ORIGINAL ARTICLE

Nutritional Support for Moderate-to-Late–Preterm Infants — A Randomized Trial

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ABSTRACT

BACKGROUND

Most moderate-to-late–preterm infants need nutritional support until they are feeding exclusively on their mother's breast milk. Evidence to guide nutrition strategies for these infants is lacking.

METHODS

We conducted a multicenter, factorial, randomized trial involving infants born at 32 weeks 0 days' to 35 weeks 6 days' gestation who had intravenous access and whose mothers intended to breast-feed. Each infant was assigned to three interventions or their comparators: intravenous amino acid solution (parenteral nutrition) or dextrose solution until full feeding with milk was established; milk supplement given when maternal milk was insufficient or mother's breast milk exclusively with no supplementation; and taste and smell exposure before gastric-tube feeding or no taste and smell exposure. The primary outcome for the parenteral nutrition and the milk supplement interventions was the body-fat percentage at 4 months of corrected gestational age, and the primary outcome for the taste and smell intervention was the time to full enteral feeding (150 ml per kilogram of body weight per day or exclusive breast-feeding).

RESULTS

A total of 532 infants (291 boys [55%]) were included in the trial. The mean (±SD) body-fat percentage at 4 months was similar among the infants who received parenteral nutrition and those who received dextrose solution (26.0±5.4% vs. 26.2±5.2%; adjusted mean difference, −0.20; 95% confidence interval [CI], −1.32 to 0.92; P=0.72) and among the infants who received milk supplement and those who received mother's breast milk exclusively (26.3±5.3% vs. 25.8±5.4%; adjusted mean difference, 0.65; 95% CI, −0.45 to 1.74; P=0.25). The time to full enteral feeding was similar among the infants who were exposed to taste and smell and those who were not (5.8±1.5 vs. 5.7±1.9 days; P=0.59). Secondary outcomes were similar across interventions. Serious adverse events occurred in one infant.

CONCLUSIONS

This trial of routine nutrition interventions to support moderate-to-late–preterm infants until full nutrition with mother's breast milk was possible did not show any effects on the time to full enteral feeding or on body composition at 4 months of corrected gestational age. (Funded by the Health Research Council of New Zealand and others; DIAMOND Australian New Zealand Clinical Trials Registry number, ACTRN12616001199404.)

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*The members of the DIAMOND Trial Group are listed in the Supplementary Appendix, available at NEJM.org.

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Among all the preterm infants born worldwide, 85% are categorized as "moderate preterm" (born between 32 weeks 0 days' and 33 weeks 6 days' gestation) or "late preterm" (born between 34 weeks 0 days' and 36 weeks 6 days' gestation).[1] Despite excellent survival, these infants are at increased risk for developmental delay,[2] cardiometabolic diseases and other disorders,[3,4,5-7] and death.[8-10]

Most moderate-to-late–preterm infants need nutritional support after birth pending a sufficient supply and intake of mother's breast milk; however, evidence for the best strategy for nutrition management is lacking, which has led to substantial variation in practice.[11-13] International consensus guidelines endorse the importance of breast milk but emphasize the lack of evidence to support recommendations regarding nutritional support pending a sufficient supply and intake of breast milk.[14-18] The American Academy of Pediatrics,[19] the National Perinatal Association,[18] and the Academy of Breastfeeding Medicine[14] recognize the increased risk of adverse health outcomes associated with preterm birth, even late-preterm birth, as well as the importance of nutritional and feeding support, and stress the importance of breast-milk feeding. However, none of these organizations provide clear guidelines with regard to when or how nutritional support beyond breastfeeding should be provided. The European Society for Paediatric Gastroenterology, Hepatology, and Nutrition[17] has identified as research gaps data on nutrition practices for moderate-to-late–preterm infants and on the benefit–risk balance of providing nutrient-enriched support. We conducted the DIAMOND (Different Approaches to Moderate and Late Preterm Nutrition: Determinants of Feed Tolerance, Body Composition and Development) trial, a factorial, randomized clinical trial, to investigate strategies for nutritional support in moderate-to-late–preterm infants and the effects of the various strategies on body composition and time to full enteral feeding.

Methods

Trial Design and Oversight

This trial was an investigator-initiated, multicenter, factorial, randomized, controlled clinical trial that was conducted at five hospitals across New Zealand. The trial was designed and managed by a steering committee consisting of the authors. The protocol (available with the full text of this article at NEJM.org) has been published previously.[20] The Northern A Health and Disability Ethics Committee provided ethics approval for the trial. Local institutional approval was obtained from each participating center. Data were gathered by the trial team and analyzed by one of the authors who was the trial statistician. The authors vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. The first author wrote the first draft of the manuscript.

