



Original Contribution

Breastfeeding and Infant Size: Evidence of Reverse Causality

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Infants who receive prolonged and exclusive breastfeeding grow more slowly during the first year of life than those who do not. However, infant feeding and growth are dynamic processes in which feeding may affect growth, and prior growth and size may also influence subsequent feeding decisions. The authors carried out an observational analysis of 17,046 Belarusian infants who were recruited between June 1996 and December 1997 and who participated in a cluster-randomized trial of a breastfeeding promotion intervention. To assess the effects of infant size on subsequent feeding, the authors restricted the analysis to infants breastfed (or exclusively breastfed) at the beginning of each follow-up interval and examined associations between weight or length at the beginning of the interval and weaning or discontinuation of exclusive breastfeeding by the end of the interval. Smaller size (especially weight for age) was strongly and statistically significantly associated with increased risks of subsequent weaning and of discontinuing exclusive breastfeeding (adjusted odds ratios = 1.2–1.6), especially between 2 and 6 months, even after adjustment for potential confounding factors and clustered measurement. The authors speculate that similar dynamic processes involving infant crying, other signs of hunger, and supplementation/weaning undermine causal inferences about the “effect” of prolonged and exclusive breastfeeding on slower infant growth.

body size; breast feeding; causal inference; evidence; infant

Abbreviations: LAZ, length-for-age z score; PROBIT, Promotion of Breastfeeding Intervention Trial; WAZ, weight-for-age z score; WHO, World Health Organization; WLZ, weight-for-length z score.

Editor's note: A related article by Al-Sahab *et al.* appears on page 0000, an invited commentary on both articles is published on page 0000, and the response by Kramer *et al.* to the commentary is on page 0000. In accordance with Journal policy, Al-Sahab *et al.* were asked if they wanted to respond to the commentary but chose not to do so.

It has long been recognized that infants who receive prolonged and exclusive breastfeeding grow more slowly during the first year of life than those who are formula fed and even those who are breastfed less exclusively or for shorter periods of time (1–8). Recognition of these different growth trajectories was largely responsible for the decision by the World Health Organization (WHO) to develop a new growth reference based on breastfed infants, which has recently been published (9). Moreover, the slower infant growth

trajectory of breastfed infants has been suggested as contributing to a long-term protective effect against obesity in childhood and even through adulthood, although an individual subject data meta-analysis with adequate control for socioeconomic status and other potential confounders (10), as well as the results of our Promotion of Breastfeeding Intervention Trial (PROBIT) (11), does not support such a long-term protective effect.

The potential protective effect of breastfeeding against long-term obesity is an important subject of debate, given the current epidemic of obesity in both developed and developing countries. It is clear that rapid infant (and even fetal) growth is associated with later obesity (12–15), but the evidence that infant growth trajectories are causally related to infant feeding practices is affected by not only confounding by socioeconomic status, physical activity, later diet, and other life-style factors but also the potential for reverse causality.

Several decades ago, Bradford Hill (16) and Sauls (17) cautioned that comparisons involving infants with prolonged breastfeeding inevitably select for infants who have grown adequately and are in good health, because infection and other problems arising during infancy are likely to affect infant feeding choices. Thus, they argued that the direction of cause and effect may be the reverse: Infection or poor health may be the cause of formula supplementation or weaning.

Although Bradford Hill's and Sauls' arguments did not specifically relate to growth trajectories, we have speculated that infants who grow more rapidly may cry more frequently from hunger (11). Such crying may suggest to mothers (and to their families and physicians) that their milk supply is inadequate and thereby lead to supplementation, which often has adverse effects on milk production and can thereby accelerate weaning (11). Thus, prolonged and exclusive breastfeeding may be a marker for infants who are growing along a slower trajectory, do not cry as often from hunger, and remain satisfied without supplementation or efforts to increase the mother's milk supply. Because both infant growth and infant feeding are dynamic processes, each of which can influence the other, diminished growth trajectories of infants with prolonged and exclusive breastfeeding do not provide convincing evidence that the former is caused by the latter.

