

Breastfeeding and Child Cognitive Development

New Evidence From a Large Randomized Trial

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Context: The evidence that breastfeeding improves cognitive development is based almost entirely on observational studies and is thus prone to confounding by subtle behavioral differences in the breastfeeding mother's behavior or her interaction with the infant.

Objective: To assess whether prolonged and exclusive breastfeeding improves children's cognitive ability at age 6.5 years.

Design: Cluster-randomized trial, with enrollment from June 17, 1996, to December 31, 1997, and follow-up from December 21, 2002, to April 27, 2005.

Setting: Thirty-one Belarussian maternity hospitals and their affiliated polyclinics.

Participants: A total of 17 046 healthy breastfeeding infants were enrolled, of whom 13 889 (81.5%) were followed up at age 6.5 years.

Intervention: Breastfeeding promotion intervention modeled on the Baby-Friendly Hospital Initiative by the World Health Organization and UNICEF.

Main Outcome Measures: Subtest and IQ scores on the Wechsler Abbreviated Scales of Intelligence, and

teacher evaluations of academic performance in reading, writing, mathematics, and other subjects.

Results: The experimental intervention led to a large increase in exclusive breastfeeding at age 3 months (43.3% for the experimental group vs 6.4% for the control group; $P < .001$) and a significantly higher prevalence of any breastfeeding at all ages up to and including 12 months. The experimental group had higher means on all of the Wechsler Abbreviated Scales of Intelligence measures, with cluster-adjusted mean differences (95% confidence intervals) of +7.5 (+0.8 to +14.3) for verbal IQ, +2.9 (-3.3 to +9.1) for performance IQ, and +5.9 (-1.0 to +12.8) for full-scale IQ. Teachers' academic ratings were significantly higher in the experimental group for both reading and writing.

Conclusion: These results, based on the largest randomized trial ever conducted in the area of human lactation, provide strong evidence that prolonged and exclusive breastfeeding improves children's cognitive development.

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AMONG THE MOST CONSISTENTLY reported benefits of breastfeeding in developed country settings have been higher results on IQ tests and other measures of cognitive development among children and adults who had been breastfed compared with those who were formula-fed. A meta-analysis by Anderson et al¹ in 1999 reported consistent IQ differences favoring breastfed over formula-fed infants, with most differences in the 2- to 5-point range. Most of the studies included in the meta-analysis were observational in design and were carried out in subjects who were born healthy and at term, although a larger difference

of 8 points was reported by Lucas et al² in follow-up of a randomized trial in preterm infants. Several of these studies demonstrated a clear dose-response relationship, with larger differences associated with longer durations of breastfeeding. With 1 recent notable exception,³ studies published since the meta-analysis have been entirely consistent with these results and conclusions.⁴⁻⁹

Despite the robustness of the reported findings, many observers remain unconvinced about the cognitive benefits of breastfeeding.^{10,11} As mentioned earlier, the evidence is based almost entirely on observational studies. The beneficial effect of breastfeeding is unlikely to be ex-

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Group Information: Additional PROBIT Study Group members are listed on page 583.

plained by the higher socioeconomic status of breastfeeding mothers because most studies have controlled statistically for socioeconomic differences. Some of the studies have even controlled for maternal IQ, with most studies reporting an attenuated but persistent and significant effect.^{1-3,9} On the other hand, the benefits are likely to be confounded by other, more subtle differences in the mother's behavior or her interaction with the infant. These differences are extremely difficult to measure and virtually impossible to control for in observational studies.

The solution to these methodological problems is a randomized controlled trial, but randomization to breastfeeding vs artificial feeding is infeasible and probably unethical. It is, however, both feasible and ethical to randomize the participants to a breastfeeding promotion intervention. One strategy would be to promote breastfeeding initiation, but most women decide whether to breastfeed early in or even before pregnancy and such a strategy is therefore difficult with regard to both timing and logistics. An alternative and more feasible strategy is to promote breastfeeding exclusivity and duration among those mothers who have already decided to initiate breastfeeding, with analysis by intention to treat. This is the strategy we used in the Promotion of Breastfeeding Intervention Trial (PROBIT), a cluster-randomized trial in the Republic of Belarus.¹² In this article, we describe measures of cognitive development among children enrolled in this trial and followed up at age 6.5 years.