Participants

Infants were eligible if they were born between 32 weeks 0 days' and 35 weeks 6 days' gestation, had been admitted to a neonatal unit, and had intravenous access that had been established for clinical reasons and if their mothers intended to breast-feed. Infants were excluded if they had a known chromosomal or genetic abnormality or congenital disorder affecting growth, body composition, or neurodevelopmental outcome or if a specific mode of nutrition was indicated. Parents were required to provide written informed consent for their infant's participation within 24 hours after the birth.

Randomization

Infants underwent randomization within 24 hours after birth and were assigned in a 1:1 ratio to one of eight possible combinations (so-called conditions; see Table S1 in the Supplementary Appendix, available at NEJM.org) of the three interventions (described below) by means of a secure, Web-based interface that was supported and concealed by an independent database controller. Twins underwent randomization as individual infants. The randomization schedule was computer generated with the use of variable block sizes, with stratification according to hospital site, sex, and gestational age (moderate preterm or late preterm). The infants' families, the clinical staff, and the investigators were aware of trial-group assignments, but outcome assessors and the statistician were unaware of the group assignments.

Trial Interventions

Each infant was randomly assigned to three interventions or their comparators: amino acid solution (parenteral nutrition) or intravenous dextrose, milk supplement (donor breast milk or infant

formula) or exclusively breast milk from the infant's mother as enteral nutrition, and exposure or no exposure to the taste and smell of milk before each tube feeding. The infants received supplemental nutrition until the supply and intake of mother's breast milk met daily enteral volumes prescribed by the clinical team. The goal for all the infants was to reach full feeds of only mothers' breast milk as quickly as possible.

Intravenous lipid emulsion was provided at the clinician's discretion. The taste intervention was provided by placing 0.2 ml of milk into the infant's mouth with a syringe immediately before the infant was fed through a nasogastric tube; the smell intervention was administered by applying 0.1 to 0.5 ml of milk onto a piece of gauze, which was placed near the infant's nose and remained there throughout the tube feeding. The taste and smell intervention continued as long as the feeding tube remained in place or until the infant was discharged from the neonatal unit.

OUTCOMES

The primary outcome for the parenteral nutrition and milk supplement interventions was the body-fat percentage at 4 months of corrected gestational age. The primary outcome for the taste and smell intervention was the time to full enteral feeding, defined as enteral feeding volume of 150 ml per kilogram of body weight per day, or exclusive breast-feeding, whichever occurred first.

Key secondary outcomes included the time to removal of the nasogastric tube for at least 24 hours (i.e., full sucking feeds) or until discharge from the hospital, whichever occurred first; the number of days in the hospital; nutritional intake during weeks 1 and 2; breast-feeding status at the time of hospital discharge and at 4 months of corrected gestational age; body composition at the time of hospital discharge and at 4 months of corrected gestational age; and change in growth measurements and z score from birth to hospital discharge and from birth to 4 months of corrected gestational age.

At the time of the infants' discharge from the neonatal unit and at 4 months (within a 2-week window before or after) of corrected gestational age, body composition (including body-fat percentage) was assessed by air-displacement plethysmography (Pea Pod, CosMed), and skin-fold thickness was measured in duplicate by trained research staff who used standardized skin-fold calipers. When the infants reached 4 months of corrected gestational age, their mothers were asked to complete a questionnaire assessing breast-feeding.

STATISTICAL ANALYSIS

We calculated that a sample size of 528 infants would provide the trial with overall power of at least 90%, with an overall two-sided type 1 error rate of less than 5%, to detect a minimal clinically significant difference of 3% in fat mass (lower boundary of the 95% confidence interval, assuming a standard deviation of 4%) at 4 months of corrected gestational age for the parenteral nutrition and milk supplement interventions (280 infants [140 per intervention]) and a reduction in the median time to full enteral feeding from 10 days to 7 days (hazard ratio, 1.43) for the taste and smell intervention (480 infants [240 per intervention]), assuming no interactions among the interventions and allowing for 10% loss to follow-up. The primary analysis population was based on the modified intention-to-treat principle and included all the infants in the groups to which they were assigned at randomization, whether or not they completed or received that intervention or comparator. Infants were excluded from the intention-to-treat population only if they did not satisfy entry criteria (i.e., if they had undergone randomization in error), if they were withdrawn from the trial and the informed consent to use their data was withdrawn, or if they provided no post-randomization data.

