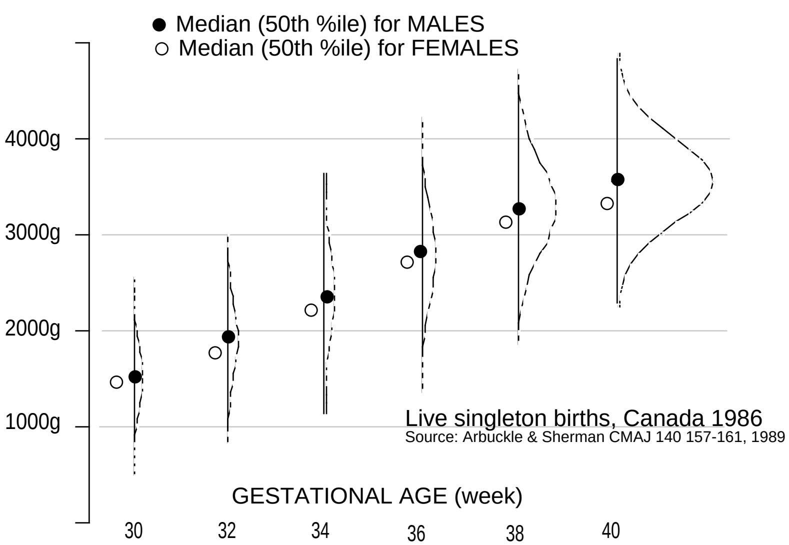
Multiple Linear Regression

references: A&B 10.1; M&M Chapter 9.2

Age. wk	MALES Tot. N.	%-ile; weight,g 10th	50th	90th	FEMALES Tot. No.	%-ile; weight,g 10th	50th	90th
25	*100*	651	810	950	*73*	604	750	924
30	*257*	1 156	1 530	2 214	*216*	1 040	1 485	2 001
31								
..								
35	*1 840*	2 060	2 570	3 140	*1 454*	1 950	2 460	3 040
36								
..								
39								
40	*68 102*	3 020	3 570	4 160	*67 149*	2 900	3 430	4 000
41								
42	*10 309*	3 200	3 770	4 390	*9 636*	3 060	3 610	4 190

BIRTH WEIGHT (DISTRIBUTION) MALES
BIRTH WEIGHT (MEDIAN) FEMALES



Multiple Linear Regression

(two or more X's)

Equation

- $\mu_{Y|X_1 \text{ and } X_2} = \alpha + \beta_1 X_1 + \beta_2 X_2$

Meaning of slope parameters β_1 and β_2 :

β_1 represents the increase/decrease in $\mu_{Y|X_1 \& X_2}$ for every unit increase in x_1 while keeping x_2 "constant" and vice versa

E.g. $\mu_{\text{weight | Age and Gender}}$

= 1500g

+ 100g if male

+ 170g/week × (# weeks over 30)

E.g. $\mu_{\text{weight | Age, Altitude and Gender}}$

= 1500g

+ 100g if male

+ 170g/week × (# weeks over 30)

- 100g/1000m × (every 1000m > sea level)

Multiple regression as a sequence of simple regressions

E.g.: Regression of Weight(lb) on age(yrs) and Height(in) in 11-16 year olds

3 SIMPLE REGRESSIONS

```
(1)   WEIGHT =  -105.378 + 3.363 * HEIGHT + RESWT

(2)   AGE    =    -0.789 + 0.226 * HEIGHT + RESAGE , so that

(2')  RESAGE =    AGE - {  -0.789 + 0.226 * HEIGHT }

(3)   RESWT  =    -0.023 + 2.822 * RESAGE + RESIDUAL (variance 187.02)
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Substitute (2') into (3) to get

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(4)   RESWT  =    -0.02337 + 2.822 * { AGE - {-0.789 + 0.226 * HEIGHT } }
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and then (4) into (1) to get ...

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(5)   WEIGHT =  -105.378 + 3.363 * HEIGHT +
                  -0.023 + 2.822 * { AGE - {-0.789 + 0.226 * HEIGHT } }

                + RESIDUAL (variance 187.02)


             =  -105.378  +                 3.363 * HEIGHT   + 2.822 * AGE
                  -0.023  +        -2.822 * 0.226 * HEIGHT   +
                2.822 * {-{-0.789}}

                + RESIDUAL (variance 187.02)

             =  -103.174  +                 2.725 * HEIGHT   + 2.822 * AGE

              + RESIDUAL (variance 187.02)
```

