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# Effects of Promoting Long-term, Exclusive Breastfeeding on Adolescent Adiposity, Blood Pressure, and Growth Trajectories

## A Secondary Analysis of a Randomized Clinical Trial

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**IMPORTANCE** Evidence that breastfeeding reduces child obesity risk and lowers blood pressure (BP) is based on potentially confounded observational studies.

**OBJECTIVE** To investigate the effects of a breastfeeding promotion intervention on adiposity and BP at age 16 years and on longitudinal growth trajectories from birth.

**DESIGN, SETTING, AND PARTICIPANTS** Cluster-randomized Promotion of Breastfeeding Intervention Trial. Belarusian maternity hospitals and affiliated polyclinics (the clusters) were allocated into intervention (n = 16) or control arms (n = 15) in 1996 and 1997. The trial participants were 17 046 breastfeeding mother-infant pairs; of these, 13 557 children (79.5%) were followed up at 16 years of age between September 2012 and July 2015.

**INTERVENTIONS** Breastfeeding promotion, modeled on the Baby-Friendly Hospital Initiative.

**MAIN OUTCOMES AND MEASURES** Body mass index (BMI, calculated as weight in kilograms divided by height in meters squared); fat and fat-free mass indices and percentage of body fat from bioimpedance; waist circumference; overweight and obesity; height; BP; and longitudinal growth trajectories. The primary analysis was modified intention-to-treat (without imputation for losses to follow-up) accounting for within-clinic clustering.

**RESULTS** We examined 13 557 children at a median age of 16.2 years (48.5% were girls). The intervention substantially increased breastfeeding duration and exclusivity compared with the control arm (exclusively breastfed: 45% vs 6% at 3 months, respectively). Mean differences at 16 years between intervention and control groups were 0.21 (95% CI, 0.06-0.36) for BMI; 0.21 kg/m$^2$ (95% CI, −0.03 to 0.44) for fat mass index; 0.00 kg/m$^2$ (95% CI, −0.21 to 0.22) for fat-free mass index; 0.71% (95% CI, −0.32 to 1.74) for percentage body fat; −0.73 cm (−2.48 to 1.02) for waist circumference; 0.05 cm (95% CI, −0.85 to 0.94) for height; −0.54 mm Hg (95% CI, −2.40 to 1.31) for systolic BP; and 0.71 mm Hg (95% CI, −0.68 to 2.10) for diastolic BP. The odds ratio for overweight/obesity (BMI ≥85th percentile vs <85th percentile) was 1.14 (95% CI, 1.02-1.28) and the odds ratio for obesity (BMI ≥95th percentile vs <95th percentile) was 1.09 (95% CI, 0.92-1.29). The intervention resulted in a more rapid rate of gain in postinfancy height (1 to 2.8 years), weight (2.8 to 14.5 years), and BMI (2.8 to 8.5 years) compared with the control arm. The intervention had little effect on BMI *z* score changes after 8.5 years.

**CONCLUSIONS AND RELEVANCE** A randomized intervention that increased the duration and exclusivity of breastfeeding was not associated with lowered adolescent obesity risk or BP. On the contrary, the prevalence of overweight/obesity was higher in the intervention arm. All mothers initiated breastfeeding, so findings may not apply to comparisons of the effects of breastfeeding vs formula feeding.

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Supplemental content

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The prevalence of childhood obesity has risen substantially in the last 3 decades around the world.[1] In turn, obese children are more likely to become obese adults[2] and experience obesity-related chronic illnesses.[3] However, few interventions to prevent childhood obesity have proven effective.[1,4] Promoting greater uptake and duration of exclusive breastfeeding is a suggested public health measure to reduce childhood obesity[5] and its metabolic consequences (eg, high blood pressure [BP]).[6] This approach is based on mechanistic studies, eg, those finding that the lower protein content of breastmilk (in comparison with formula milk) may reduce adipocyte development[7] and a body of observational human data suggesting inverse associations of breastfeeding and its duration with later obesity.[6,8-12] However, observational studies are prone to confounding by social patterning of both breastfeeding and growth,[13] the epidemiologic evidence is inconsistent[6,13-23] and publication bias is a concern.[24,25] Furthermore, weight and BP change dynamically during development, but most previous studies measure these outcomes on a single occasion rather than on multiple occasions at different ages among the same individuals.