Owing to the pragmatic nature of the trial, strict adherence to the protocol was not always possible. Therefore, the trial steering group defined a protocol deviation as occurring when infants, before day 5 after birth, received additional nutritional support (i.e., parenteral nutrition or milk supplement) to which they had not been assigned at randomization. From day 5 after birth and beyond, additional nutrition was considered an appropriate clinical decision, on the basis of a previous survey.[11]

Our primary analysis was of the main effect of each intervention against its comparator, with adjustment for cointerventions in the same condition (see Table S1). For the parenteral nutrition and milk supplement interventions, linear-regression models were used to test the effect of the intervention on the primary outcome. The model-adjusted mean difference between the groups was

estimated with a 95% confidence interval and associated P value. For the taste and smell exposure intervention, the time to full enteral feeding was analyzed with the use of the Cox proportional-hazards model, with an adjusted hazard ratio and 95% confidence interval. Analyses were adjusted for stratification factors (i.e., hospital, gestation category [moderate or late preterm], and sex); the nonindependence of multiple births was controlled in the models with the use of a cluster effect. Possible interactions among the main interventions were tested with the use of a test for three-way interaction, and model-adjusted estimates were compared between each combination of intervention conditions and the control condition. We did not correct for multiplicity when conducting additional tests for secondary outcomes or in subgroup analyses; results are reported as point estimates and 95% confidence intervals that have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

RESULTS

TRIAL PARTICIPANTS

From March 2017 through March 2022, a total of 532 infants were enrolled at five centers (Fig. 1). Data on the primary outcome were available for 324 infants (61%) for body-fat percentage at 4 months of corrected gestational age and for 526 infants (99%) for the time to full enteral feeding. Overall, the intervention and comparator groups were balanced with respect to characteristics of the infants at baseline (Table 1). Infants from ethnic and socioeconomic groups associated with a higher-than-average incidence of preterm birth were well represented (Table 1 and Table S2). Three serious adverse events (necrotizing enterocolitis, gastrointestinal surgery, and death) not considered by the independent safety monitoring committee to be trial-related occurred in one infant, who was assigned to parenteral nutrition, mother's breast milk only, and no smell and taste intervention (Table 2). A total of 14 adverse events occurred in 12 infants (Table 2).

In the parenteral nutrition intervention, protocol deviations occurred in 6 of 269 infants (2.2%) assigned to the intervention and in 16 of 263 infants (6.1%) assigned to the comparator. In the milk supplement intervention, protocol deviations occurred only in the group assigned to receive mother's breast milk exclusively, with 89 of 271 infants (32.8%) receiving either infant formula or donor breast milk within 5 days after birth. For the smell and taste intervention, protocol deviations occurred only in the control group, with 20 of 272 infants (7.4%) provided with taste and smell intervention (Table S3).

PRIMARY OUTCOMES

Body-fat percentage at 4 months of corrected gestational age was similar with the parenteral nutrition and dextrose interventions (26.0±5.4% vs. 26.2±5.2%; adjusted mean difference, −0.20; 95% confidence interval [CI], −1.32 to 0.92; P=0.72) and with the milk supplement and mother's breast milk–only interventions (26.3±5.3% vs. 25.8±5.4%; adjusted mean difference, 0.65; 95% CI, −0.45 to 1.74; P=0.25) (Table 3). The time to full enteral feeding was similar among the infants who received the taste and smell intervention and those who did not (5.8±1.5 days vs. 5.7±1.9 days; adjusted hazard ratio, 0.95; 95% CI, 0.80 to 1.14; P=0.59) (Fig. 2C). Tests for all interaction effects among the interventions with regard to the primary outcomes showed no significant interactions (Table S5).

SECONDARY OUTCOMES

Characteristics of body composition, measured by air-displacement plethysmography, were largely similar in the intervention and comparator groups for all interventions at hospital discharge and at 4 months of corrected gestational age (Table 3 and Table S4). The time to full sucking feeds also was similar with parenteral nutrition and dextrose (22.7±12.0 vs. 22.5±11.2 days; adjusted hazard ratio, 1.06; 95% CI, 0.81 to 1.37), with milk supplement and mother's breast milk only (23.0±11.6 vs. 22.2±11.6 days; adjusted hazard ratio, 0.91; 95% CI, 0.69 to 1.19), and with taste and smell and no taste and smell (22.5±10.9 vs. 22.7±12.2 days; adjusted hazard ratio, 0.88; 95% CI, 0.67 to 1.16). The time to full enteral feeding was similar with parenteral nutrition and dextrose (5.7±1.7 vs. 5.8±1.8 days; adjusted hazard ratio, 1.05; 95% CI, 0.88 to 1.25) and with milk supplement and mother's breast milk only (5.7±1.7 vs. 5.8±1.7 days; adjusted hazard ratio, 1.13; 95% CI, 0.88 to 1.34) (Fig. 2A and 2B and Table S6).

