reduced risk of type 1 diabetes (61) and asthma (62), as well as greater cognitive development (15)].

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