METHODS

The detailed methods of PROBIT and the results during the first year of follow-up have been previously reported.¹² The experimental intervention was based on the Baby-Friendly Hospital Initiative, which was developed by the World Health Organization and UNICEF to promote and support breastfeeding,¹³ particularly among mothers who have chosen to initiate breastfeeding (>95% of mothers in Belarus during the period of recruitment), while the control maternity hospitals and polyclinics continued the practices and policies in effect at the time of randomization. The units (clusters) of randomization were maternity hospitals and 1 affiliated polyclinic per hospital, with double randomization based on both a random-numbers table and a coin flip.¹² The trial results are based on a total of 17 046 healthy breastfed infants from 31 maternity hospitals and their affiliated polyclinics; all of the infants were born from June 17, 1996, to December 31, 1997, at term, weighed at least 2500 g, and were enrolled during their postpartum stay.¹² To our knowledge, PROBIT is the largest randomized trial ever undertaken in the area of human lactation. It conforms to the recent Consolidated Standards of Reporting Trials recommendations¹⁴ for the design, analysis, and reporting of cluster-randomized trials.

As previously reported,¹² the 2 randomized groups were similar in baseline sociodemographic and clinical variables, including maternal age, education, number of other children at home, the proportion of mothers who had breastfed a previous child for at least 3 months, cesarean delivery, maternal smoking during pregnancy, birth weight, gestational age, and 5-minute Apgar score. The experimental intervention led to a substantial difference in the duration of any breastfeeding that was maintained throughout the first year of follow-up: for the experimental group vs the control group, 72.7% vs 60.0%, respectively, were still breastfeeding at 3 months, 49.8% vs 36.1%, respectively, were still breastfeeding at 6 months, 36.1% vs

24.4%, respectively, were still breastfeeding at 9 months, and 19.7% vs 11.4%, respectively, were still breastfeeding at 12 months. In addition, the prevalence of exclusive breastfeeding (ie, no foods or liquids other than breast milk) was 7-fold higher in the experimental group as compared with the control group at 3 months (43.3% vs 6.4%, respectively), although it was low in both groups at 6 months (7.9% vs 0.6%, respectively).¹²

Follow-up interviews and examinations at age 6.5 years were performed from December 21, 2002, to April 27, 2005, by 1 polyclinic pediatrician in each of 24 of the 31 polyclinics; in the remaining 7 high-volume clinics, follow-up visits were shared by 2 pediatricians. One of the components of these visits was the administration of the Wechsler Abbreviated Scales of Intelligence (WASI).¹⁵ The WASI consists of 4 subtests of the Wechsler scales (vocabulary, similarities, block designs, and matrices) and takes about 30 minutes to administer. The WASI was translated from English to Russian and then back-translated to ensure comparability of the Russian version. Extensive training and follow-up monitoring of the polyclinic pediatricians were ensured by collaborating child psychologists and psychiatrists in Minsk, Belarus. During a 1-week training workshop held at a residential facility for school-aged children near Minsk, high interpediatrician agreement was achieved in a convenience sample of 45 children selected from this facility, with Pearson correlation coefficients (95% confidence intervals [CIs]) of 0.80 (0.67 to 0.89) for vocabulary, 0.72 (0.54 to 0.83) for similarities, 0.80 (0.67 to 0.89) for block designs, and 0.79 (0.66 to 0.88) for matrices.

Children who had begun school by the time of their 6.5-year follow-up visit were also evaluated by their teachers in 4 academic subject areas: reading, writing, mathematics, and other subjects. Based on items in the Teacher Report Form of the Child Behavior Checklist,¹⁶ each child was rated on a 5-point Likert scale as far below, somewhat below, at, somewhat above, or far above his or her grade level. The teachers were blind to the children's treatment status.