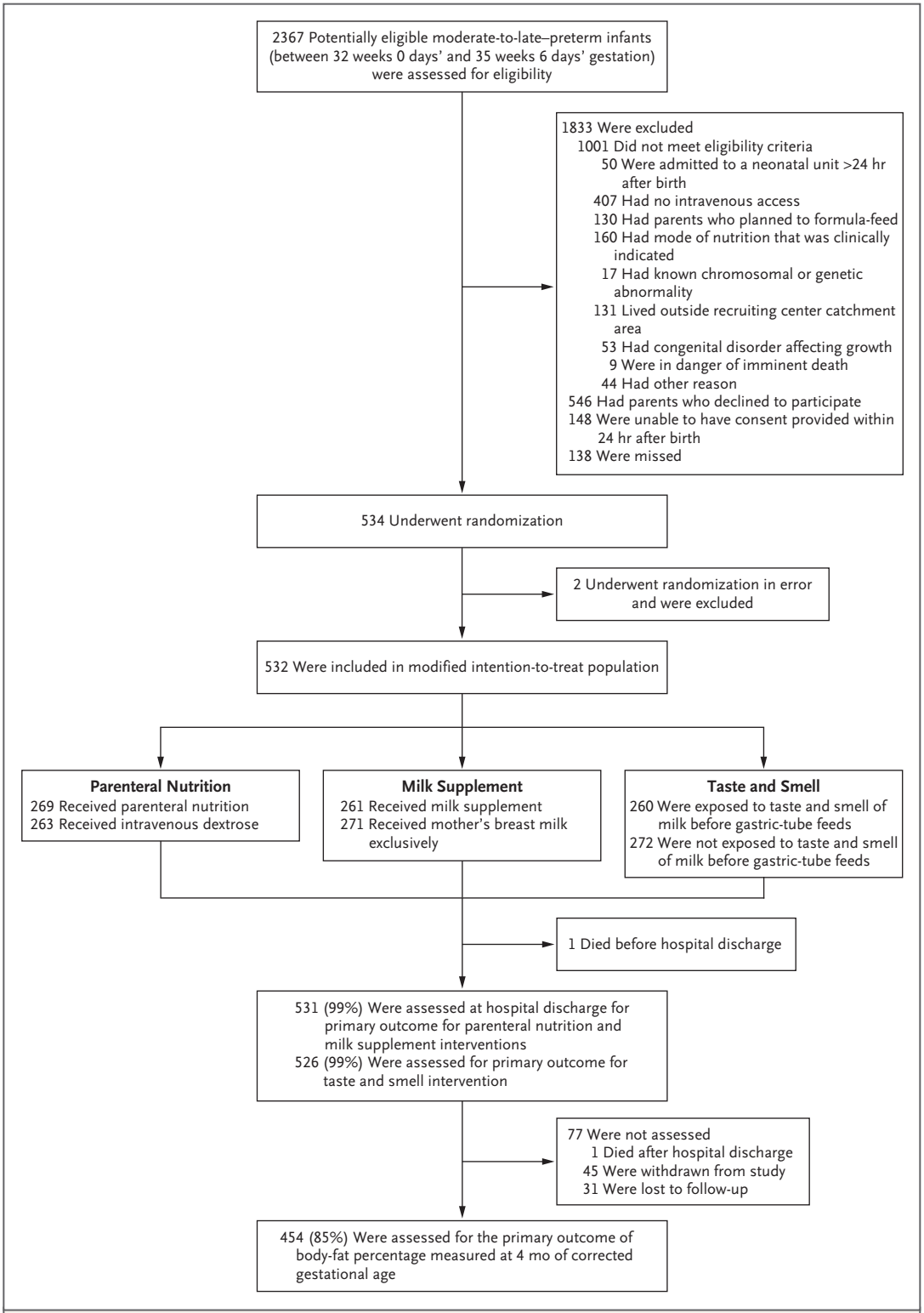

Figure 1. Screening, Randomization, and Follow-up of the Participants.