In PROBIT, we collected no information on infant crying or other possible symptoms of hunger, but we did obtain frequent measurements of infant feeding and growth during the first year of life. This feature, along with its large sample size and high follow-up rates, has led to several PROBIT publications relating infant feeding to growth (7, 18–20). Our intention-to-treat analysis (based on randomized treatment allocation) found significantly increased weight and length gains in the first 3 months of life in the experimental (breastfeeding promotion) group, followed by complementary “catch-down” and “catch-up” trajectories in the experimental and control groups, respectively, with no significant differences remaining by 12 months of life (18). Although our observational analyses have suggested slower trajectories in infants with prolonged and exclusive breastfeeding (7, 18–21), those analyses are subject to the same sorts of bias as previous observational studies. In this paper, we examine the association between infant size and subsequent feeding decisions; that is, we have reversed the usual direction of the presumed cause and effect. By ensuring the temporal precedence of weight and length measurements, this type of analysis permits us to explore empirically the evidence for reverse causation.

MATERIALS AND METHODS

A detailed description of the PROBIT methods has been previously published (22). Briefly, 31 maternity hospitals and 1 each of their affiliated polyclinics (i.e., the outpatient clinics where children are followed for routine health care) in the Republic of Belarus were randomly assigned to receive a breastfeeding promotion intervention modeled on the WHO/United Nations Children's Fund (UNICEF) Baby-Friendly Hospital Initiative (experimental group) or

to continue the maternity hospital and polyclinic practices in effect at the time of randomization (control group). Overall, 17,046 full-term, healthy, singleton newborns who weighed at least 2,500 g at birth and who were initially breastfed were recruited during their postpartum stay between June 1996 and December 1997. Follow-up data on infant feeding and growth (weight, length, and head circumference) were collected at scheduled polyclinic visits at 1, 2, 3, 6, 9, and 12 months; 96.7% of the children were followed through 12 months of age. Because differences in infant growth were not major hypotheses of PROBIT, no attempts were made to standardize anthropometric measurements.

The main “exposures” of interest in this study were weight and length at the visit preceding the follow-up visit at which the infant feeding information was obtained. The weights and lengths were expressed as *z* scores standardized for age and sex, on the basis of the recently published WHO reference (9). The weight-for-age (WAZ), length-for-age (LAZ), and weight-for-length (WLZ) *z* scores were divided into 3 groups (<-1 , -1 to 1 , and >1) to assess their associations with weaning (i.e., discontinuation of any breastfeeding) and discontinuation of exclusive breastfeeding by the next follow-up polyclinic visit. For each of these assessments, we restricted the analysis to those infants who were either breastfed to some degree (for analysis of weaning) or exclusively breastfed (for analysis of discontinuation of exclusive breastfeeding) at the previous visit. In other words, all analyses were restricted to infants who were breastfed (or exclusively breastfed) at the beginning of each study interval. Our definition of exclusive breastfeeding is that recommended by WHO (23), as has been detailed previously (22), whereby infants were considered as having been exclusively breastfed at a given age if the mother indicated no receipt of any nonbreast milks, other liquids, or solid foods at that age and at all previous PROBIT follow-up visits.

In addition to bivariate analyses comparing risks of weaning and discontinuation of exclusive breastfeeding in the ensuing interval as a function of weight and length at the beginning of the interval, we also carried out a multivariable analysis with GLIMMIX, a generalized linear mixed-model procedure in SAS statistical software (version 9; SAS Institute, Inc., Cary, North Carolina) that uses penalized quasi-likelihood to estimate model parameters and yields adjusted odds ratios for a dichotomous outcome. The multivariable models included the primary exposure (WAZ, LAZ, or WLZ at the previous visit), maternal smoking at the onset of the interval, maternal education, and ecologic-level variables (East vs. West and urban vs. rural location of the maternity hospital and polyclinic), as well as a random-effects term for hospital/polyclinic to account for clustered measurement among children followed at the same polyclinic. To control for genetic potential, the multivariate analyses also adjusted for maternal and paternal height and body mass index, which were reported by the mother at follow-up at 6.5 years of age, based on the 13,889 children followed up at that age. As previously reported (11, 22), baseline characteristics in those followed up at 6.5 years were similar to those reported at randomization.

RESULTS

Table 1 describes baseline factors for the PROBIT cohort, as well as maternal and paternal height and body mass index for the children followed up at 6.5 years. Shown in Table 2 are the mean (standard deviation) of weight, length, WAZ, LAZ, and WLZ and the percentage of infants breastfed and exclusively breastfed at birth and at each follow-up visit. Because very few study infants were exclusively breastfed beyond 6 months, data on exclusive breastfeeding are included only through 6 months of follow-up. PROBIT infants closely followed the reference mean for weight during the first 3 months but were longer than the reference at birth. They progressively exceeded the reference means (especially for WAZ and WLZ) from 6 to 12 months.