The Promotion of Breastfeeding Intervention Trial (PROBIT) was designed to overcome limitations inherent in observational studies of the long-term effects of breastfeeding on child outcomes including adiposity and blood pressure. We cluster-randomized 17 046 children from 31 clinics, born between 1996 and 1997, to either a control arm or breastfeeding promotion intervention (based on the World Health Organization and United Nations Children's Fund Baby-Friendly Hospital Initiative).[26] Trial inclusion criteria required (1) healthy, term (≥37 weeks' gestation), and normal-weight (≥2500 g) singleton infants with an Apgar score of at least 5 at 5 minutes and (2) mothers who initiated breastfeeding with no condition expected to interfere with their ability to breastfeed.[26] The breastfeeding promotion intervention substantially increased breastfeeding duration and exclusivity when compared with the control arm (exclusively breastfed: 45% vs 6% at 3 months and 6.6% vs 0.7% at 6 months).[26] Therefore, our trial provides a unique opportunity to test in an intention-to-treat analysis the extent to which breastfeeding causally influences adiposity, stature, and BP, making an important contribution to the debate about whether breastfeeding is protective against obesity.[5,27]

We previously reported no evidence of a protective effect of the breastfeeding intervention on adiposity or BP at 6.5 and 11.5 years.[28-30] We now analyze these outcomes at 16 years, when the children were beyond adiposity rebound, most had attained (or nearly attained) adult stature, and adiposity and BP measures should better predict adult levels than at earlier ages. In addition to outcomes at single times reported in previous publications, we take advantage of repeated weight and length/height measures taken from birth to adolescence to examine the effects of the intervention on longitudinal growth trajectories that, to our knowledge, have not been examined in previous studies of breastfeeding.

### Key Points

**Question** What is the effect of a randomized intervention that increased breastfeeding duration and exclusivity on growth, adiposity, and blood pressure at age 16 years?

**Findings** This secondary analysis of a randomized clinical trial showed that mean body mass index was higher in the intervention vs control groups, with no differences in mean systolic or diastolic blood pressures.

**Meaning** A randomized intervention that increased breastfeeding intensity was not associated with reduced obesity or lower blood pressure levels at age 16 years.

## Methods

### Randomization

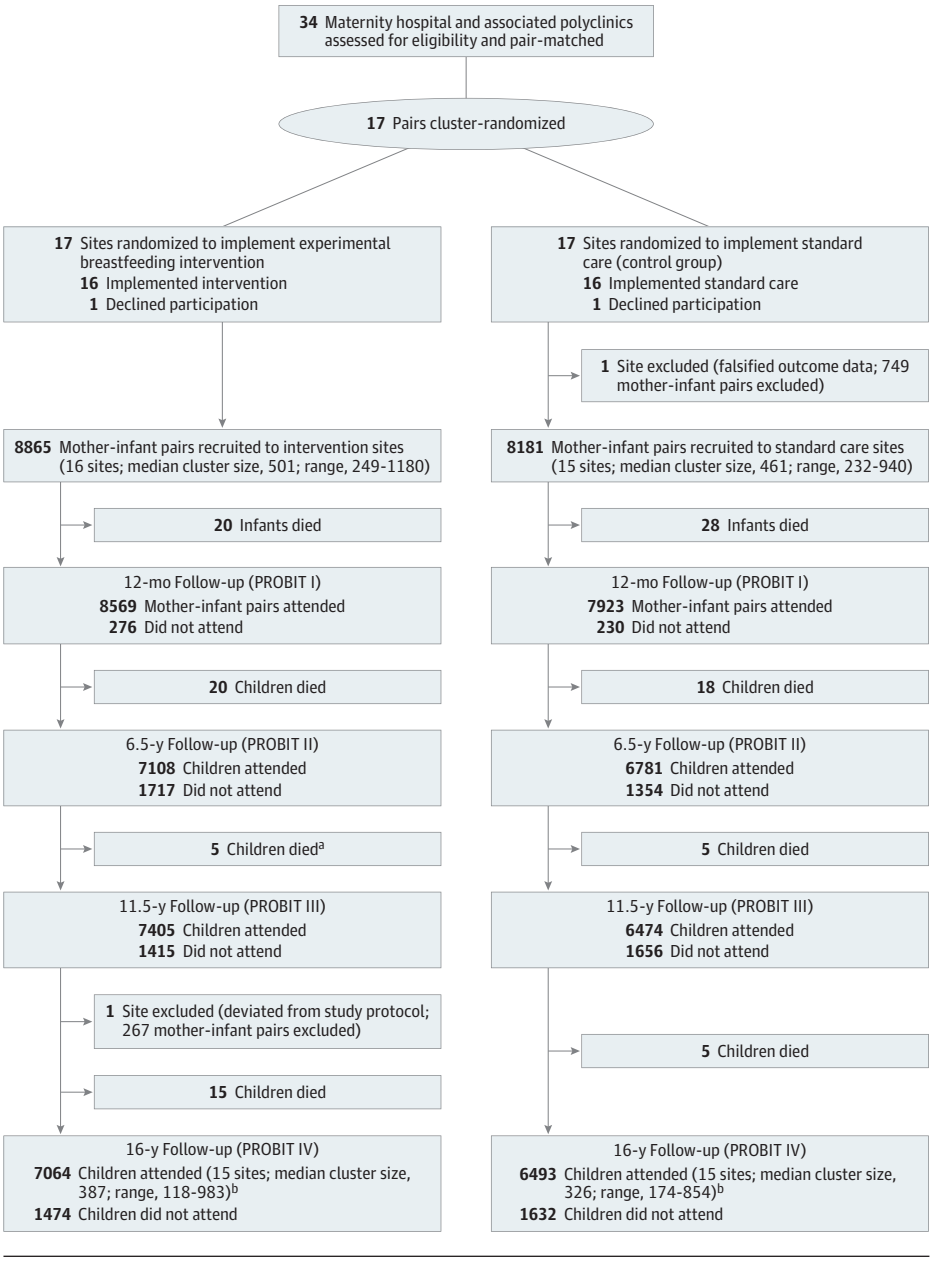
A detailed description of the trial design has previously been published.[26] Briefly, the units of randomization (clusters) were 31 maternity hospitals and their associated outpatient polyclinics (which treat both well and ill children) in Belarus (**Figure 1**). These units were randomized to either (1) a control arm that continued the breastfeeding practices and policies already in effect at the time of randomization (which were typically characterized by a short duration of exclusive breastfeeding, early introduction of other drinks or foods, and weaning at about 3 months)[31] or (2) an experimental intervention arm based on the Baby-Friendly Hospital Initiative.[26] The formal trial protocols can be found in Supplement 1.