Table 1. Characteristics of the Mothers and Infants at Baseline.*

Characteristic		Intervention 1		Intervention 2		Intervention 3	
	Total (N=532)	Parenteral Nutrition (N=269)	Dextrose (N=263)	Milk Supplement (N=261)	Mother's Breast Milk Only (N=271)	Taste and Smell Exposure (N=260)	No Taste and Smell Exposure (N=272)
Mother							
Age — yr	30.9±5.8	31.1±5.8	30.8±5.8	31.1±6.1	30.7±5.5	30.9±6.2	30.9±5.4
Socioeconomic status — no. (%)†							
Quintile 1	70 (13.2)	40 (14.9)	30 (11.4)	22 (8.4)	48 (17.7)	35 (13.5)	35 (12.9)
Quintile 2	85 (16.0)	44 (16.4)	41 (15.6)	47 (18.0)	38 (14.0)	46 (17.7)	39 (14.3)
Quintile 3	99 (18.6)	55 (20.4)	44 (16.7)	55 (21.1)	44 (16.2)	44 (16.9)	55 (20.2)
Quintile 4	111 (20.9)	51 (19.0)	60 (22.8)	57 (21.8)	54 (19.9)	52 (20.0)	59 (21.7)
Quintile 5	166 (31.2)	79 (29.4)	87 (33.1)	80 (30.7)	86 (31.7)	82 (31.5)	84 (30.9)
Race or ethnic group — no. (%)‡							
Asian	153 (28.8)	73 (27.1)	80 (30.4)	77 (29.5)	76 (28.0)	73 (28.1)	80 (29.4)
European or Other	199 (37.4)	107 (39.8)	92 (35.0)	105 (40.2)	94 (34.7)	100 (38.5)	99 (36.4)
Maori	84 (15.8)	47 (17.5)	37 (14.1)	31 (11.9)	53 (19.6)	44 (16.9)	40 (14.7)
Pacific Islander	96 (18.0)	42 (15.6)	54 (20.5)	48 (18.4)	48 (17.7)	43 (16.5)	53 (19.5)
Highest level of education — no. (%)							
Primary	56 (10.5)	24 (8.9)	32 (12.2)	26 (10.0)	30 (11.1)	26 (10.0)	30 (11.0)
Secondary	221 (41.5)	112 (41.6)	109 (41.4)	117 (44.8)	104 (38.4)	107 (41.2)	114 (41.9)
University	243 (45.7)	127 (47.2)	116 (44.1)	116 (44.4)	127 (46.9)	119 (45.8)	124 (45.6)
Other or unknown	12 (2.3)	6 (2.2)	6 (2.3)	2 (0.8)	10 (3.7)	8 (3.1)	4 (1.5)
Medical history — no. (%)							
Antenatal glucocorticoids	414 (77.8)	204 (75.8)	210 (79.8)	204 (78.2)	210 (77.5)	203 (78.1)	211 (77.6)
Maternal diabetes	101 (19.0)	45 (16.7)	56 (21.3)	57 (21.8)	44 (16.2)	46 (17.7)	55 (20.2)
Caesarean section	332 (62.4)	170 (63.2)	162 (61.6)	161 (61.7)	171 (63.1)	158 (60.8)	174 (64.0)

Infant							
Gestation							
Moderate preterm: 32 wk 0 d to 33 wk 6 d — no. (%)	277 (52.1)	139 (51.7)	138 (52.5)	136 (52.1)	141 (52.0)	133 (51.2)	144 (52.9)
Late preterm: 34 wk 0 d to 35 wk 6 d — no. (%)	255 (47.9)	130 (48.3)	125 (47.5)	125 (47.9)	130 (48.0)	127 (48.8)	128 (47.1)
Gestational age — wk	33.8±1.1	33.8±1.1	33.8±1.1	33.9±1.1	33.8±1.1	33.8 ±1.1	33.8±1.1
Anthropometric variables at birth							
Weight — g	2121.8±424.5	2124.4±424.5	2119.2±425.2	2125.1±441.8	2118.6±407.9	2146.5±419.3	2098.1±428.8
Weight z score§	–0.1±0.9	–0.1±0.9	–0.1±0.9	–0.1±0.9	–0.1±0.9	0.0±0.9	–0.2±0.9
Length — cm¶	44.5±2.9	44.5±2.9	44.6±3.0	44.6±3.0	44.5±2.9	44.8±2.7	44.3±3.1
Length z score§	0.2 (1.1)	0.1 (1.0)	0.2 (1.1)	0.2 (1.0)	0.1 (1.1)	0.2 (1.0)	0.1 (1.1)
Head circumference — cm‖	31.2±1.7	31.2±1.6	31.3±1.8	31.3±1.7	31.2±1.6	31.4±1.7	31.1±1.6
Head circumference z score§	0.3±1.0	0.3±0.9	0.4±1.1	0.4±1.0	0.3±1.0	0.4±1.0	0.2±1.0
Male sex — no. (%)	291 (54.7)	149 (55.4)	142 (54.0)	143 (54.8)	148 (54.6)	145 (55.8)	146 (53.7)
Small for gestational age — no. (%)	59 (11.1)	27 (10.0)	32 (12.2)	29 (11.1)	30 (11.1)	27 (10.4)	32 (11.8)
Singleton birth — no. (%)	403 (75.8)	203 (75.5)	200 (76.0)	202 (77.4)	201 (74.2)	197 (75.8)	206 (75.7)

* Plus–minus values are means ±SD.

