A randomised multicentre study of human milk versus formula and later development in preterm infants

A Lucas, R Morley, T J Cole, S M Gore

Abstract
Whether breast milk influences later neurodevelopment has been explored in non-randomised studies, potentially confounded by social and demographic differences between feed groups. Here in a strictly randomised prospective multicentre trial, Bayley psychomotor and mental development indices (PDI and MDI) were assessed at 18 months post-term in survivors of 502 preterm infants assigned to receive, during their early weeks, mature donor breast milk or a preterm formula. These diets were compared as sole enteral feeds or as supplements to the mother's expressed breast milk. No differences in outcome at 18 months were seen between the two diet groups despite the low nutrient content of donor milk in relation to the preterm formula and to the estimated needs of preterm infants. These results contrast with those reported from our parallel two centre study that compared infants randomly assigned a standard term formula or the preterm formula during their early weeks; those fed standard formula, now regarded as nutritionally insufficient for preterm infants, were substantially disadvantaged in PDI and MDI at 18 months post-term. It is shown here that infants from that study fed solely on standard formula had significantly

lower developmental scores at 18 months than those fed on donor breast milk in the present study; yet the standard formula had a higher nutrient content than the donor milk. Thus, donor milk feeding was associated with advantages for later development that may have offset any potentially deleterious effects of its low nutrient content for preterm infants. As these outcome advantages were not confounded by the social and educational biases usually associated with mothers' choice to breast feed, our data add significant support to the view that breast milk promotes neurodevelopment.
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MRC Dunn Nutrition Unit and University Department of Paediatrics, Cambridge
A Lucas
R Morley
T J Cole

MRC Biostatistics Unit, Cambridge
S M Gore

Correspondence to:
Dr A Lucas, MRC Dunn Nutrition Unit, Downhams Lane, Milton Road, Cambridge CB4 1XJ.
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Recently we showed that the diet given to preterm infants for on average the first month postpartum had a major impact on developmental scores at 18 months corrected age.¹ That such a brief period of early dietary manipulation had such profound effects underlined an unexpected sensitivity of these infants to their dietary management, with important implications for clinical practice. In that study, conducted in two of five centres taking part in a larger five centre investigation² (table 1), infants were randomly assigned to a standard 'term' formula or a nutrient enriched 'preterm formula' as sole diets or supplements to their mother's milk. Those fed the standard formula had a major disadvantage in developmental scores at 18 months compared with those fed the preterm formula.

In the other three of our five centres, a corresponding comparison was made between infants randomly assigned to banked donated breast milk or preterm formula. We now report the main results on developmental outcome in this three centre study for these babies at 18 months post-term, the first formal follow up period.

Previous studies (see below) have indicated that human milk might have a favourable long term effect on developmental status. Such studies, involving non-randomised comparisons of breast milk and formula fed infants, may be highly confounded by the many social and demographic differences reported between breast compared with formula feeding mothers. We have used data from both the current three centre study and our previous two centre study to explore this critical issue in circumstances where all the mothers had chosen not to provide their breast milk thus avoiding the major differences normally

Table 1 Summary of the overall design of the multicentre feeding trials. Follow up periods and summary of publications on developmental outcome

	Three centre study	Two centre study
Centres	Cambridge, Ipswich, King's Lynn	Norwich, Sheffield
No randomised	502	424
Neonatal diets assigned randomly		
Trial A: Diets used as sole enteral feed (mother chose not to provide her EBM)	BBM v PTF	TF v PTF
Trial B: Diets used as supplements to mother's EBM	BBM (+EBM) v PTF (+EBM)	TF (+EBM) v PTF (+EBM)
Follow up periods		
9 Months post-term	Pilot follow up completed Developmental outcome data reported (3)	No pilot follow up
18 Months post-term	Follow up completed Developmental outcome data reported in this paper	Follow up completed Developmental outcome data reported ¹ . Data from trial A included also in this paper for comparison
7.5–8 years	Follow up complete by 1993 (unpublished)	Follow up complete by 1993 (unpublished)

Randomised trial developmental outcome data for 7.5–8 years unreported, but epidemiological (non-randomised) developmental data on the first 300 children seen at 7.5–8 years were analysed according to whether mother provided her own expressed breast milk (EBM) or not and reported previously.¹³
BBM=banked (donated) breast milk; PTF=preterm formula; TF=standard term formula.

found between breast and formula feeding mothers.