### Follow-up

We have previously reported on anthropometry and BP outcomes between birth and 12 months (anthropometry only[32]), at 6.5 years,[28] and at 11.5 years.[29,30] The outcomes reported in this follow-up are at mean age 16 years, measured between September 2012 and July 2015. At the 16-year follow-up, all anthropometric outcomes were measured in duplicate at dedicated research clinics using uniform research-specific equipment. These outcomes were weight, percentage body fat, fat mass, and fat-free (lean) mass, measured by foot-to-foot bioelectrical impedance (Tanita TBF 300GS body fat analyzer); waist circumference measured using a nonstretchable measuring tape; standing height using a wall-mounted stadiometer (Medtechnika); and systolic and diastolic BP measured in duplicate using a digital oscillometric device (705IT; Omron Healthcare). The outcome measurements and their timing for the earlier research visits are summarized in eTable 1 in Supplement 2.

Training and quality assurance procedures have been described in detail.[26,28,29,33] Our quality assurance processes raised concerns about the validity of the 16-year follow-up data from 1 polyclinic (n = 267 originally enrolled), and we therefore excluded the 16-year data from this clinic in this analysis. In the remaining 30 polyclinics (15 intervention and 15 control), the children were followed up by 1 or 2 research pediatricians depending on clinic volume.

Figure 1. Flow Diagram of Progress of Clusters and Individuals Through Promotion of Breastfeeding Intervention Trial (PROBIT) Recruitment and Follow-up Phases I, II, III, and IV




[a] During PROBIT III, 6 deaths were reported in the intervention arm. Data checking during PROBIT IV found 1 of these children had been incorrectly reported as deceased, and data were amended.

[b] Of the 13 557 seen at PROBIT IV, 12 072 were seen at both PROBIT II and III, 274 were not seen at either PROBIT II and III, 449 were seen at PROBIT II but not seen at III, and 762 were seen at PROBIT III but not seen at II. Of the 3489 children randomized but not followed up at 16 years, 267 attended the excluded site, 116 died following randomization, 2674 were lost to follow-up, and 432 were unable or unwilling to come for their clinic visit.

## Derived Variables

Duplicate measures of height and waist circumference were taken. If the measurements differed by more than 0.5 cm, third (and fourth, if necessary) measurements were taken and all readings averaged. We calculated the body mass index (BMI), fat mass index, and fat-free mass index as weight, fat mass, and fat-free mass in kilograms divided by height in meters squared. We calculated waist-to-height ratio by dividing waist circumference in centimeters by standing height in centimeters. We defined overweight as BMI between the 85th to 95th percentiles and obesity as BMI at or greater than the 95th percentile based on the Centers for Disease Control and Prevention 2000 age- and sex-specific reference data.[34] We used 3 dichotomous outcomes: BMI at or greater than the 95th percentile vs less than the 95th percentile, BMI at or greater than the 85th percentile vs less than the 85th percentile, and BMI at or greater than 25 vs less than 25. For the longitudinal trajectory analysis, BMI *z* scores were calculated using the World Health Organization standard/reference.[35-37]

The analyses of growth trajectories included 17 042 children (99%) with at least 1 measurement of weight, length (at up to age 2 years), or height (after age 2 years). We parameterized the relationships of weight, stature, or BMI *z* score with age using linear splines with 5 knot points at 3 months, 12 months, 2.8 years, 8.5 years, and 14.5 years to describe periods of approximately linear growth based on the data.[38] Although a linear

spline model is an approximation of the true nonlinear growth function, its coefficients are easily interpretable and have produced a good model fit in this and other cohorts.[39-44] The knot points at 8.5 and 14.5 years were chosen because those were the oldest ages at the 6.5- and 11.5-year follow-ups. Setting the knot points at the median age of the 6.5- and 11.5-year follow-ups (or 25% or 75%) resulted in similar findings.

The parent or guardian (usually the mother) who accompanied the child at the 6.5-year follow-up reported weight and height for herself and her partner; at the 11.5-year follow-up we measured the mother's weight and height if she attended. The most recent measurements of parental height and calculated BMI were used for analysis.