This is numerically equivalent (apart from some rounding errors introduced by not using enough decimal places) to performing a multiple linear regression:

```
DEP VAR:  WEIGHT      N:     233  MULTIPLE R: 0.703  SQUARED MULTIPLE R: 0.494
ADJUSTED SQUARED MULTIPLE R: 0.490    STANDARD ERROR OF ESTIMATE:     13.70530

VARIABLE  COEFFICIENT    STD ERROR     STD COEF TOLERANCE    T   P(2 TAIL)

CONSTANT   -103.14981     14.19908      0.00000    .      -7.26454  0.00000
HEIGHT        2.72315      0.29462      0.55333   0.61379  9.24288  0.00000
AGE           2.82220      0.80680      0.20941   0.61379  3.49802  0.00056

                       ANALYSIS OF VARIANCE

SOURCE       SUM-OF-SQUARES   DF  MEAN-SQUARE     F-RATIO       P
REGRESSION     42186.19420     2  21093.09710   112.29578     0.00000
RESIDUAL       43202.08906   230    187.83517
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Case Study 1. multiple regression as "poor-person's substitute for 'matching' "

BREAST MILK AND SUBSEQUENT INTELLIGENCE QUOTIENT
IN CHILDREN BORN PRETERM

There is considerable controversy over whether nutrition in early life has a long-term influence on neurodevelopment. We have shown previously that, in preterm infants, mother's choice to breast milk was associated with higher developmental scores at 18 months. We now report data on intelligence quotient (IQ) in the same children seen at 7.5 - 8 years.

IQ was assessed in 300 children with an abbreviated version of the Weschler Intelligence Scale for Children (revised Anglicised). Children who had consumed mother's milk in early weeks of life had a significantly higher IQ at 7.5 - 8 years than did those who received no maternal milk. An 8.3 point advantage (over half a standard deviation) in IQ remained even after adjustment for differences between groups in mother's education and social class (p < 0.0001). This advantage was associated with being fed mother's milk by tube rather than with the process of breastfeeding. There was a dose- response relation between the proportion of mother's milk in the diet and subsequent IQ. Children whose mothers chose to provide milk but failed to do so had the same IQ as those whose mothers elected not to provide breast milk.

Although these results could be explained by differences between groups in parenting skills or genetic potential (even after adjustment for social and educational factors), our data point to a beneficial effect of human milk on neuro-development.

(A. Lucas, R. Morley, T.J. Cole, G. Lister, C. Leeson-PayneLancet 1992; 339: 261-64.)

TABLE I - CHARACTERISTICS OF STUDY POPULATION

Characteristics	No mother's milk (group I) (n = 90)		Mother's milk (group II) (n = 210)	
Mean (SEM) birthweight (g)	1420	(30)	1440	(20)
Mean (SEM) gestation (wk)	31.4	(0.3)	31.4	(0.2)
% males (no)	42	(38)	55	(116)*
Days in study:median (1/4 s)	30	(22,45)	28	(20,40)
Days to full enteral feeds: median (quartiles)	8	(6,11)	7	(6,9)
% ventilated > 5 days (no)	12	(11)	12	(26)
% in social class I and II (no)	11	(10)	30	(63)+
% mothers with higher educational status (no)@	24	(22)	52	(109)+

*p < 0.05. +p < 0.001 @ GCE O levels or above (see text).

Table II - IQ AT 7.5 - 9 YEARS IN TWO GROUPS

Abbreviated WISC-R

Mean (SEM) scores

	Group I	Group II	Advantage for group II babies (95% CI)
Verbal scale	92.0(2.0)	102.1(1.3)	10.1 (4.7, 15.5)*
Performance scale	93.2(1.7)	103.3(1.2)	10.1 (6.0, 14.2)*
Overall IQ	92.8(1.6)	103-0(1.2)	10.2 (6.3, 14.1)*

*p < 0.001, group 1 vs group II CI = confidence interval

Children and methods

Babies under 1850 g at birth, admitted to the special-care baby units in Cambridge, Ipswich, Kings Lynn, Norwich, and Sheffield between January, 1982, and March, 1985, were entered into four parallel trials of preterm infant feeding, details of which are published elsewhere. Mothers chose whether or not to provide breast milk for their infant within 72 hours of delivery. Here, in an interim analysis, we have examined how mother's milk feeding related to IQ at 7~8 years. We collected information about family structure, social class, mother's education, pregnancy, labour, delivery, and the neonatal period.