Methods

STUDY DESIGN: AN OVERVIEW

Table 1 summarises the overall design of our parallel two and three centre randomised dietary intervention studies, the follow up periods, and the developmental outcome data published to date. The three centre study compares children who were fed in their early weeks on banked (donated) breast milk versus preterm formula as sole diets (trial A) or as supplements to mothers' expressed breast milk (trial B). The two centre study correspondingly compares children fed previously a standard term formula or preterm formula as sole diets (trial A) or as supplements to mothers' milk (trial B).

In this paper, two aspects are included: firstly, the 18 month developmental outcome results for the three centre study (trials A and B); and secondly, the non-randomised comparison of 18 month developmental scores from babies fed solely on donor breast milk (trial A from the three centre study) with those fed solely on term formula (trial A from the two centre study).

THE CURRENT STUDY

A total of 502 infants weighing under 1850 g at birth and admitted to the neonatal units in Cambridge, Ipswich, and King's Lynn between January 1982 and April 1985, were enrolled. Ethical approval for the study was obtained in each centre, and parental consent always sought; no parent refused. Only babies with major congenital malformations known to impair growth or development (for example, Down's syndrome) were ineligible.

Infants of mothers choosing not to express their breast milk were randomly allocated to pasteurised banked breast milk donated by unrelated lactating women to the milk bank in each centre, or to a preterm formula (Farley's Osterpremi; Crookes Health Care) as their sole diet (trial A). Those whose mothers chose to provide their own breast milk were randomly allocated to banked breast milk or preterm formula as a supplement to mothers' milk (trial B). The intake of trial diet in trial B depended on the mother's success in providing her own milk and varied from 100% down to 0%; the median intake of maternal milk was 53% (lower and upper quartiles: 17%, 91%), with no significant difference between babies supplemented with banked breast milk (median 50% or preterm formula (55%).

Trials A and B can be treated independently or combined to compare babies randomly assigned banked breast milk (as sole diet or supplement) with those fed preterm formula (as sole diet or supplement). Randomisation (designed by SMG), done in the first 48 hours after birth, was by use of opaque, sealed and numbered envelopes, and was conducted independently in each centre.¹⁻³ Assignments

were based on permuted blocks of variable length. Within each trial, randomisation was stratified by birth weight (below 1200 g and 1200 g or above) to increase the likelihood of equal distribution of small, sick babies between groups.

The banked breast milk contained a mean protein content of 1.1 g/100 ml and a mean energy content below 209.0 kJ (50 kcal)/100 ml. The low energy content was due to the fact that donated breast milk collected in the early 1980s in Britain was frequently drip breast milk which, like foremilk, has a low fat content.^{4,5}

This low energy density in the diet was offset partly by the higher milk volume intake of the donor milk fed group of up to 200 ml/kg/day as opposed to a maximum 180 ml/kg/day on the preterm formula (previously we reported that in the third week infants fed solely on donor milk consumed on average 15% more milk than those fed solely on preterm formula).² The preterm formula contained 2.0 g protein and 334.4 kJ (80 kcal)/100 ml and, compared with donor milk (or standard formula), was also enriched in sodium, calcium, phosphorus, copper, zinc, vitamins D, E, K, water soluble vitamins, carnitine, and taurine. The standard term formula used in our previously reported two centre study contained 1.45 g/100 ml protein and 284.2 kJ (68 kcal)/100 ml.

Feeds were given by nasogastric tube. In all, 90 babies required initial parenteral nutrition including amino acid (with or without lipid) infusion. The median number of days to full enteral feeds in the whole study population was 7 (quartiles 6, 9). The trial diet was discontinued when body weight was 2000 g or at discharge from the unit, whichever was sooner.

Extensive demographic, social, clinical, anthropometric, and biochemical data were collected on the infants. Social class was coded according to the registrar general's classification and mother's education according to categories published previously.¹

Each surviving infant was invited by an assessor blind to diet allocation (RM) for follow up 18 months after expected date of delivery. A detailed history and physical examination were undertaken and the Bayley scales of infant development⁶ were administered to derive the mental development index (MDI) and psychomotor development index (PDI), in each case corrected for prematurity.