### Reproducibility

Audit visits were conducted to assess interobserver reproducibility of the outcome measurements, an important feature given that blinding of pediatricians to the intervention vs control group assignment was not feasible. In the 24 lower-volume polyclinics with a single pediatrician, 4 children were randomly selected to return for remeasurement of all variables. For the 6 higher-volume clinics with 2 study pediatricians, 3 children per pediatrician were selected. Thus, a total of 132 children were audited. So that all children seen in follow-up were eligible for the repeated measurements, the selection was carried out after completion of primary data collection, a mean of 1.2 years (range, 0.02-2.5) after the initial visit. The audit was carried out by 1 of 3 Minsk-based pediatricians not involved in primary data collection and blinded to the measures obtained at the initial visit but not to trial arm. Because of the time elapsed between the audit and initial visits, reproducibility was assessed using Pearson correlation coefficients.

### Governance and Ethics

The 16-year follow-up was approved by the Belarussian Ministry of Health and received ethical approval from the McGill University Health Centre research ethics board, the institutional review board at Harvard Pilgrim Health Care, and the Avon Longitudinal Study of Parents and Children law and ethics committee. A parent or legal guardian provided written informed consent in Russian at enrollment and at all follow-up visits, and all children provided written assent at the 11.5- and 16-year clinic visits.

### Statistical Analysis

Comparisons between the intervention and control groups were based on a modified intention-to-treat analysis without imputation for missing outcome data (ie, based on the 13 557 children with observed outcomes). We accounted for possible nonindependence of measurements within individual clinics (clustering) using mixed-effects models. In a sensitivity analysis, we used SAS multiple imputation for 17 046 individuals to impute 20 values for each missing observation (including outcomes at 16 years) and combined multivariable modeling estimates using Proc MI ANALYZE in SAS (SAS Institute Inc, eMethods in Supplement 2).[45,46] For the trajectory analyses we used a 3-level multilevel model: (1) measurement occasion, (2) individual child, and (3) clinic site where the child was examined; these analyses were conducted in STATA, version 13.1 (StataCorp)[47] and MLwiN, version 2.36 (Centre for Multilevel Modelling).[48]

Results are presented for (1) the simple cluster-adjusted model; (2) the model after additional adjustment for age at follow-up and baseline characteristics: stratum-level variables (urban vs rural and East vs West Belarus residence), maternal and paternal education, child sex, and birth weight (for adiposity, standing height, and BP outcomes); and (3) the model after further adjustment for measured parental BMI (for adiposity and weight gain), parental height (for child height outcomes), or parental BMI and height (for BP and BMI gain). Models 2 and 3 were implemented in case of baseline imbalances, given the relatively small number of randomized clusters.

The intention-to-treat analysis likely underestimates the magnitude of effect of breastfeeding exclusivity and duration, owing to overlap in breastfeeding between the randomized groups: many intervention mothers did not exclusively breastfeed for 3 or 6 months, and some control mothers did. In a secondary analysis, we applied instrumental variable methods[49] to account for nonadherence. The instrumental variable analysis robustly estimates the causal effect of having been exclusively breastfed for at least 3 months (vs <3 months), using randomization status as an instrument (ie, a variable causally related to exclusive breastfeeding but not to the adiposity outcomes except through breastfeeding), assuming that randomization status is independent of any confounders of the exposure-outcome relationships. As such, the effect estimates from instrumental variable analyses are not affected by measured or unknown variables that may confound the exposure-outcome association. We performed instrumental variable estimation of continuous outcomes using the generalized 2-stage least squares estimator and of dichotomous outcomes using a probit model for instrumental variable analysis,[50] both of which account for within-clinic clustering.

For comparison with previous observational studies, we conducted observational analyses (ie, disregarding randomization status) to estimate associations of the duration of any or exclusive breastfeeding on the same outcomes as the intention-to-treat analysis, also accounting for clustering and the same baseline characteristics as described previously, using multiple linear regression for continuous outcomes and multiple logistic regression for dichotomous outcomes. In a sensitivity analysis, we stratified the results by whether the children correctly identified their originally allocated trial arm to determine whether this knowledge biased the outcomes. A $P$ value less than .05 was considered significant, and all $P$ values were 2-sided.

To provide context, we also present the observational associations of study outcomes with other nonbreastfeeding baseline characteristics previously suggested to be early-life determinants of overweight and obesity.

## Results

A total of 13 557 children were examined at a median (SD) age of 16.2 years (0.5; IQR, 15.8-16.4), representing 79.5% of the 17 046 originally randomized and 80.8% of the 16 779 from