Social class was coded with the Registrar General's classification based on occupation of the income-providing parent or on father's occupation if both parents were earning, and with class III subdivided into non-manual and manual. Mother's education was coded as follows: no educational qualifications (1); up to four passes for the certificate of secondary education (CSE) (2); any general certificate of education (GCE) at ordinary (O) level or more than four CSEs (3); any GCE at advanced (A) level (4); and degree or higher professional qualification (5). Birth rank was defined as the child's birth order in the surviving children of the family, with infants from multiple births being assigned equal rank. Mode of delivery was categorised as caesarean or vaginal.

Overall, 300 children were studied, representing a 96% followup rate of 313 survivors. Those not seen were principally children of US Air Force personnel who had resumed to the USA; when these are excluded, follow-up rate of survivors was 99% (300/303). We assessed IQ with the Weschler Intelligence Scale for Children (revised Anglicised version: WISC-R UK). Because of the extensive additional data collected at this follow-up, we had to use one of the abbreviated versions of the WISC-R, with five subtests—namely, similarities, arithmetic and vocabulary (verbal scale), and block design and object assembly (performance scale). The overall WISC-R IQ assessed from the five subscales has a correlation coefficient with the full scale WISC-R IQ of over 0.96. 13

Statistical analyses used were Student's t test, chi-square test, and multiple regression. The variables used in the regression model (see below) were those that we had shown previously to be related to mental development at 18 months that could potentially confound the relation between early dietary choice and later neurodevelopmental outcome. Social class and mother's education were grouped to give a linear relation with the WISC scores.

Results

Demographic characteristics of the children whose mothers chose not to provide breast milk (group I) and those who chose to do so (group II) are shown in table l. There were more baby boys in group II than in group I, as shown previously. As expected, there were more mothers with degrees/higher professional qualifications and families in social class I or II in group II. The two groups were well matched with respect to birthweight, gestation, need for ventilation, days in the study (days until discharge or attainment of 2000 g body weight), and time to establish full enteral feeds. The groups were also matched for the use of diets other than breast milk: the proportions fed on preterm formula, mature pasteurised donor drip breast milk, and term formula were 51% (n =46), 31% (28), and 18% (16), respectively, in group I infants and 50% (105), 31% (65), and 19% (40) in group II infants, who were given these supplements in volumes according to mother's success at producing mill`. The distribution of diets between the two groups was similar because of the experimental design in the randomised part of the trials;'°" this similarity would reduce to a minimum any differences in outcome between groups I and II that could be accounted for by diets other than mother's milk. (Performance of children previously fed on donor breast milk will be published elsewhere.)

Table II shows the unadjusted verbal, performance, and IQ scores in children in the two groups. Group II children had a highly significant advantage over group I children. Babies in group II were then divided into those mothers did (193) or did not (17) succeed in providing any breast milk. The mean IQ of children in these two subsets were compared with that of children in group I. children whose mothers chose to provide breast milk, but failed to do so (group IIa), had subsequent IQ scores similar to group I children, and in both instances these scores were significantly lower than in babies whose mothers were successful in providing their milk (group IIb).

Group	*Mean (SE) IQ*
I (n = 90)	92 8 (1.6)
Ila (n = 17)	94.8 (4.6)
lIb (n = 193)	103.7 (1.1)

Group I vs Group IIa p=NS; Group I vs Group IIb p<0.001; Group IIa vs Group IIb p<0.02.

There was no significant difference in the proportion of Group IIa and group IIb mothers in social class I/II (31% [60/193] vs 24% [4/17] compared with 10% in group I). Similarly, there was no difference in the proportion of such mothers who had at least some GCE O levels (52% [101/193] vs 41% [7/17], compared with 24% in group I).