† Socioeconomic status was determined according to the New Zealand Deprivation Index 2018[21] and stratified by quintiles from 1 (least deprived) to 5 (most deprived). Data are missing for 1 mother and infant.

‡ Race or ethnic group was reported by the caregiver and categorized according to the prioritization framework of the Ethnicity New Zealand Standard Classification.[22]

§ The z scores were calculated with the use of Fenton growth charts.[23]

¶ Data were available for 519 infants in the total trial population and for 262 infants in the parenteral nutrition group, 257 in the dextrose group, 255 in the milk supplement group, 264 in the mother's breast milk only group, 254 in the taste and smell group, and 265 in the no taste and smell control group.

‖ Data were available for 531 infants in the total trial population and for 268 infants in the parenteral nutrition group, 263 in the dextrose group, 260 in the milk supplement group, 271 in the mother's breast milk only group, 260 in the taste and smell group, and 271 in the no taste and smell control group.

Table 2. Adverse Events.

Event	Intervention 1		Intervention 2		Intervention 3	
	Parenteral Nutrition (N=269)	Dextrose (N=263)	Milk Supplement (N=261)	Mother's Breast Milk Only (N=271)	Taste and Smell Exposure (N=260)	No Taste and Smell Exposure (N=272)
	number of infants (percent)					
Serious adverse event*						
Death	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)
Necrotizing enterocolitis	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)
Gastrointestinal surgery	1 (0.4)	0	0	1 (0.4)	0	1 (0.4)
Adverse event†						
Extravasation injury requiring treatment or referral to plastic surgery team‡	5 (1.9)	0	2 (0.8)	3 (1.1)	3 (1.2)	2 (0.7)
Nonelective removal of a central venous line	0	1 (0.4)	0	1 (0.4)	1 (0.4)	0
Culture-proven late-onset sepsis§	3 (1.1)	1 (0.4)	1 (0.4)	3 (1.1)	2 (0.8)	2 (0.7)
Probable late-onset sepsis§	3 (1.1)	1 (0.4)	1 (0.4)	3 (1.1)	2 (0.8)	2 (0.7)

* Three serious adverse events occurred in the same infant.
† A total of 14 adverse events occurred in 12 infants. There were no occurrences of central-line–associated bloodstream infection.
‡ Treatment consisted of infusion of isotonic fluid into the subcutaneous space through a small-gauge needle to flush out the extravasated fluid.
§ Two of the 12 infants had both culture-proven late-onset sepsis and probable late-onset sepsis.

Breast-milk feeding status at the time of hospital discharge and at 4 months of corrected gestational age was similar in all the intervention and comparator groups. The length of stay in the hospital was also similar across groups (Table S6). Changes in z score for weight, length, and head circumference from birth to hospital discharge and from birth to 4 months of corrected gestational age were similar with all interventions and their comparators (Table S7). Skin-fold thickness was also similar across all interventions and comparators (Table S8). As expected, energy, protein, and fat intakes in the first week were generally higher with parenteral nutrition and milk supplement interventions than with the comparators (Tables S9, S10, and S11).

DISCUSSION

In this multicenter, factorial, randomized trial of three nutrition interventions in moderate-to-late–preterm infants whose mothers intended to breast-feed but for whom sufficient mother's breast milk was not immediately available, nutritional support with an amino acid solution (delivered intravenously) or formula (the milk supplement used in almost all the infants) resulted in a percentage of fat mass at 4 months of corrected gestational age that was similar to that in infants who received intravenous dextrose or in infants who were assigned to receive only mother's breast milk as their enteral nutrition. The time to full enteral feeding was similar among the infants who received exposure to smell and taste before tube feeding and those who were not exposed to taste and smell. The time to removal of the nasogastric tube for at least 24 hours (or until discharge from the hospital) and the length of stay in the hospital were also similar in all the groups. These findings suggest that for infants of mothers who intend to breast-feed, the mode of nutritional support provided should be chosen to best support the eventual provision of mother's breast milk as the sole enteral feed.