Table 1. Baseline Characteristics (in 13 557 Children)

| Characteristic | Total, No. (%) (N = 13 557) | Intervention, No. (%) (n = 7064) | Control, No. (%) (n = 6493) |
|---|---|---|---|
| Measured at child's birth | | | |
| Maternal age, y | | | |
| <20 | 1820 (13.4) | 979 (13.9) | 841 (13.0) |
| 20-34 | 11 173 (82.4) | 5792 (82.0) | 5381 (82.9) |
| ≥35 | 564 (4.2) | 293 (4.1) | 271 (4.2) |
| Maternal education | | | |
| Completed university | 1842 (13.6) | 1002 (14.2) | 840 (12.9) |
| Advanced secondary or partial university | 6925 (51.1) | 3365 (47.6) | 3560 (54.8) |
| Common secondary | 4318 (31.9) | 2406 (34.1) | 1912 (29.4) |
| Did not complete secondary | 472 (3.5) | 291 (4.1) | 181 (2.8) |
| Paternal education | | | |
| Completed university | 1737 (12.8) | 936 (13.3) | 801 (12.3) |
| Advanced secondary or partial university | 6205 (45.8) | 2910 (41.2) | 3295 (50.7) |
| Common secondary | 4883 (36.0) | 2828 (40.0) | 2055 (31.6) |
| Did not complete secondary or unknown | 732 (5.4) | 390 (5.5) | 342 (5.3) |
| Stratum-level variable | | | |
| East/urban | 4150 (30.6) | 2215 (31.4) | 1935 (29.8) |
| East/rural | 2152 (15.9) | 1075 (15.2) | 1077 (16.6) |
| West/urban | 3524 (26.0) | 2296 (32.5) | 1228 (18.9) |
| West/rural | 3731 (27.5) | 1478 (20.9) | 2253 (34.7) |
| No. of older children in household | | | |
| 0 | 7707 (56.8) | 4152 (58.8) | 3555 (54.8) |
| 1 | 4717 (34.8) | 2365 (33.5) | 2352 (36.2) |
| >2 | 1133 (8.4) | 547 (7.7) | 586 (9.0) |
| Maternal smoking during pregnancy | | | |
| No | 13 287 (98.0) | 6898 (97.7) | 6389 (98.4) |
| Yes | 270 (2.0) | 166 (2.3) | 104 (1.6) |
| Child sex | | | |
| Female | 6576 (48.5) | 3474 (49.2) | 3102 (47.8) |
| Male | 6981 (51.5) | 3590 (50.8) | 3391 (52.2) |
| Birth weight, mean (SD), kg | 3.44 (0.42) | 3.44 (0.42) | 3.44 (0.42) |

included sites (Figure 1). Follow-up rates were similar in the intervention arm (82%; n = 7064 of 8597) and control arm (79%; n = 6493 of 8181) overall, although they varied from 41% (n = 191 of 461) to 98% (n = 983 of 1002) at the different clinics. The children followed up at 16 years in the intervention and control groups were similar in baseline characteristics, with small differences paralleling those previously reported at randomization (**Table 1**).[26] The audit showed high correlations (Pearson $r \geq 0.83$) between initial clinic results and blinded repeated measures of weight, fat mass, fat-free mass, percentage fat, waist circumference, and standing height. The correlations were lower for systolic ($r = 0.55$) and diastolic ($r = 0.37$) BP (eTable 2 in Supplement 2). All 16-year outcome measures showed a low degree of within-polyclinic clustering (intraclass correlation coefficient range, 0.003-0.09).[33]

The results of the primary analysis are shown in **Table 2**. There was little consistent evidence that the intervention effects differed in boys compared with girls (*P* values for sex interactions in Table 2). The raw mean values of BMI, fat mass index, percentage body fat, standing height and BP, and the prevalence of overweight and obesity were slightly higher in the intervention vs control arms. The cluster-adjusted odds ratio for overweight/obesity was 1.14 (95% CI, 1.02-1.28), and the odds ratio for obesity was 1.09 (95% CI, 0.92-1.29). Further controlling for baseline (Table 2) and parental characteristics (eTable 3 in Supplement 2) or multiplying imputing outcomes (eTable 4 and eMethods in Supplement 2) did not alter these conclusions.

Compared with the control arm, infants in the intervention arm had more rapid weight and length gain in the first 3 months followed by lower weight and length gain between 3 and 12 months (**Table 3** and **Figure 2**), as reported previously.[32] In this updated analysis, we found that the intervention resulted in more rapid growth in length than the control arm between 1 and 2.8 years and in more rapid weight gain between 2.8 and 14.5 years. The rate of BMI change between 2.8 and 8.5 years was slightly higher in the intervention arm, reflecting the greater weight gain during this period. Sex-specific results are presented in eTable 5 in Supplement 2.

Using multilevel models to estimate mean differences in weight, height, and BMI *z* scores between intervention and control groups at the mean clinic age revealed differences broadly in line with the cluster-adjusted estimates (Figure 2). Although children were heavier in the intervention arm compared with the control arm, they were also taller, and their BMI *z* scores showed little overall difference from midchildhood.

The instrumental variable results are in line with those of the primary analysis (eTable 6 in Supplement 2). Overall, 32.1% of the intervention group and 25.4% of the control group correctly identified the randomization arm to which they belonged, but such knowledge made little difference to the effect estimates (data not shown). In observational analyses, increased duration of exclusive breastfeeding (eTable 7 in Supplement 2) or any breastfeeding (eTable 8 in Supplement 2) was positively associated with several measures of adiposity, in line with the intention-to-treat results. eTable 9 in Supplement 2 presents the association of baseline characteristics with BMI category at 16 years. Estimates were in the expected direction for several sociodemographic and early-life variables.