Because blinding of pediatricians to the experimental vs control group assignment was infeasible, 5 children per pediatrician (n=38) were randomly selected for audit, for a total of 190 audited children. For all of the children seen in follow-up to be eligible for selection, the audit was carried out after primary data collection had been completed, an average of 17.7 months (range, 5.3 to 32.6 months) after the initial clinic visit. The audit WASI test was administered by 1 of our collaborating Minsk-based child psychologists or psychiatrists (E.M., S.I., S.D., O.S., O.T., or L.K.), all of whom were blind to both the child's treatment allocation and the WASI measures obtained at the initial clinic visit. Because of the time elapsed between the audit and initial polyclinic visits, results were compared using Pearson correlation coefficients.

All of the statistical comparisons were based on intention to treat. Differences in outcome between the experimental and control groups were analyzed using the MIXED procedure in SAS version 8.2 statistical software (SAS Institute, Inc, Cary, North Carolina). This procedure accounts for the clustered randomization, thus permitting inference at the level of the individual child rather than at the level of the cluster (maternity hospital and polyclinic). For analysis of the teachers' academic ratings, the model also accounted for clustering of teachers within the hospital and polyclinic clusters. Unless otherwise indicated, the modeled differences presented in the "Results" section are based on these models adjusted for clustering only. However, they are very similar to those obtained from sensitivity analyses that also adjusted for stratum-level variables, including geographic region (west vs east) and urban vs rural location, as well as the following individual-level covariates: age at follow-up, sex, birth weight, and both maternal and paternal education (results available on request). Missing data were not imputed.

Table 1. Baseline Comparison of Children Followed Up at Age 6.5 Years in Experimental vs Control Groups

Variable	Experimental Group ^a (n=7108)	Control Group ^a (n=6781)
Maternal age, y		
<20	14.3	13.2
20-34	81.4	82.6
≥35	4.3	4.2
Maternal education		
Incomplete secondary	4.4	3.0
Complete secondary	34.3	29.7
Advanced secondary or partial university	47.8	54.5
Complete university	13.5	12.9
Older children living in household, No.		
0	58.8	54.5
1	33.3	36.1
≥2	7.9	9.4
Maternal smoking during pregnancy	2.6	1.6
Male child	51.4	52.0
Birth weight, mean (SD), g	3440 (418)	3441 (423)

^aValues are expressed as percentages unless otherwise indicated.

Table 2. Pearson Correlations of Wechsler Abbreviated Scales of Intelligence Audit Results With Original Polyclinic Results for the 190 Audited Children

Cognitive Measure	r (95% CI)
Vocabulary	0.59 (0.48 to 0.67)
Similarities	0.56 (0.45 to 0.65)
Block designs	0.68 (0.59 to 0.75)
Matrices	0.63 (0.54 to 0.71)
Verbal IQ	0.62 (0.52 to 0.70)
Performance IQ	0.71 (0.63 to 0.77)
Full-scale IQ	0.70 (0.62 to 0.76)

Abbreviation: CI, confidence interval.

RESULTS

A total of 13 889 children were seen in follow-up for PROBIT II, representing 81.5% of the 17 046 children originally randomized. Of the 3157 children randomized but not followed up, 88 had died, 2938 were lost to follow-up, and 131 were unable or unwilling to come for their PROBIT II visit. Follow-up rates were similar in the experimental (80.2%) and control (82.9%) polyclinics but varied considerably by polyclinic: from 56.1% at one of the Minsk polyclinics to 94.6% at Klimovich, a small, rural-based polyclinic. As shown in **Table 1**, the children followed up in the experimental and control groups were similar in baseline characteristics, with small differences paralleling those seen (and previously reported¹²) at randomization. The mean (SD) ages at follow-up were nearly identical in the experimental and control groups: 6.7 (0.3) and 6.6 (0.2) years, respectively.

The audit results for the WASI are shown in **Table 2**. The Pearson correlation coefficients for comparing the test results at the initial clinic visit and those at the au-

dit were high, particularly considering differences in the tester (pediatrician vs auditing psychologist or psychiatrist), the 18-month average time between the 2 administrations of the test, and the fact that most of the children were in school and thus may have experienced differences in rates of cognitive development due to variations in school instruction and environment.