We hypothesized that infants who received parenteral nutrition or milk supplement (or both) when the maternal milk supply did not meet demand would have altered body composition as compared with infants who were supported only by dextrose, owing to prevention of a nitrogen deficit and protein catabolism.[25] However, all measures of body composition by air-displacement plethysmography at 4 months of corrected gestational age were similar in the groups, irrespec-

Table 3. Body Composition at 4 Months of Corrected Gestational Age.*

Variable	Intervention 1			Intervention 2			Intervention 3		
	Parenteral Nutrition (N=168)	Dextrose (N=156)	Adjusted Mean Difference (95% CI)	Milk Supplement (N=166)	Mother's Breast Milk Only (N=158)	Adjusted Mean Difference (95% CI)	Taste and Smell Exposure (N=143)	No Taste and Smell Exposure (N=181)	Adjusted Mean Difference (95% CI)
Fat mass									
Body-fat percentage	26.0±5.4	26.2±5.2	−0.2 (−1.3 to 0.9)	26.3±5.3	25.8±5.4	0.6 (−0.4 to 1.7)	26.4±5.1	25.9±5.5	0.5 (−0.7 to 1.6)
Fat mass — kg	1.8±0.5	1.8±0.5	0.0 (−0.1 to 0.1)	1.8±0.5	1.7±0.5	0.1 (0.0 to 0.2)	1.8±0.5	1.7±0.5	0.1 (−0.1 to 0.2)
Fat-mass z score	−0.4±1.1	−0.4±1.1	0.0 (−0.2 to 0.2)	−0.4±1.1	−0.5±1.1	0.1 (−0.1 to 0.4)	−0.4±1.2	−0.4±1.1	0.1 (−0.1 to 0.3)
Fat-mass index — kg/m	4.3±1.1	4.3±1.1	0.0 (−0.3 to 0.2)	4.4±1.1	4.2±1.1	0.2 (−0.1 to 0.4)	4.4±1.1	4.2±1.1	0.1 (−0.1 to 0.4)
Fat-free mass									
Percentage of fat-free mass	74.0±5.4	73.8±5.3	0.2 (−0.9 to 1.3)	73.7±5.3	74.2±5.4	−0.6 (−1.7 to 0.4)	73.6±5.1	74.1±5.5	−0.5 (−1.6 to 0.7)
Fat-free mass — kg	4.9±0.6	4.9±0.6	0.1 (−0.1 to 0.2)	4.9±0.6	4.9±0.6	0.0 (−0.1 to 0.1)	4.9±0.6	4.9±0.6	0.0 (−0.1 to 0.1)
Fat-free mass z score	−0.7±1.2	−0.8±1.5	0.0 (−0.2 to 0.3)	−0.7±1.4	−0.7±1.3	0.0 (−0.3 to 0.3)	−0.7±1.2	−0.7±1.4	0.0 (−0.2 to 0.3)
Fat-free mass index — kg/m	12.0±1.0	12.0±1.1	0.1 (−0.1 to 0.3)	12.1±1.0	12.0±1.0	0.1 (−0.2 to 0.3)	12.0±1.0	12.0±1.1	0.0 (−0.2 to 0.2)

* Plus–minus values are means ±SD. The z-score calculations for fat mass and fat-free mass were based on data from a reference group.[24] The widths of the confidence intervals have not been adjusted for multiplicity and may not be used in place of hypothesis testing.