## Discussion

In this large cluster-randomized clinical trial, an intervention to promote increased duration and exclusivity of breastfeeding was not associated with reduced levels of general or central adiposity or lower BP in children aged 16 years. Beyond infancy, the intervention resulted in more rapid growth in height and then more rapid weight gain in early and midchildhood, respectively, but the intervention had little effect on BMI *z* scores after 8.5 years.

Our findings are similar to results in the same children at age 6.5 years and 11.5 years.[28,29] The minimal imbalances in baseline characteristics at enrollment and among those followed up provide reassurance that the randomization was successful and that confounding and selection bias are unlikely

Table 2. Modified Intention-to-Treat Analysis (Without Imputation) Showing Differences in Adiposity Measures, Height, and Blood Pressure Comparing Intervention vs Control Groups

| Outcome at 16 y (n = 13 557) | Intervention | | Control | | Difference, Mean (95% CI) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | No. | Mean (SD) | No. | Mean (SD) | Cluster Adjusted | *P* Value | *P* Value for Sex Int | Further Adjusted for Baseline Factors and Age at Follow-up[a] | *P* Value |
| BMI | 7057 | 21.5 (3.4) | 6480 | 21.2 (3.3) | 0.21 (0.06-0.36) | .01 | .92 | 0.19 (0.04-0.34) | .01 |
| FMI | 6997 | 4.2 (2.6) | 6462 | 4.0 (2.5) | 0.21 (−0.03 to 0.44) | .09 | .41 | 0.20 (−0.01 to 0.42) | .06 |
| FFMI | 6997 | 17.2 (2.1) | 6462 | 17.2 (2.1) | 0.00 (−0.21 to 0.22) | .98 | .13 | 0.00 (−0.21 to 0.21) | >.99 |
| Body fat, % | 7043 | 18.9 (9.0) | 6462 | 18.2 (8.8) | 0.71 (−0.32 to 1.74) | .18 | .02 | 0.69 (−0.26 to 1.64) | .16 |
| Waist circumference, cm | 7061 | 73.6 (8.5) | 6482 | 74.7 (8.1) | −0.73 (−2.48 to 1.02) | .41 | <.001 | −0.44 (−2.13 to 1.24) | .60 |
| Waist-to-height ratio (× 100) | 7059 | 43.2 (4.7) | 6479 | 43.9 (4.6) | −0.45 (−1.50 to 0.59) | .92 | .97 | −0.30 (−1.25 to 0.64) | .82 |
| Standing height, cm | 7061 | 170.4 (8.5) | 6489 | 170.3 (8.5) | 0.05 (−0.85 to 0.94) | .40 | <.001 | 0.08 (−0.60 to 0.76) | .53 |
| Blood pressure, mm Hg | | | | | | | | | |
| Systolic | 7061 | 120.5 (11.7) | 6484 | 119.9 (11.1) | −0.54 (−2.40 to 1.31) | .57 | .64 | −0.48 (−2.10 to 1.13) | .56 |
| Diastolic | 7061 | 68.8 (7.6) | 6484 | 67.8 (7.0) | 0.71 (−0.68 to 2.10) | .32 | .14 | 0.52 (−0.73 to 1.76) | .41 |
| BMI, No. (%) | | | | | | | | | |
| ≥25 vs <25 | NA | 892 (12.6) | NA | 696 (10.7) | 1.20 (1.06-1.37) | .004 | .85 | 1.19 (1.04-1.35) | .01 |
| ≥85th vs <85th Percentile[b] | NA | 1026 (14.5) | NA | 842 (13.0) | 1.14 (1.02-1.28) | .03 | .76 | 1.15 (1.01-1.30) | .04 |
| ≥95th vs <95th Percentile[b] | NA | 319 (4.5) | NA | 270 (4.2) | 1.09 (0.92-1.29) | .31 | .53 | 1.12 (0.94-1.33) | .20 |

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); FFMI, fat free mass index (calculated as weight in kilograms divided by height in meters squared); FMI, fat mass index (calculated as weight in kilograms divided by height in meters squared); Int, interaction; NA, not applicable.

[a] Additionally adjusted for stratum-level variables (urban vs rural and East vs West Belarus residence), maternal and paternal education, child sex, birth weight, and age at follow-up.