Table 3 shows the percentage of infants at 1, 2, 3, 6, 9, and 12 months of age who were weaned or in whom exclusive breastfeeding was discontinued, as a function of the 3 growth measurements at the previous visit. Infants who were smaller (z score, <-1) at the previous visit were significantly more likely to be weaned or to have discontinued exclusive breastfeeding by the subsequent visit, especially from 2 to 6 months of age. Conversely, infants who were larger (z score, >1) were significantly less likely to experience these feeding changes by the next visit. The results were similar for the 3 size measures, but associations were

strongest for WAZ and, thus, the multivariable analyses were restricted to WAZ.

Table 4 shows the results of the multivariable generalized linear mixed model (GLIMMIX) analyses for WAZ. The results are shown for both the entire cohort and (in order to incorporate data on maternal and paternal size) those infants who were followed up at age 6.5 years. These results clearly show that breastfeeding infants who were lighter at the previous visit were significantly more likely to be weaned by the subsequent visit, and, if they were exclusively breastfed at the onset of the interval, to have discontinued exclusive breastfeeding. The results were most striking between 2 and 6 months, with adjusted odds ratios ranging from 1.2 to 1.6, indicating that smaller infants (those with WAZ, <-1) had 20%–60% higher odds of being weaned or discontinuing exclusive breastfeeding by the next visit.

DISCUSSION

In the conventional approach to infant feeding and growth, infant size or growth is examined in association with contemporaneous infant feeding. As we argued in the introduction, the conventional analytical approach cannot establish the temporal precedence of feeding decisions with respect to infant size or growth, thus making it impossible to establish cause-and-effect relations, or even the direction of causality, between these 2 variables. Reverse causality in the association between infant size and subsequent breastfeeding has been demonstrated in several previous studies from developing countries (24, 25), but the direction has been opposite to that shown here. In those settings, stunting was associated with longer duration of subsequent breastfeeding. In a study from the Philippines, however, Adair et al. (26) observed the same direction that we did: A higher ponderal index at ages 2, 4, and 6 months was associated with longer duration of subsequent breastfeeding.

Our empirical exploration of reverse causality was based on infant size measurements that preceded changes in infant feeding and was restricted to infants with equivalent breastfeeding experience at the onset of each interval (i.e., at the time that the size measurement was obtained). The effect of infant size on subsequent changes in breastfeeding was particularly strong in the first 6 months of life, when breastfeeding constitutes the major (and sometimes the exclusive) component of the infant diet. Our approach thus contrasts with those of previous studies from developed countries, including our own observational analyses of PROBIT (7, 18–21). These previous studies have defined breastfeeding over the entire period or periods of study and thus cannot distinguish whether breastfeeding leads to slower weight or length gain or whether slower growth causes weaning or discontinuation of exclusive breastfeeding (supplementation).

As mentioned in Materials and Methods, infant growth was not one of PROBIT's primary outcomes. Anthropometric measurements were carried out by 31 different pediatricians, with no attempt to standardize measuring instruments or techniques. The absence of standardization, however,

Table 1. Baseline Descriptors of the PROBIT Cohort Recruited in Belarus in 1996–1997

Baseline Characteristic	%	Mean (SD)
Maternal age at delivery, years		
<20	14.0	
20–34	81.7	
≥35	4.2	
Maternal education		
Incomplete secondary	3.9	
Completed secondary	32.2	
Advanced secondary or partial university	50.3	
Completed university	13.6	
Older siblings, no.		
0	58.0	
1	33.5	
≥2	8.5	
Smoking during pregnancy	2.3	
Cesarean delivery	11.6	
Male sex	51.8	
Gestational age, weeks		39.4 (1.0)
Maternal height, cm		164.4 (5.6) ^a
Maternal body mass index, kg/m ²		24.5 (4.4) ^a
Paternal height, cm		176.1 (6.6) ^a
Paternal body mass index, kg/m ²		25.7 (3.3) ^a

Abbreviations: PROBIT, Promotion of Breastfeeding Intervention Trial; SD, standard deviation.

^a Data were obtained at the 6.5-year follow-up ($n = 13,889$).

