Breast-feeding and cognitive development: a meta-analysis[1–3]

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ABSTRACT

Background: Although the results of many clinical studies suggest that breast-fed children score higher on tests of cognitive function than do formula-fed children, some investigators have suggested that these differences are related to confounding covariables such as socioeconomic status or maternal education.

Objective: Our objective was to conduct a meta-analysis of observed differences in cognitive development between breast-fed and formula-fed children.

Design: In this meta-analysis we defined the effect estimate as the mean difference in cognitive function between breast-fed and formula-fed groups and calculated average effects using fixed-effects and random-effects models.

Results: Of 20 studies meeting initial inclusion criteria, 11 studies controlled for ≥5 covariates and presented unadjusted and adjusted results. An unadjusted benefit of 5.32 (95% CI: 4.51, 6.14) points in cognitive function was observed for breast-fed compared with formula-fed children. After adjustment for covariates, the increment in cognitive function was 3.16 (95% CI: 2.35, 3.98) points. This adjusted difference was significant and homogeneous. Significantly higher levels of cognitive function were seen in breast-fed than in formula-fed children at 6–23 mo of age and these differences were stable across successive ages. Low-birth-weight infants showed larger differences (5.18 points; 95% CI: 3.59, 6.77) than did normal-birth-weight infants (2.66 points; 95% CI: 2.15, 3.17) suggesting that premature infants derive more benefits in cognitive development from breast milk than do full-term infants. Finally, the cognitive developmental benefits of breast-feeding increased with duration.

Conclusion: This meta-analysis indicated that, after adjustment for appropriate key cofactors, breast-feeding was associated with significantly higher scores for cognitive development than was formula feeding. *Am J Clin Nutr* 1999;70:525–35.

KEY WORDS Breast-feeding, formula feeding, infant nutrition, premature infants, docosahexaenoic acid, arachidonic acid, long-chain fatty acids, intelligence quotient, cognitive development

INTRODUCTION

Since the report of Hoefer and Hardy in 1929 (1), many studies have reported that children who are breast-fed score higher on tests of cognitive development than do children who are formula fed (2–19). Although many investigators report that differences in cognitive development persist after adjustment for important covariates (3–8, 11–13, 16, 17), other investigators (9, 18, 19) suggest that these differences are not significant after appropriate covariate adjustment.

The cognitive development of an infant is a complex process influenced by multiple genetic and environmental factors that interact with one another (20). Because randomized controlled trials are not feasible in this area, observational cohort and case-control studies have been performed. Some studies do not address questions of exclusivity or duration of breast-feeding, making the dose-response effects difficult to assess (20). The method of infant feeding is correlated with socioeconomic factors such as smoking, parental intelligence and educational attainment, socioeconomic status, family size, birth order, and population density (20). This meta-analysis was performed to more accurately quantitate differences in cognitive development between breast-fed and formula-fed children with and without adjustment for covariates.

METHODS

Identification of studies

We defined 3 initial inclusion criteria in evaluating the literature for the comparative effects of breast-feeding and formula feeding on cognitive development: *1*) studies that compared subjects who were predominantly breast-fed with subjects who were predominantly formula fed, *2*) the primary outcome measure was a widely applied test of cognitive development or ability yielding a single score for purposes of comparison, and *3*) subjects were tested between infancy and adolescence.

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A search of MEDLINE for the period from 1966 to June 1996 identified candidate studies. Additional studies published during this period or before 1966 were identified by using the "ancestry approach" (21) by consulting reference lists from single studies and pertinent literature reviews.