Because developmental tests for children at this age rely heavily on age appropriate fine motor skills, they are an inadequate measure of a neurologically impaired child's cognitive ability. Children with such problems were therefore excluded from most analyses, but included in a separate analysis for the main results to demonstrate whether their exclusion influenced the principal findings.

Results were analysed by Student's *t* test, χ^2 test, and multiple regression. A sample size of 380 was calculated at the outset as necessary to detect a 5 point difference in developmental scores between feed groups (trials A and B

Table 2 Characteristics of subjects followed to 18 months post-term and effect of diet on physical growth

	Trial A (BBM or PTF as sole diet)		Trial B (BBM or PTF as supplements)		Combined trials A and B	
	BBM	PTF	BBM	PTF	BBM	PTF
Total enrolled	83	76	170	173	253	249
Deaths <18 months	7	9	13	16	20	25
Follow up (% survivors)	72 (95)	64 (96)	149 (95)	153 (97)	221 (95)	217 (97)
Cerebral palsy cases	4	8	13	11	17	19
Boys	31	24	75	78	106	102
Small for gestation (<10th centile)	27	22	38	52	65	74
Apgar score <4 at 5 min	2	2	4	6	6	8
Social class ≥3	58	44	96	92	154	136
Ventilated						
>5 days	7	11	22	16	29	27
>10 days	2	4	6	8	8	12
Mean (SE) gestation (weeks)	31.5 (0.4)	31.0 (0.4)	31.1 (0.2)	31.1 (0.2)	31.2 (0.2)	31.1 (0.2)
Mean (SE) birth weight (g)	1414 (37)	1386 (40)	1385 (26)	1390 (24)	1394 (21)	1389 (20)
Mean (SE) steady state weight gain while on diet (g/kg/day)	12.6 (0.4)	17.2 (0.6)†	13.8 (0.3)	15.5 (0.3)†	13.4 (0.3)	16.0 (0.3)†
Mean (SE) head circumference gain while on diet (mm/day)	1.28 (0.05)	1.49 (0.08)*	1.31 (0.04)	1.45 (0.05)*	1.30 (0.03)	1.46 (0.04)**
Median days in study (quartiles)	31 (22, 47)	30 (20, 39)	31 (25, 50)	27 (18, 40)	31 (22, 49)	27 (18, 40)

*p=<0.03; **p=<0.01; †p=<0.001. BBM=banked (donated) breast milk; PTF=preterm formula.

combined) at the 5% significance level with 80% power (accounting for the larger standard deviation of scores in infants born preterm).

Results

Mortality before 18 months was 9% (45/501) with no difference between feed groups (table 1). The overall follow up rate in survivors was 96% (438/457); the small loss of subjects was principally due to emigration of families of US Air Force personnel. There were only four recorded refusals.

Babies fed the preterm formula gained weight and head circumference significantly faster than those fed on banked breast milk, both when these diets were used alone or as supplements to maternal milk (table 2).

Otherwise the infants followed up showed no significant differences in the clinical, social, or demographic characteristics listed in table 2. Time spent in the study was similar in the two diet groups.

Median age at follow up was 81 weeks post-term (quartiles: 80, 85 weeks). In 16 of the 438 children followed up, the Bayley index could not be obtained either for medical reasons (severe deafness or blindness) or because follow up data were obtained by telephone for geographical reasons.

For the main trial comparisons (table 3), no significant developmental differences between diet groups emerged in either trial A or B.

In babies born small for gestation (table 4), small advantages for preterm formula were seen (5.1 points for both MDI and PDI in trial B), but these did not reach statistical significance.

In our previous two centre study there was a greater effect of diet on development in boys than girls.¹ Here this sex difference was less marked. Nevertheless, in trial A boys tended to have higher PDI scores on the preterm formula than on banked milk: benefit 7.6 points, 95% confidence interval (CI) -0.3 to 15.5.