Table 2. Anthropometric Measures (Mean (SD)) and Breastfeeding (%) of Infants in the PROBIT Cohort Recruited in Belarus in 1996–1997^a

	Birth (n = 17,046)		1 month (n = 16,692)		2 months (n = 16,420)		3 months (n = 16,629)		6 months (n = 16,405)		9 months (n = 16,089)		12 months (n = 16,471)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Weight, kg	3.44 (0.42)		4.33 (0.50)		5.23 (0.58)		6.12 (0.68)		8.10 (0.85)		9.50 (0.94)		10.58 (1.01)	
Length, cm	51.9 (2.1)		54.8 (2.3)		57.8 (2.4)		61.0 (2.5)		67.2 (2.7)		71.9 (2.7)		75.9 (2.7)	
WAZ	0.3 (0.8)		0.0 (0.8)		−0.2 (0.8)		0.0 (0.9)		0.5 (0.9)		0.8 (0.8)		1.1 (0.8)	
LAZ	1.3 (1.1)		0.3 (1.2)		0.0 (1.2)		0.2 (1.2)		0.2 (1.2)		0.3 (1.1)		0.4 (1.1)	
WLZ	−1.1 (1.2)		−0.5 (1.2)		−0.2 (1.2)		−0.1 (1.1)		0.6 (1.0)		1.0 (0.9)		1.2 (0.9)	
Any breastfeeding		100		91.3		77.9		64.9		41.8		28.8		21.3
Exclusive breastfeeding		100		54.3		36.9		26.8		4.0				

Abbreviations: LAZ, length-for-age z score; PROBIT, Promotion of Breastfeeding Intervention Trial; SD, standard deviation; WAZ, weight-for-age z score; WLZ, weight-for-length z score.

^a Sample sizes denote the numbers of infants with weight at the indicated age. Numbers of infants with other measurements may differ slightly.

should increase random error (nondifferential with respect to either true infant size or feeding) and, thus, attenuate the associations that we examined.

As illustrated by the above-cited studies from Senegal (24), Peru (25), and the Philippines (26), the potential for reverse causality bias between infant size and subsequent feeding is likely to vary in direction and magnitude according to culture, setting, and time. Nonetheless, the salience of infant size for subsequent feeding decisions is probably universal. In settings with a high prevalence of undernutrition, breastfeeding may be encouraged as a way of compensation for small size, whereas in developed country settings, smaller size is likely to undermine the mother's confidence in her ability to provide sufficient nutrition for her infant, thus leading to supplementation and weaning. The effect of infant size on breastfeeding decisions and the variation of this effect across settings are likely to at least partly explain the mixed findings of associations between infant feeding

and infant growth and long-term associations between infant feeding and subsequent obesity.

The effect of smaller infant size on subsequent weaning or discontinuing exclusive breastfeeding cannot, however, explain the subsequent slower growth of infants who continue any or exclusive breastfeeding. Our analysis and some other observational analyses of infant feeding and subsequent growth have adjusted for size at the beginning of each study interval, thus controlling for regression to the mean (the tendency of previously small infants to grow more rapidly over the interval). In an analysis of the PROBIT data based on structural mean models, we reported significantly slower weight and length gains among infants who continued breastfeeding at 2, 3, 6, and 9 months (20). For exclusive breastfeeding, we reported significantly smaller weight and length gains between 3 and 6 months among infants who continued exclusive breastfeeding to 6 months compared with those who exclusively breastfed to 3 months

Table 3. Bivariate Associations Between WAZ, LAZ, and WLZ at Previous Visit and Weaning/Discontinuation of Exclusive Breastfeeding at Subsequent Visit in the PROBIT Cohort Recruited in Belarus in 1996–1997

Anthropometry Category	% Weaned						% Discontinued Exclusive Breastfeeding			
	1 month	2 months	3 months	6 months	9 months	12 months	1 month	2 months	3 months	6 months
WAZ		***	***	***				***	***	*
<−1	9.9	20.9	23.1	42.4	28.9	32.1	47.4	41.6	36.8	87.1
−1 to 1	8.5	15.0	16.9	35.4	31.2	26.2	45.1	34.8	30.0	85.9
>1	8.9	10.4	12.4	27.2	31.2	25.9	47.5	26.2	26.0	81.5
LAZ		***					***	**		
<−1	12.6	18.7	17.8	38.0	30.4	26.3	44.5	36.0	32.4	84.3
−1 to 1	9.0	15.3	17.9	34.7	31.4	26.7	43.5	35.2	30.5	86.0
>1	8.4	13.5	15.7	34.9	30.5	24.3	47.4	31.5	28.8	84.8
WLZ		***	***	***			***	***	*	*
<−1	8.4	17.0	20.0	41.1	33.6	29.0	48.9	37.4	33.3	87.2
−1 to 1	9.0	14.7	17.7	34.9	31.3	26.4	42.4	33.9	30.1	85.7
>1	7.8	11.8	13.2	29.6	30.3	25.7	41.3	29.3	29.2	83.1