Regression analysis was used to adjust for confounding factors. As independent variables, we used the factors that at our 18 months follow-up were related to developmental scores that might confound the comparison of WISC IQ scores between groups. These factors included social class and mother's education, birthweight, gestational age, birth rank, days of ventilation required, the child's sex, and mother's age. Of these, only social class, mother's education, days of ventilation, and infant's sex were related to later IQ (see below). After adjustment for these factors there were highly significant advantages for infants in group II with respect to verbal scale, performance scale, and overall IQ (table II). These advantages were slightly greater for infants in group II who actually received mother's milk, with an 8.3 point advantage in overall IQ (table III). Of the five factors that were related to IQ at 7.5 to 8 years, early mother's milk feeding was the most significant (table IV).

TABLE III—ADJUSTED ADVANTAGE IN WISC IQ SCORES FOR GROUP II BABIES

Whole group*	**Advantage**	**95% CI**
Verbal score	**7.7**	**3.3, 12 1 †**
Performance scale	**7.9**	**3.9, 11.9 ††**
Overall IQ	**7.6**	**4.0, 11 2 ††**
Successful §		
Verbal scale	**8.9**	**4.7, 13.1 †**
Performance scale	**8.1**	**4.3, 11.9 ††**
Overall IQ	**8.3**	**4.9, 11.7 ††**

*All 210 babies in group II (compared with 90 in group I)
† p < 0 001, †† p < 0 0001.
§ 193 babies from group II who received breast milk (compared with infants from group I. plus those from group II who received no breast milk. n = 107)

TABLE IV—FACTORS RELATING TO IQ AT 7-8 YEARS

factor	Increase in IQ	95% CI	p value
Received mother's milk	**8.3**	**4.9, 11.7**	**<0.0001**
Social class	**–3.5/class***	**-1 5, -5.5**	**0.0004**
Mother's education	**2.0/group†**	**0.5, 3.5**	**0.01**
Female sex	**4.2**	**1.0, 7.4**	**0.01**
Days of ventilation	**–2.6/week**	**–3.7, –1.5**	**0.02**

*Registrar General's social class recorded as 4 categories: social class I or I, social class III non-manual, social class III manual, social class IV or V.
†Mother's education coded on a 5-point scale from 1 (no educational qualifications) to 5 (degree or higher professional qualification).
CI - confidence interval.

Subsidiary analyses

To explore further a dose-response relation between mother's milk and subsequent advantage with respect to IQ, a separate analysis was done on babies whose mothers chose to provide their milk. When the proportion of the diet consumed as mother's milk during hospital stay was regressed against IQ, while adjusting for the potentially confounding factors listed above, there was a significant linear relation ($p < 0.05$) - a finding that was greatest for the verbal scale ($p<0.01$), with a 9.0 point advantage (95% confidence interval [CI] 6.6, 12.4) for babies consuming 100% mother's milk over those consuming none. Nevertheless, many clinical factors could have influenced the proportion or volume of mother's milk consumed, and it is not certain that these could be adjusted for adequately; hence, precise qualification of the dose-response relation would be unrealistic.

In hospital, infants who were given breast milk were fed principally by nasogastric tube. However, a small proportion of the infants (35/300) went home breastfeeding. Could the observed advantage in IQ for the infants fed breast milk have been related to breastfeeding (and associated parental behaviours) rather than to the breast milk itself? In a attempt to address this question we did a further regression analysis comparing children in groups I and II, but excluding the 35 children in group II who were still breastfeeding on discharge. The children in group II continued to have a highly significant advantage of 7.5 points (95% CI 3.5, 11.5; $p < 0.001$).

We explored the possibility that the developmental advantage seen with mother's milk feeding might be different within individual social class or maternal education bands by testing for interactions between diet and social class or mother's education. Such interactions were not found. For instance, there was no evidence that high social class or education diminished the relation between breastfeeding and IQ.

Discussion

We have shown that preterm babies whose mothers provided breast milk had a substantial advantage in subsequent IQ at 70 years over those who did not receive mother's milk, even after adjustment for a wide range of factors that might have confounded this comparison. Indeed, consumption of mother's milk was more significantly related to later IQ than to any other factor. Furthermore, among babies whose mothers chose to provide breast milk, there was a significant dose-response relation between the proportion of mother's milk consumed and later IQ, which persisted after adjustment for potential confounding.