INTERSTUDY COMPARISON

In our previous two centre study, infants fed on a diet that did not meet the estimated nutrient needs for preterm infants (that is, standard term formula), had a major deficit in developmental scores at 18 months corrected age, compared with those fed a specially designed preterm formula. In this study, the surprising lack of outcome disadvantage for donor breast milk versus preterm formula, despite the very low nutrient content of donor milk, raised the hypothesis that breast milk might confer advantages for neurodevelopment that offset possible adverse effects of its poor nutrient content. To explore this further, we elected to compare infants fed on donor milk in this study with those fed a standard term formula in our previous one. In this comparison, macronutrient intakes were more similar than those of infants fed donor milk versus preterm

Table 3 MDI and PDI at 18 months by diet group. In trial A BBM or PTF was used as the sole diet and in trial B as a supplement to mother's milk. Data are mean (SE)

Developmental test	Diet		Advantage for PTF (95% CI)
	BBM	PTF	
Trial A*	n=62	n=52	
MDI	94.8 (2.1)	95.3 (2.7)	0.5 (-6.2 to 7.1)
PDI	93.0 (1.8)	94.2 (2.2)	1.2 (-4.4 to 6.8)
Trial B†	n=134	n=139	
MDI	102.2 (1.7)	103.8 (1.7)	1.6 (-3.1 to 6.2)
PDI	95.5 (1.3)	94.5 (1.4)	-1.0 (-4.8 to 2.7)
Trials A plus B*	n=196	n=191	
MDI	99.9 (1.3)	101.5 (1.4)	1.6 (-2.3 to 5.5)
PDI	94.7 (1.1)	94.4 (1.2)	-0.26 (-3.4 to 2.8)
All subjects†	n=212	n=210	
MDI	98.6 (1.3)	100.1 (1.5)	1.5 (-2.4 to 5.4)
PDI	92.2 (1.2)	90.9 (1.3)	-1.25 (-4.8 to 2.3)

*Excluding cerebral palsy. †Trials A plus B including cerebral palsy. BBM=banked (donated) breast milk; PTF=preterm formula.

Table 4 Small for gestational age infants: MDI and PDI at 18 months by diet group. In trial A BBM or PTF was used as the sole diet and in trial B as a supplement to mother's milk. Data are mean (SE)

Developmental test	Diet		Advantage for PTF (95% CI)
	BBM	PTF	
All subjects*	n=61	n=70	
MDI	98.2 (2.2)	102.4 (2.3)	4.2 (-2.1 to 10.6)
PDI	93.7 (2.0)	96.7 (1.9)	3.0 (-2.5 to 8.5)
Trial A*	n=23	n=19	
MDI	95.5 (3.2)	95.5 (4.5)	0 (-11.0 to 11.0)
PDI	95.5 (2.8)	93.9 (4.3)	-1.6 (-11.6 to 8.3)
Trial B	n=38	n=51	
MDI	99.9 (3.0)	105.0 (2.5)	5.1 (-2.7 to 13.0)
PDI	92.6 (2.7)	97.7 (2.1)	5.1 (-1.7 to 11.9)

*Excluding cerebral palsy. BBM=banked (donated) breast milk; PTF=preterm formula.

Table 5 MDI* and PDI at 18 months in infants fed as sole diets BBM or PTF (three centre study) compared with outcome in infants fed TF versus PTF (two centre study). Data are mean (SE)

			Advantage for PTF (95% CI)
(A) All infants			
MDI			
Three centre study	BBM n=62 94.8 (2.1)	PTF n=52 95.3 (2.7)	0.5 (-6.2 to 7.1)
Two centre study	TF n=55 92.6 (2.7)	PTF n=59 98.6 (2.4)	6.0 (-1.2 to 13.2)
Advantage for BBM over TF (95% CI) 2.1 (-4.4 to 8.7)			
PDI			
Three centre study	BBM n=62 93.0 (1.8)	PTF n=52 94.2 (2.2)	1.2 (-4.4 to 6.8)
Two centre study	TF n=55 84.2 (2.1)	PTF n=59 98.9 (2.2)	14.7 (8.7 to 20.7)†
Advantage for BBM over TF (95% CI) 8.8 (3.3 to 14.3)§			
(B) Infants born small for gestational age			
MDI			
Three centre study	BBM n=23 95.5 (3.2)	PTF n=19 95.5 (4.5)	0.0 (-10.7 to 10.7)
Two centre study	TF n=21 90.1 (4.0)	PTF n=21 101.6 (4.1)	11.5** (0.1 to 22.9)
Advantage for BBM over TF (95% CI) 5.4 (-4.7 to 15.5)			
PDI			
Three centre study	BBM n=23 95.5 (2.8)	PTF n=19 93.9 (4.3)	-1.6 (-11.4 to 8.2)
Two centre study	TF n=21 81.2 (3.7)	PTF n=21 104.1 (2.3)	22.9† (14.2 to 31.6)
Advantage for BBM over TF (95% CI) 14.3** (5.2 to 23.4)			