Table 3 shows the results of the WASI tests as assessed by the polyclinic pediatricians, including the number of children who completed each subtest and had calculable IQ measures, the crude individual-based means (standard deviations) in the experimental and control groups, the intraclass correlation coefficients reflecting the degree of within-polyclinic clustering, and the cluster-adjusted differences in means (95% CIs). The results demonstrated a high degree of clustering, with intraclass correlation coefficients in the 0.2 to 0.3 range, largely reflecting systematic differences in means among the 31 polyclinics. The consequence of this clustering was wide CIs around the adjusted differences. Nonetheless, the cluster-adjusted means on the 2 verbal subtests, vocabulary and similarities, were about 5 points higher in the experimental group; both differences were statistically significant. Smaller, nonsignificant differences in the same direction were observed for the nonverbal subtests (block designs and matrices). The cluster-adjusted difference in verbal IQ was 7.5 points higher, and statistically significantly higher, in the experimental group. The performance IQ also favored the experimental group, but the cluster-adjusted difference (2.9 points) was smaller and statistically nonsignificant. The cluster-adjusted difference in full-scale IQ (5.9 points) was of intermediate magnitude.

As would be expected from the audit correlations (**Table 2**), the auditors also rated children in the experimental group higher than those in the control group on all of the WASI tests and subtests. All of the differences favored the experimental group. The crude individual-based means for the experimental group vs the control group were 51.7 vs 50.6, respectively, for vocabulary, 54.2 vs 51.2, respectively, for similarities, 55.9 vs 53.7, respectively, for block designs, and 50.2 vs 48.9, respectively, for matrices, with means of 105.2 vs 102.1, respectively, for verbal IQ, 105.2 vs 102.6, respectively, for performance IQ, and 105.7 vs 102.6, respectively, for full-scale IQ. After accounting for the clustered randomization, the differences in means were of smaller magnitude than those seen in the test results from the pediatricians (mean differences [95% CIs], +2.8 [-3.2 to +8.8] for verbal IQ, +2.9 [-3.1 to +8.9] for performance IQ, and +3.1 [-2.9 to +9.2] for full-scale IQ).

As mentioned earlier, wide differences were observed in the mean WASI scores among the 31 polyclinics. We therefore carried out a sensitivity analysis by comparing the WASI results after excluding those polyclinics (n=12) with mean full-scale IQ scores greater than 110 or less than 90. The results continued to favor the experimental group, but with narrower CIs and verbal and performance IQ differences of similar magnitude (mean differences [95% CIs], +4.7 [0 to +9.4] for verbal IQ, +4.0 [+0.6 to +7.4] for performance IQ, and +4.9 [+1.1 to +8.6] for full-scale IQ).

Although no sex-specific differences in effects of breastfeeding were hypothesized a priori, we observed slightly

Table 3. Wechsler Abbreviated Scales of Intelligence Results

Outcome	Score, Mean (SD)		ICC	Cluster-Adjusted Mean Difference (95% CI)
	Experimental Group	Control Group		
Vocabulary (n=13 838)	53.5 (11.6)	46.9 (11.4)	0.28	+4.9 (+0.4 to +9.3)
Similarities (n=13 836)	56.6 (9.9)	50.7 (11.7)	0.29	+4.6 (+0.2 to +9.0)
Block designs (n=13 840)	57.2 (9.4)	54.6 (10.3)	0.21	+1.9 (-1.7 to +5.5)
Matrices (n=13 841)	52.8 (10.1)	50.9 (9.9)	0.20	+1.8 (-1.9 to +5.5)
Verbal IQ (n=13 828)	108.7 (16.4)	98.7 (16.0)	0.31	+7.5 (+0.8 to +14.3)
Performance IQ (n=13 836)	108.6 (15.1)	104.8 (15.4)	0.24	+2.9 (-3.3 to +9.1)
Full-scale IQ (n=13 824)	109.7 (15.4)	101.9 (15.8)	0.31	+5.9 (-1.0 to +12.8)

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient.