[b] Based on Centers for Disease Control and Prevention 2000 reference data.[34]

Table 3. Modified Intention-to-Treat Analysis (Without Imputation) Showing Differences in Growth Trajectories Comparing Intervention vs Control Groups

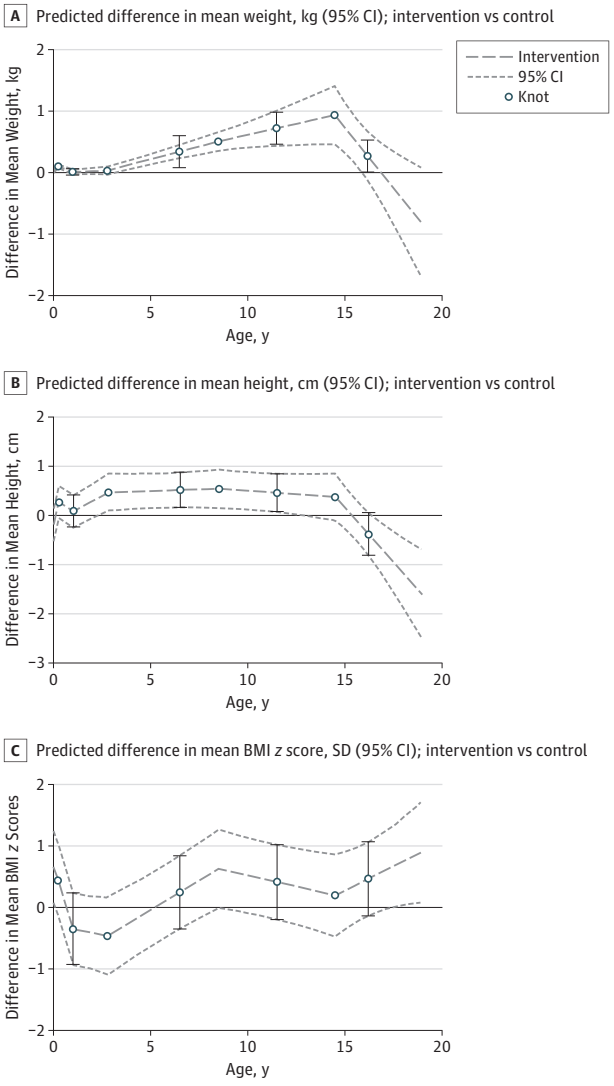
| Growth (n = 17 042) | Mean (95% CI) | | Difference, Mean (95% CI) | | | | |
|---|---|---|---|---|---|---|---|
| | Intervention (n = 8864) | Control (n = 8178) | Cluster Adjusted | *P* Value | *P* Value for Sex Int | Further Adjusted for Baseline Factors[a] | *P* Value |
| Birth weight, kg | 3.4 (3.38-3.41) | 3.38 (3.37-3.4) | 0.01 (−0.01 to 0.04) | .38 | | 0.02 (−0.01 to 0.04) | .17 |
| Weight gain, kg/y | | | | | | | |
| Birth-3 mo | 11.4 (11.35-11.45) | 11.05 (11-11.1) | 0.35 (0-0.42) | <.001 | | 0.32 (0.25-0.39) | <.001 |
| 3-12 mo | 6.17 (6.14-6.19) | 6.29 (6.26-6.31) | −0.12 (−0.16 to −0.08) | <.001 | | −0.09 (−0.12 to −0.05) | <.001 |
| 1-2.8 y | 1.81 (1.79-1.83) | 1.8 (1.78-1.82) | 0.01 (−0.02 to 0.04) | .48 | | 0.01 (−0.03 to 0.04) | .69 |
| 2.8-8.5 y | 2.26 (2.24-2.28) | 2.18 (2.16-2.19) | 0.08 (0.06-0.11) | <.001 | .02[b] | 0.07 (0.04-0.1) | <.001 |
| 8.5-14.5 y | 4.65 (4.6-4.7) | 4.58 (4.53-4.63) | 0.07 (0 to 0.14) | .04 | | 0.09 (0.02-0.16) | .01 |
| 14.5-18.9 y | 4.62 (4.45-4.78) | 5.01 (4.83-5.19) | −0.39 (−0.63 to −0.15) | .002 | | −0.29 (−0.52 to −0.07) | .01 |
| Birth length, cm | 51.69 (51.46-51.91) | 51.86 (51.63-52.09) | −0.17 (−0.49 to 0.16) | .31 | | −0.05 (−0.35 to 0.24) | .73 |
| Stature gain, cm/y | | | | | | | |
| Birth-3 mo | 37.9 (37.7-38.09) | 36.12 (35.91-36.32) | 1.78 (1.5-2.06) | <.001 | | 1.24 (0.97-1.52) | <.001 |
| 3-12 mo | 20.98 (20.9-21.07) | 21.24 (21.15-1.32) | −0.25 (−0.37 to −0.14) | <.001 | | −0.3 (−0.42 to −0.18) | <.001 |
| 1-2.8 y | 9.83 (9.76-9.91) | 9.62 (9.54-9.7) | 0.22 (0.11-0.33) | <.001 | | 0.16 (0.05-0.27) | .005 |
| 2.8-8.5 y | 6.87 (6.84-6.91) | 6.86 (6.82-6.9) | 0.01 (−0.04 to 0.07) | .65 | <.001[b] | 0.04 (−0.01 to 0.1) | .11 |
| 8.5-14.5 y | 5.2 (5.16-5.24) | 5.23 (5.18-5.27) | −0.03 (−0.09 to 0.04) | .39 | | −0.06 (−0.12 to 0.01) | .08 |
| 14.5-18.9 y | 3.23 (3.07-3.39) | 3.67 (3.5-3.85) | −0.44 (−0.68 to −0.21) | <.001 | | −0.26 (−0.45 to −0.07) | .007 |
| BMI at birth, *z* score | −0.52 (−0.58 to −0.46) | −0.62 (−0.68 to −0.56) | 0.1 (0.01-0.19) | .03 | | 0.06 (−0.02 to 0.15) | .15 |
| BMI gain, *z* score/y | | | | | | | |
| Birth-3 mo | 1.66 (1.56-1.76) | 1.79 (1.69-1.9) | −0.13 (−0.27 to 0.01) | .07 | | 0.01 (−0.14 to 0.15) | .92 |
| 3-12 mo | 1.8 (1.76-1.83) | 1.95 (1.92-1.99) | −0.16 (−0.21 to −0.11) | <.001 | | −0.12 (−0.16 to −0.07) | <.001 |
| 1-2.8 y | −0.5 (−0.52 to −0.49) | −0.49 (−0.51 to −0.48) | −0.01 (−0.04 to 0.02) | .47 | | −0.01 (−0.03 to 0.02) | .67 |
| 2.8-8.5 y | −0.07 (−0.08 to −0.07) | −0.1 (−0.11 to −0.09) | 0.03 (0.02-0.04) | <.001 | .30[b] | 0.01 (0 to 0.03) | .02 |
| 8.5-14.5 y | 0.06 (0.05-0.07) | 0.07 (0.06-0.08) | −0.01 (−0.02 to 0) | .07 | | 0 (−0.01 to 0.02) | .56 |
| 14.5-18.9 y | −0.08 (−0.1 to −0.06) | −0.11 (−0.13 to −0.08) | 0.02 (0 to 0.05) | .10 | | 0 (−0.03 to 0.03) | .81 |