§p<0.02, **p<0.01, †p<0.001. *Excluding cerebral palsy. BBM=banked (donated) breast milk; PTF=preterm formula; TF=standard term formula.

formula; thus any outcome effects relating to the unique properties of breast milk compared to formula might emerge. Our analyses were confined to infants fed donor milk or term formula as sole diets (trial A) to avoid the confounding effects of human milk usage in both comparison groups when donor milk or formula was used as a maternal milk supplement.

In table 5, infants fed banked milk versus preterm formula as sole diets are contrasted with those from our previous two centre study,¹ which compared term formula versus preterm formula as sole diets. In the latter two centre study there was a substantial (14.7 point) advantage in psychomotor development for preterm formula over term formula, and in the small for gestational age subgroup the advantages for preterm formula in MDI and PDI were 11.5 and 22.9 points. These highly significant differences in outcome between the term and preterm formula fed groups contrast with the relative lack of outcome differences after breast milk versus preterm formula feeding, as described above.

In the non-randomised comparison of banked milk (three centre study) and term formula (two centre study) there were significant advantages for the banked breast milk fed group in later motor development of 8.8 points overall and of 14.4 points in the small for gestational age subgroup (table 5). The corresponding 2.1 and 5.4 advantages for donor breast milk over term formula in mental development did not reach statistical significance, though detection of a 5 point difference in mental development between groups would

have required a substantially larger sample size.

Discussion

In a previous two centre study, we found that premature babies who were fed for an average of one month on a standard term formula, showed a major reduction in developmental attainment at 18 months post-term, compared with that in infants fed over the same period on a preterm formula designed to meet the calculated increased nutrient needs of this population.¹ It was therefore surprising to find in the large prospective randomised study reported here, that preterm babies fed during their early weeks on unsupplemented bank donated drip breast milk, a diet particularly low in nutrient and energy content in relation to the needs of preterm infants, were not disadvantaged in their Bayley developmental indices at 18 months post-term when compared with those fed the nutrient enriched preterm infant formula. These findings raised the hypothesis that breast milk might confer benefits for later development that offset any potentially deleterious effects of its low nutrient content. If so, these data would have potentially important biological and clinical implications.

In order to test this hypothesis further, we elected to compare babies fed on banked donor breast milk in the current study with those fed on a standard term formula from our previous two centre study. This comparison is not a randomised one but is nevertheless justified as the same preterm formula was used in both studies, acting as an 'internal standard'. The value of this comparison is that because term formulas are modelled on breast milk composition, the donor breast milk and term formula should have relatively similar nutrient contents allowing any potentially beneficial non-nutrient or specific nutrient effects unique to breast milk to emerge. In fact, the mature donated drip breast milk had lower contents of a number of nutrients than those in the standard formula; for instance, protein and energy contents of the formula were 1.45 g/100 ml and 284.2 kJ (68 kcal)/100 ml compared with 1.1 g/100 ml and <209.0 kJ (50 kcal)/100 ml in the donor milk, the latter representing an extreme that would now, in our view, be unacceptably low for current practice.⁷ Yet, despite this, infants fed solely on unsupplemented donor breast milk rather than term formula, had significantly and substantially higher psychomotor developmental scores, with a 9 point advantage overall and a 14 point advantage (nearly 1 SD) in the vulnerable subgroup of small for gestational age infants. These data therefore support the hypothesis that breast milk promotes long term neurodevelopment in children born preterm.

Furthermore the advantages we report for donor breast milk over term formula are likely to be an underestimate. Infants in our current three centre study (that include the donor milk fed group) had lower developmental scores in

general than those in the previously reported two centre study. This is apparent from the performance of the preterm formula fed group (table 5), the internal standard for the two randomised studies. Thus when this small interstudy difference is adjusted for, the overall advantage in PDI rises to 14 (95% CI 5 to 22) points and the trend to an advantage in MDI rises to 5 (–5 to 15) points. The more substantial developmental advantages for breast milk fed infants in the small for gestational age subgroup reported here are, for the same reason, likely to be conservative.