Abbreviations: LAZ, length-for-age z score; PROBIT, Promotion of Breastfeeding Intervention Trial; WAZ, weight-for-age z score; WLZ, weight-for-length z score.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ based on χ^2 test for trend.

Table 4. Multivariable Analysis of Associations (Adjusted OR (95% CI)) Between Weight-for-Age z Score at Previous Visit and Weaning or Discontinuation of Exclusive Breastfeeding at Subsequent Visit in the PROBIT Cohort Recruited in Belarus in 1996–1997

	Entire Cohort				Restriction to Infants Followed Up at 6.5 Years			
	Weaning		D/C EBF		Weaning		D/C EBF	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
1 month								
<−1	1.2	1.0, 1.5	1.1	1.0, 1.4	1.3	1.005, 1.7	1.1	0.9, 1.4
−1 to 1	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
>1	1.1	0.9, 1.2	1.1	1.03, 1.3	1.0	0.8, 1.2	1.1	0.9, 1.2
2 months								
<−1	1.5	1.3, 1.7	1.4	1.2, 1.6	1.5	1.3, 1.7	1.4	1.2, 1.7
−1 to 1	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
>1	0.7	0.6, 0.8	0.7	0.6, 0.8	0.7	0.6, 0.8	0.7	0.6, 0.9
3 months								
<−1	1.5	1.3, 1.7	1.4	1.2, 1.6	1.5	1.3, 1.7	1.3	1.04, 1.5
−1 to 1	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
>1	0.7	0.6, 0.9	0.8	0.7, 1.0	0.7	0.5, 0.9	0.8	0.6, 1.1
6 months								
<−1	1.3	1.2, 1.5	1.2	0.9, 1.7	1.4	1.2, 1.6	1.1	0.7, 1.6
−1 to 1	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
>1	0.7	0.6, 0.8	0.7	0.5, 0.9	0.7	0.6, 0.8	0.7	0.5, 0.9
9 months								
<−1	0.9	0.7, 1.2			1.0	0.7, 1.4		
−1 to 1	1.0	Referent			1.0	Referent		
>1	1.0	0.9, 1.1			1.0	0.8, 1.1		
12 months								
<−1	1.4	0.8, 2.6			1.6	0.8, 3.1		
−1 to 1	1.0	Referent			1.0	Referent		
>1	1.0	0.9, 1.2			1.1	0.9, 1.3		

Abbreviations: CI, confidence interval; D/C EBF, discontinuation of exclusive breastfeeding; OR, odds ratio; PROBIT, Promotion of Breastfeeding Intervention Trial.

but partially breastfed at 6 months (19). Although these slower growth trajectories could reflect a causal effect of prolonged and exclusive breastfeeding on reducing weight and length gain, our intention-to-treat analysis (i.e., based on randomization to the breastfeeding promotion intervention) showed no net difference in weight gain or length over 12 months of age.

As we have previously speculated (11), the slower growth trajectories observed in the observational analyses may reflect reverse causality: More slowly growing infants are “satisfied” with their mothers’ own milk production. Thus, they do not show signs (crying, fussing, poor sleeping) of hunger, do not receive formula supplements, and continue breastfeeding. Empirical demonstration of this source of reverse causality, however, would require not only detailed data on crying, fussing, and sleeping but also data on the mother’s responses to these signs. We did not collect such data in PROBIT, nor are we aware of such data from other studies (observational or experimental) of infant feeding and growth.

This potential for reverse causality has important implications for future research, as well as for public health policy recommendations. Although our analysis in no way undermines the importance of prolonged and exclusive breastfeeding for many other aspects of infant and child health and development, breastfeeding should not be expected to play an important role in slowing the current obesity epidemic.

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