Abbreviations: BMI, body mass index; NA, not applicable; Sex Int, sex interaction.

[a] Additionally adjusted for stratum-level variables (urban vs rural and East vs West Belarus), both maternal and paternal education, and child sex.

[b] *P* value for sex interaction for entire trajectory.

Figure 2. Predicted Difference in Mean Weight, Height, and BMI *z* score (With 95% Confidence Intervals) in the Intervention Arm Compared With Control Arm




Predicted size in the intervention compared with the control arm at age 1, 6.5, 11.5, and 16.2 years.

explanations for the results. In an observational analysis, we did not observe the inverse associations of increased breastfeeding with overweight and obesity reported in previous observational studies, possibly owing to differences in confounding structures in Belarus compared with Western countries. The Pelotas (Brazil) cohort found no association of socioeconomic position with breastfeeding and no strong association of breastfeeding with BMI or BP (similar to our observational analysis in Belarus).[13] This contrasts with the Avon Longitudinal Study of Parents and Children cohort in the United Kingdom, in which higher socioeconomic position was strongly associated with increased breastfeeding, and breastfeeding was associated with lower BMI and BP even after adjusting for socioeconomic position.[13] Such cross-cohort comparisons suggest that reported associations of breastfeeding with child BMI and BP in Avon Longitudinal Study of Parents and Children are likely to reflect residual confounding.[13]

Higher-than-expected breastfeeding duration was observed in the control group, which may have been owing to deteriorating economic conditions in Belarus during the trial and the higher cost of formula.[26] Nonetheless, the intervention led to a substantial increase in breastfeeding duration and exclusivity compared with the control arm.[26] Breastfeeding was initiated in all study participants, so our findings may not apply to comparisons of breastfeeding vs formula feeding. Given the (expected) overlap in breastfeeding in the intervention and control arms, we used instrumental variable analysis to estimate unconfounded associations of the difference in breastfeeding exclusivity and duration achieved between the 2 randomized groups with adiposity and BP. The instrumental variable analysis supports our primary findings that the breastfeeding promotion intervention did not substantially lower the outcomes of interest. The small positive associations of the intervention with overweight and obesity could be a chance finding, but we cannot exclude a true increase in risk caused by the intervention. One suggested physiological mechanism whereby prolonged breastfeeding could increase the risk of obesity is longer exposure to maternal hormones present in breastmilk, which could theoretically alter the infant's lipid metabolism and increase body fat composition in later life.[51]

### Limitations

Belarus has low overall levels of obesity and overweight (in our study, 4% to 5% were obese at 16 years and 13% to 15% were overweight or obese at 16 years). Hence, our findings may not be generalizable to other settings with higher prevalence of overweight and obesity. While many observational studies suggest that longer-term and exclusive breastfeeding reduces childhood obesity risk,[6] these studies are prone to confounding by lifestyle factors and publication bias.[27]

## Conclusions

An intervention that achieved substantially greater duration and exclusivity of breastfeeding in Belarus did not prevent overweight or obesity or lower BP levels at age 16 years, despite differences in growth rates between the trial arms at various ages. On the contrary, overweight and obesity were more prevalent in the breastfeeding promotion intervention arm. While there are many reasons for promoting breastfeeding duration and exclusivity, our trial does not indicate that breastfeeding prevents obesity or lowers BP in childhood or adolescence.

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