During the early 1980s donated drip breast milk was in widespread use in neonatal units in Britain. Drip breast milk, like foremilk, has a very low energy content. It is now recognised that such milk requires fortification with protein, energy, and other nutrients to meet modern recommendations for intake in premature babies.⁷ The observation in this study that babies fed unsupplemented banked milk fared so well developmentally could imply that banked milk has specific factors in it that promote neurodevelopment and ameliorate any detrimental effects of its low nutrient content. Candidate factors in breast milk for such an effect include long chain ω -6 and ω -3 fatty acids, for instance arachidonic and docosahexanoic acid, found in abundance in brain and retina,⁸ and the many hormones and growth factors in breast milk with hitherto undefined roles.⁹

In two previous publications we have explored the possibility that human milk could indeed have a long term beneficial effect on development at 18 months¹⁰ and IQ at 7.5–8 years¹¹ in infants born preterm. In these studies we found that preterm infants fed on their own mother's milk had higher test scores than those who were not, even after adjusting for a wide range of social and demographic factors that could confound this comparison. Of critical importance, however, these previous studies and those of other investigators^{12–16} involve non-randomised comparisons between breast milk and formula fed infants that may be significantly flawed by the major sociobiological differences between these groups, notably the higher socioeconomic status, higher educational level, and more marked positive health behaviour in the population who choose to breast feed. The major advantage of this study is that these sociobiological differences do not apply here as the comparison of banked milk with either preterm or term formula can be made in infants whose mothers have all chosen not to provide breast milk.

In our nine month pilot follow up of the three centre study cohort (table 1), we showed that those fed in their early weeks on preterm formula rather than banked milk, had a significant benefit in adaptive, fine motor, language and personal social skills, and in overall developmental quotient.³ The lack of difference in developmental outcome between these same diet groups reported here at 18 months may well represent recovery with time from the early nutritional effects. We have shown previously that the effects of early diet are most

seen in infants born small for gestational age and in boys.^{1 3 17} In this study there was a trend to a better outcome for motor development in boys fed preterm formula rather than banked milk: a difference of 8 points significant at the 6% level. In small for gestational age infants, those fed preterm formula rather than donor milk also had a small, non-significant advantage in developmental outcome. Perhaps these results reflect a minor residual developmental disadvantage for donor milk at 18 months in high risk groups, though it is possible that these non-significant trends were due to chance.

In summary, we show here that children fed unsupplemented donor milk are substantially advantaged in their development at 18 months compared with those fed a standard term formula and were not disadvantaged compared with those fed a nutrient enriched preterm formula. The positive advantage we have seen previously¹¹ in children who were fed their *own* mother's expressed breast milk versus preterm formula, even after adjusting for social and educational differences between groups, might reflect residual sociobiological confounding or, alternatively, that mothers' own early preterm milk has an even more beneficial effect on development than the donor milk we used on account of its higher nutrient content (for example a mean protein and energy content of 1.5 g/100 ml and 259.2 kJ (62 kcal)/100 ml compared with 1.1 g/100 ml and 209.0 kJ (<50 kcal)/100 ml in donor milk).

Collectively, these findings suggest that human milk has a beneficial effect on development. However, they suggest that developmental outcome benefit is also achieved by meeting these infants special early nutrient needs, and this is further emphasised by our previous two centre randomised trial showing infants fed the standard term formula performed substantially less well at 18 months than those fed the nutrient enriched preterm formula.

Our findings have implications for the nutritional care of preterm infants. If, as suggested, human milk and a nutrient enriched diet both have independent, perhaps additive, effects on later development in infants born preterm, it would be logical to combine both benefits by using nutrient fortified human milk. Several multinutrient fortifiers have been designed to be added to breast milk, and further work on these products is warranted. Preterm formulas will continue to have an important place when insufficient breast milk is available, whereas standard term formulas neither provide the apparent benefits of breast milk nor the nutrient needs of preterm infants and are associated with the worst developmental outcome of all the commonly available enteral diets. This study also provides a new line of evidence that strongly supports the more general thesis that breast milk can exert a favourable effect on neurodevelopment, as our data are not subject to the inevitable social and demographic biases found in most epidemiological studies on preterm and full term infants that address this challenging biological issue.

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