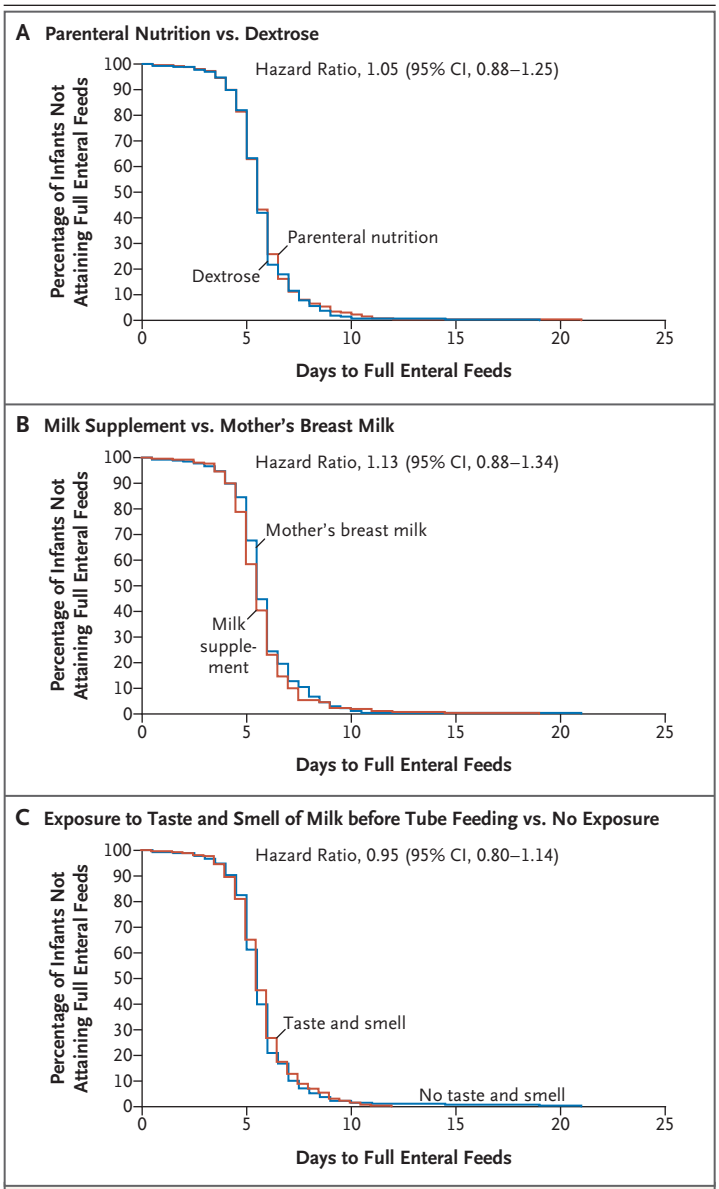

Figure 2. Days to Full Enteral Feeding with Interventions and Comparators.
Kaplan–Meier curves show the number of days to full enteral feeding in the infants who received parenteral nutrition as compared with those who received dextrose (Panel A), infants who received a milk supplement as compared with those who received mother's breast milk only (Panel B), and infants who received taste and smell exposure as compared with those who received no exposure (Panel C; a primary outcome).

tive of the nutritional support intervention the infants received until they could receive full enteral feeds. These findings suggest that there is no benefit with respect to body composition in providing enriched nutritional support while waiting for sufficient mother's breast milk to become available, even if the process takes several days. The lack of effect of the interventions on body composition may be due to the short period of time nutritional support was provided, with most infants reaching full enteral feeding within a week after birth.

We also hypothesized that providing exposure to the smell and taste of milk would stimulate the cephalic phase response, which would aid gastrointestinal function and the metabolic response to food[26,27] and lead to reduced time to full enteral feeding. Our results do not support a recent Cochrane review[28] that indicated the potential for benefit with respect to time to hospital discharge but are in keeping with results of a randomized, controlled trial of a similar intervention in infants born at less than 29 weeks' gestation and with a birth weight of less than 1250 g.[29] The lack of any discernible effect of smell and taste exposure in this trial may be attributable to the multiple stimuli in a neonatal intensive-care environment, including numerous odors, which might have overcome any potential effect of the smell and taste of milk.

We speculated that the provision of parenteral nutrition might provide reassurance to caregivers that the infants were receiving adequate levels of energy and protein intake,[30] thereby reducing the urgency to transition to full enteral feeding. Similarly, provision of milk supplement can aid the removal of intravenous access and ensure that desired macronutrient intakes are attained. However, neither of these interventions altered the time to full enteral feeding or the time to discharge home, and there was no difference in anthropometric variables at 4 months of corrected gestational age. These findings indicate that among infants in neonatal nurseries in which there is dedicated lactation support for mothers who intend to breast-feed, as was the case in this trial, there is no benefit in providing infant formula or parenteral nutrition with respect to any of the outcomes we measured, and effort can be focused on ensuring that the mother's milk supply is optimized. We would note that the length of hospital stay also was unaffected by the interventions. Our findings support an approach that concentrates on providing mothers with necessary lactation support, thereby maximizing the likelihood of attaining exclusive breast-milk feeding.

Our trial has several strengths. It was a large, multicenter trial of nutritional support in moderate-to-late–preterm infants and investigated com-

mon interventions for which there is an evidence gap. Primary outcome data were available for 99% of the cohort for the time to full enteral feeding.

The trial also has limitations. It was unblinded, which may have resulted in bias from the treating clinicians. Although we assessed 85% of the infants at 4 months, many of these assessments were undertaken in the infants' homes rather than in a clinic, owing to family preference during the coronavirus disease 2019 pandemic. Thus, the percentage of fat mass at 4 months of corrected gestational age, one of the primary outcomes, was ascertained in 324 infants (61%); this number exceeds that required by the sample-size calculation for this outcome. Most other secondary outcomes were analyzed in the majority of the infants assessed. Birth characteristics of the infants not assessed at 4 months of corrected gestational age were similar to those of the infants who were assessed (Table S12). The current trial may not be generalizable to all moderate-to-late–preterm infants because only infants born up to 35 weeks 6 days' gestation were eligible, and well infants cared for in maternity wards were not eligible. Although the outcomes are clinically important, they are relatively short-term. Two-year follow-up of the infants enrolled in this trial to assess neurodevelopment is ongoing.

This trial of routine nutritional interventions to support moderate-to-late–preterm infants until full nutrition with mother's breast milk was possible did not show any effects on the time to full enteral feeding or on body composition at 4 months of corrected gestational age.

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