Table 4. Teacher Ratings of Academic Performance

Outcome	Rating, Mean (SD)		ICC	Cluster-Adjusted Mean Difference (95% CI)
	Experimental Group	Control Group		
Reading (n=10 406)	3.26 (0.82)	3.19 (0.80)	0.02	+0.07 (-0.01 to +0.16)
Writing (n=10 569)	3.19 (0.78)	3.13 (0.73)	0.02	+0.08 (-0.03 to +0.17)
Mathematics (n=10 778)	3.23 (0.79)	3.20 (0.77)	0.02	+0.06 (-0.04 to +0.15)
Other subjects (n=10 474)	3.30 (0.66)	3.27 (0.65)	0.02	+0.05 (-0.04 to +0.13)

Abbreviations: CI, confidence interval; ICC, intraclass correlation coefficient.

higher treatment effects in boys for verbal IQ (8.0 points for boys vs 7.0 points for girls) but not for performance IQ (2.9 points for boys vs 3.0 points for girls); the differences for full-scale IQ were 6.1 points for boys vs 5.7 points for girls. Formal tests of interaction in mixed models including both boys and girls revealed no statistically significant sex differences in intervention effects.

Table 4 shows the results of the teacher ratings, including the number of ratings for each subject, the crude individual-based means (standard deviations) in the experimental and control groups, the intraclass correlation coefficients, and the cluster-adjusted differences in means (95% CIs). Ratings were completed for about 75% of the children; most of those without a rating had not yet begun school by the time of follow-up. Mean ratings were slightly above 3, ie, slightly above grade level, for all 4 of the academic subjects in both groups. For each academic subject, however, the mean score was slightly higher in the experimental group, with larger differences for reading and writing. Clustering was low and similar for all 4 of the subject areas. The full, covariate-adjusted models had no effect on the point estimates but improved the precision of the estimated treatment effects; the differences favoring the experimental group were +0.07 (95% CI, +0.004 to +0.14) for reading and +0.08 (95% CI, +0.01 to +0.15) for writing. The teacher ratings were moderately and highly significantly associated with the WASI scores (all $P < .001$), with Pearson correlation coefficients ranging from 0.20 to 0.32.

Finally, we explored whether the higher WASI scores and teacher academic ratings observed in the experimental group were paralleled by similar differences according to breastfeeding duration and exclusivity, irrespec-

tive of randomized treatment allocation and ignoring within-polyclinic clustering. Higher WASI scores were observed with both increased duration of any breastfeeding and with increased duration of exclusive breastfeeding. Exclusive breastfeeding for 3 to less than 6 months was associated with a higher verbal IQ by 4.7 (95% CI, 4.0 to 5.3) points compared with exclusive breastfeeding for less than 3 months. Exclusive breastfeeding for 6 months or more was associated with an increase of 5.2 (95% CI, 3.7 to 6.7) points. The effects on performance IQ were 1.2 (95% CI, 0.6 to 1.8) points for 3 to less than 6 months of exclusive breastfeeding and 2.1 (95% CI, 0.8 to 3.5) points for 6 or more months of exclusive breastfeeding, and the effects on full-scale IQ were 3.3 (95% CI, 2.7 to 4.0) and 4.2 (95% CI, 2.8 to 5.6) points, respectively. For the teachers' academic ratings, statistically significant increases were observed for exclusive breastfeeding for 3 to less than 6 months for all 4 of the subject areas, ranging from 0.03 for other subjects to 0.06 for writing, but the increases were nonsignificant for exclusive breastfeeding for 6 months or more.

COMMENT

Our results, based on the largest randomized trial ever conducted in the area of human lactation, strongly suggest that prolonged and exclusive breastfeeding improves cognitive development as measured by IQ and teachers' academic ratings at age 6.5 years. High interpediatrician variability in the WASI IQ results, however, led to wide CIs around the observed IQ differences (and thus to considerable uncertainty about the true mag-

nitude of the observed effects) and to statistical nonsignificance of differences in the nonverbal subtests and performance IQ. Although this variability may be partly due to differences in the socioeconomic attributes or genetic endowment of parents living in different regions or communities or to differences in fluency in Russian (some children spoke Belarussian, or even Polish, at home), systematic pediatrician-specific variation in test administration or scoring probably also contributed. The results of our audit and sensitivity analyses, however, suggest that the overall direction of the observed differences is robust.