Could there be other reasons for our finding? We acknowledge that social class and mother's education are factors that may not be satisfactory measures of parenting skills and positive health behaviour. Such parental attributes could have been associated with the mother's choice to provide breast milk and might also have contributed to or perhaps accounted for the advantage in IQ that we observed. If this had been so, however, our data would show that for any social class or level of maternal education, choosing to provide breast milk was a proxy for parental behaviours that conferred a benefit of more than half a standard deviation of IQ (SD 15-16 points). Therefore, we might have expected to find an association between mothers who chose to provide their milk but failed to do so and at least some benefit in subsequent IQ in the child. On the contrary, we found that the IQ of children in this category was virtually identical to that in children whose mothers chose not to provide milk at all. Additionally, our data did not support the argument that the observed advantage in IQ for children whose mothers chose to provide breast milk was due to the interaction between mother and child fostered by the process of suckling, since this IQ advantage was seen even in babies who only received mothers milk by nasogastric tube while they were in hospital.

We cannot exclude the possibility that our findings can still be explained by differences in parental behaviour or genetic potential between the groups, even after adjustment for social and educational factors. Nevertheless, our data are also consistent with the hypothesis that breast milk could have a beneficial effect on neurodevelopment. It is noteworthy that the benefit that we have seen in the present study is larger than that observed in studies of children born at term. Mothers who provided breast milk for our premature babies might be regarded as an especially motivated and tenacious subgroup, conferring a greater advantage to their children. However, this notion, which has been suggested previously, is not consistent with our finding that the overall proportion of mothers (around 70%) who planned to provide their milk 48-72 hours after delivery (as stipulated in this study) was similar to our local figures (unpublished) for breastfeeding in term infants from 48- 72 hours onwards. Alternatively, preterm babies may be especially sensitive to their early nutrition, since we found previously that meeting their special nutrient needs with preterm rather than standard formula led to a major neurodevelopmental benefit. Perhaps inclusion of maternal milk in the diet of this sensitive group confers substantial, additional advantage for cognitive development.

Various criteria that support the hypothesised causal role of breast milk in promoting neurodevelopment have been satisfied: these include a strong correlation after adjustment for confounding factors, consistency of the observation in several studies conducted in term and preterm infants under different test conditions, a temporal relation, and, as we have shown here, evidence of a dose-response relation. It is important also that this hypothesis should be supported by experimental evidence; moreover, it should be plausible and consistent with the known biology of breast milk. We now have some experimental evidence (unpublished) from our randomised trials suggesting that the shortfall in developmental scores of preterm infants at 18 months who were fed term rather than preterm formula was not nearly so pronounced when they were fed donor breast milk rather than preterm formula. This finding suggests that human milk might contain factors that compensate for its poor (for preterm infants) nutrient density. With regard to the biological plausibility of the hypothesis, human milk contains various factors that might affect nervous system development. For example, long-chain lipids, which are not present in formulas, are important for the structural development of the nervous system (eg, docosahexanoic acid [22:6w-3, which is accumulated in large amounts in the developing brain and retina). Human milk also contains numerous hormones and trophic factors that might influence brain growth and maturation. Work is needed to explore further whether the advantage in intelligence seen with human milk feeding is due to coincidental parenting or genetic factors or, rather, to factors in human milk itself, which would have important implications for neonatal care and for infant nutritional policy.

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