We found larger effects on verbal measures than on performance measures, both on the WASI and the teachers' ratings. However, the imprecision (wide CIs) in our effect estimates suggests the need for caution in inferring a selective effect on verbal cognitive development, especially in light of the absence of such a trend in our audit and sensitivity analyses and the mixed results reported from observational studies.⁴⁻⁷

Although our findings confirm those of most previous observational studies,^{1,2,4-9} the negative results recently reported by Der et al³ merit more detailed discussion. They found that the positive association between breastfeeding and child IQ was no longer significant after controlling for the mother's cognitive ability. Several other observational studies that controlled for maternal IQ, however, have reported a persistent, albeit attenuated, benefit of breastfeeding on child IQ.^{1,5} In a randomized trial like PROBIT, maternal (and paternal) IQ should be distributed randomly between the treatment groups, as demonstrated for measured baseline characteristics (Table 1), and thus should not confound the treatment effect. Der and colleagues also reported a between-sibling comparison, but such a comparison assumes that the mother's choice of how she feeds successive siblings is random. The decision to bottle-feed an infant after breastfeeding a previously born child is likely to reflect an unsatisfactory breastfeeding experience with the earlier child. If the order is reversed (ie, the mother attempts to breastfeed after bottle-feeding her previous infant), the mother lacks the experience of having already successfully breastfed, and the previous bottle-feeding experience may be a marker for a lesser commitment or ability to breastfeed.

The major limitation of our study is the fact that the pediatricians who administered the WASI were aware of (ie, were not blinded to) the experimental vs control intervention status of the children they examined. As previously reported,¹² pediatricians from the polyclinics that were randomized to the experimental intervention contributed themselves to the intervention by supporting and encouraging exclusive and prolonged breastfeeding following the infant's discharge from the maternity hospital. Even if other pediatricians from the polyclinic had carried out the follow-up assessments, they would have known about the intervention (and probably changed their own practices accordingly) and thus would also have been aware of the experimental vs control status of their own polyclinic. Unfortunately, it was infeasible for both geographic and economic reasons to have pediatricians working at one polyclinic examine children enrolled in other

polyclinics. This was much less of a problem for the teachers' ratings because clustering was far less for the teacher ratings (4038 teachers vs 31 polyclinics). Nonetheless, all of the study pediatricians were trained, monitored, and audited in their administration of the WASI, which itself provides clear and unambiguous instructions for testing and scoring. Moreover, the fact that no beneficial treatment effects were observed for other outcomes (eg, blood pressure and skinfold thicknesses,¹⁷ allergies and asthma,¹⁸ dental caries,¹⁹ or child behavior²⁰) equally subject to random and/or systematic measurement error provides some reassurance that the WASI assessments were unbiased.

Even more reassuring, however, are the differences in the WASI results obtained by the auditing child psychologists and psychiatrists, who were blinded both to treatment allocation and to the WASI results at the initial clinic visit, and in the teachers' blinded assessments of the children's academic performance. Although the sample size for the blinded audit of the WASI was clearly insufficient in and of itself to detect modest treatment effects, the smaller differences observed in the audit IQ results and in the teachers' blinded assessments should be free of systematic bias due to nonblinding and may provide a closer estimate of the true treatment effect. Our observational analyses revealed benefits in IQ with more prolonged and exclusive breastfeeding, although the magnitude of the benefits was somewhat smaller than the differences between the randomized treatment groups, again suggesting some overestimation of the treatment effect. It is also important to emphasize, however, that the true effect of the experimental intervention will systematically underestimate the causal effect of prolonged and exclusive breastfeeding because the substantial overlap of breastfeeding behaviors in the experimental and control groups dilutes the real (but immeasurable) effects of those behaviors.

Even though the treatment difference appears causal, it remains unclear whether the observed cognitive benefits of breastfeeding are due to some constituent of breast milk or are related to the physical and social interactions inherent in breastfeeding. Concentrations of essential long-chain polyunsaturated fatty acids are higher in human milk than in infant formula. Randomized trials of supplementation of infant formula with long-chain polyunsaturated fatty acids, however, have yielded inconsistent results in both term²¹ and preterm²² infants. Another potentially important component of breast milk that could be responsible for the observed cognitive differences is insulinlike growth factor I, which is contained in higher concentration in breast milk than in formula²³ and has been shown to be absorbed intact across the newborn infant's gastrointestinal tract.²⁴

On the other hand, studies showing long-term epigenetic behavioral effects of licking and grooming by mother rats of their pups²⁵ suggest that the physical and/or emotional act of breastfeeding might also lead to permanent physiologic changes that accelerate neurocognitive development. Finally, it is possible that the increased frequency and duration of maternal-infant contact implicit in breastfeeding vs bottle-feeding could increase verbal interaction between mother and infant, which might also have a stimulatory effect on cognitive development.

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Irrespective of the mechanism, our experimental results confirm the cognitive benefits of prolonged and exclusive breastfeeding reported in observational studies. Although breastfeeding initiation rates have increased substantially during the last 30 years, much less progress has been achieved in increasing the exclusivity and duration of breastfeeding.²⁶⁻²⁹ Because protection against infections in developed country settings does not have the life-and-death implications for infant and child health that it does in less-developed settings, cognitive benefits may be among the most important advantages for breastfed infants in industrialized societies. The consistency of our findings based on a randomized trial with those reported in previous observational studies should prove helpful in encouraging further public health efforts to promote, protect, and support breastfeeding.

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REFERENCES

1. Anderson JW, Johnstone BM, Remley DT. Breast-feeding and cognitive development: a meta-analysis. *Am J Clin Nutr.* 1999;70(4):525-535.
2. Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. *Lancet.* 1992;339(8788):261-264.
3. Der G, Batty GD, Deary IJ. Effect of breast feeding on intelligence in children: prospective study, sibling pairs analysis, and meta-analysis [published online ahead of print October 4, 2006]. *BMJ.* 2006;333(7575):945. doi:10.1136/bmj.38978.699583.55.
4. Jacobson SW, Chiodo LM, Jacobson JL. Breastfeeding effects on intelligence quotient in 4- and 11-year-old children. *Pediatrics.* 1999;103(5):e71. doi:10.1542/peds.103.5.e71.
5. Angelsen NK, Vik T, Jacobsen G, Bakkeiteig LS. Breast feeding and cognitive development at age 1 and 5 years. *Arch Dis Child.* 2001;85(3):183-188.
6. Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM. The association be-

- tween duration of breastfeeding and adult intelligence. *JAMA*. 2002;287(18):2365-2371.
7. Oddy WH, Kendall GE, Blair E, de Klerk NH, Stanley FJ, Landau LI, Silburn S, Zubrick S. Breast feeding and cognitive development in childhood: a prospective birth cohort study. *Paediatr Perinat Epidemiol*. 2003;17(1):81-90.
 8. Gómez-Sanchiz M, Cañete R, Rodero I, Baeza JE, Avila O. Influence of breastfeeding on mental and psychomotor development. *Clin Pediatr (Phila)*. 2003;42(1):35-42.
 9. Lawlor DA, Najman JM, Batty D, O'Callaghan MJ, Williams GM, Bor W. Early life predictors of childhood intelligence: findings from the Mater-University study of pregnancy and its outcomes. *Paediatr Perinat Epidemiol*. 2006;20(2):148-162.
 10. Drane DL, Logemann JA. A critical evaluation of the evidence on the association between type of infant feeding and cognitive development. *Paediatr Perinat Epidemiol*. 2000;14(4):349-356.
 11. Jain A, Concato J, Leventhal JM. How good is the evidence linking breastfeeding and intelligence? *Pediatrics*. 2002;109(6):1044-1053.
 12. Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, Collet JP, Vanilovich I, Mezen I, Ducruet T, Shishko G, Zubovich V, Mknuk D, Gluchanina E, Dombrovskiy V, Ustinovitch A, Kot T, Bogdanovich N, Ovchinskova L, Helsing E; PROBIT (Promotion of Breastfeeding Intervention Trial) Study Group. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA*. 2001;285(4):413-420.
 13. World Health Organization; UNICEF. *Protecting, Promoting and Supporting Breastfeeding: The Special Role of Maternity Services*. Geneva, Switzerland: World Health Organization; 1989.
 14. Campbell MK, Elbourne DR, Altman DG; CONSORT Group. CONSORT statement: extension to cluster randomised trials. *BMJ*. 2004;328(7441):702-708.
 15. Wechsler D. *Wechsler Abbreviated Scales of Intelligence*. San Antonio, TX: Psychological Corp; 1999.
 16. Achenbach TM, Rescorla LA. *Manual for the ASEBA School-Age Forms and Profiles*. Burlington: University of Vermont, Research Center for Children, Youth, and Families; 2001.
 17. Kramer MS, Matush L, Vanilovich I, Platt RW, Bogdanovich N, Sevkovskaya Z, Dzikovich I, Shishko G, Collet JP, Martin RM, Davey Smith G, Gillman MW, Chalmers B, Hodnett E, Shapiro S; PROBIT Study Group. Effects of prolonged and exclusive breastfeeding on child height, weight, adiposity, and blood pressure at age 6.5 y: evidence from a large randomized trial. *Am J Clin Nutr*. 2007;86(6):1717-1721.
 18. Kramer MS, Matush L, Vanilovich I, Platt R, Bogdanovich N, Sevkovskaya Z, Dzikovich I, Shishko G, Mazer B; Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group. Effect of prolonged and exclusive breast feeding on risk of allergy and asthma: cluster randomised trial [published online ahead of print September 11, 2007]. *BMJ*. 2007;335(7624):815.
 19. Kramer MS, Vanilovich I, Matush L, Bogdanovich N, Zhang X, Shishko G, Muller-Bolla M, Platt RW. The effect of prolonged and exclusive breast-feeding on dental caries in early school-age children: new evidence from a large randomized trial [published online ahead of print September 18, 2007]. *Caries Res*. 2007;41(6):484-488.
 20. Kramer MS, Fombonne E, Igunnov S, Vanilovich I, Matush L, Mironova E, Bogdanovich N, Tremblay RE, Chalmers B, Zhang X, Platt RW; Promotion of Breastfeeding Intervention Trial (PROBIT) Study Group. Effects of prolonged and exclusive breastfeeding on child behavior and maternal adjustment: evidence from a large, randomized trial. *Pediatrics*. 2008;121(3):e435-e440.
 21. Simmer K. Longchain polyunsaturated fatty acid supplementation in infants born at term [update of: *Cochrane Database Syst Rev*. 2000;(2):CD000376]. *Cochrane Database Syst Rev*. 2001;(4):CD000376. doi:10.1002/14651858.CD000376.
 22. Simmer K, Patole S. Longchain polyunsaturated fatty acid supplementation in preterm infants [update of: *Cochrane Database Syst Rev*. 2000;(2):CD000375]. *Cochrane Database Syst Rev*. 2004;(1):CD000375. doi:10.1002/14651858.CD000375.pub2.
 23. Nagashima K, Itoh K, Kurume T. Levels of insulin-like growth factor I in full- and preterm human milk in comparison to levels in cow's milk and in milk formulas. *Biol Neonate*. 1990;58(6):343-346.
 24. Philipps AF, Rao R, Anderson GG, McCracken DM, Lake M, Koldovsky O. Fate of insulin-like growth factors I and II administered orogastrically to suckling rats. *Pediatr Res*. 1995;37(5):586-592.
 25. Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, Dymov S, Szyf M, Meaney MJ. Epigenetic programming by maternal behavior. *Nat Neurosci*. 2004;7(8):847-854.
 26. Giovannini M, Banderali G, Radaelli G, Carmine V, Riva E, Agostini C. Monitoring breastfeeding rates in Italy: national surveys 1995 and 1999. *Acta Paediatr*. 2003;92(3):357-363.
 27. Callen J, Pinelli J. Incidence and duration of breastfeeding for term infants in Canada, United States, Europe, and Australia: a literature review. *Birth*. 2004;31(4):285-292.
 28. Li R, Darling N, Maurice E, Barker L, Grummer-Strawn LM. Breastfeeding rates in the United States by characteristics of the child, mother, or family: the 2002 National Immunization Survey. *Pediatrics*. 2005;115(1):e31-e37.
 29. Ryan AS, Zhou W. Lower breastfeeding rates persist among the special supplemental nutrition program for women, infants, and children participants, 1978-2003. *Pediatrics*. 2006;117(4):1136-1146.