Twenty separate published reports (1–19, 22) met the initial criteria. Three reports were excluded from all meta-analysis calculations because insufficient data were reported to calculate effect estimates (18, 22) or because the study design was not comparable with that of others (14). Three additional studies were excluded from those meta-analyses that calculated absolute test score differences because insufficient information was reported to derive this effect estimate (2, 6, 10). Of the remaining 14 reports, 11 studies (3–5, 7, 8, 11–13, 16, 17, 19) reported both unadjusted and covariate-adjusted findings comparing cognitive development of breast-fed and formula-fed subjects (ie, "matched" unadjusted and adjusted results). We made the meta-analysis calculations separately for the total sample of observations and the subset of 11 matched studies. We present results from the matched subset to maximize statistical control and interpretability of covariate-adjusted findings. However, there were no material differences between these findings and those obtained from the total sample of observations (these results are available from the authors).

Covariate-adjusted effects

Our review identified 15 key cofactors that would be desirable to control for when evaluating the relation between breast-feeding and cognitive development: duration of breast-feeding, sex, maternal smoking history, maternal age, maternal intelligence, maternal education, maternal training, paternal education, race or ethnicity, socioeconomic status, family size, birth order, birth weight, gestational age, and childhood experiences. Studies were considered covariate-adjusted if they controlled statistically for a minimum of 5 characteristics in models to estimate effects of breast-feeding compared with those of formula feeding on cognitive development. Sixteen studies met this criterion. Pooled estimates of effect were separately calculated for unadjusted and adjusted results.

Additional classification of studies

Calculation of effect estimates from 11 studies that reported absolute test score differences in a comparable metric yielded a total of 32 unadjusted and 30 adjusted effect estimates. Sometimes, more than one effect estimate was derived from a single publication because it reported results of multiple general tests of cognitive development or results of testing at more than one age. Study results were additionally classified into 2 subgroupings within unadjusted and adjusted categories as follows: *1*) matched disaggregated observations (n = 28 unadjusted and 28 adjusted observations) consisted of all observations from the subset of studies that reported both unadjusted and adjusted (matched) results for the same sample; and *2*) matched composite observations (n = 11 unadjusted and 11 adjusted observations) consisted of weighted aggregates of all observations within a single study, yielding a single composite observation for each study. The latter subcategory was established to reduce potential estimation problems resulting from interdependency between multiple alternative or prospective test results reported in a single study (23). In some cases, a single sample generated more than one published report; composite estimates were not calculated across publications because in these instances different sample subsets were used. Findings for both subgroups are presented in tables as a cross check for sensitivity of results.

Meta-analysis

All included studies were observational in design because it was rarely possible to randomly assign infants to breast- or formula-feeding regimens. Meta-analysis of observational studies is appropriate in the absence of randomized studies (24–26) but careful attention must be given to choosing statistical models used to pool results, to investigating the heterogeneity between results of studies, and to evaluating potential confounding factors (27–29).

In our study, estimates of the average effect of breast-feeding compared with formula feeding on cognitive development, and 95% CIs for this value, were calculated by using both fixed effects and random-effects model assumptions (30); homogeneity of results across studies was evaluated before and after adjustment for potential covariates. Fixed-effects models assume that each study estimates the same true population value for the effect of interest, and thus that differences between observed results of studies can be fully accounted for by sampling variation. The appropriateness of this assumption can be formally evaluated by tests of homogeneity of results between studies (29). If significant heterogeneity between outcomes exists in initial analyses (ie, differences in study findings are not fully explained by sampling variation), the contribution of particular study characteristics (eg, presence or absence of statistical control for confounders) to variation between results may be investigated. Random-effects models assume that a distribution of population effects exists and is generated by a distribution of possible study effect situations. Thus, outcomes of studies may differ both because of sampling variation and true differences in effects.

Fixed- and random-effects models can be appropriately applied to pooling of data to evaluate the sensitivity of results to differing model assumptions (31). In tables we reported primarily fixed-effects estimates because most of the pooled results obtained were statistically homogeneous. For sensitivity analysis, we also reported results of random-effects models for principal analyses in text. All analyses were conducted by using SAS-PC version 6.11 (SAS Institute, Inc, Cary, NC) with the formulas provided and by adapting the template code provided by Shadish and Haddock (32).

For each study, summary results of all reported tests and additional relevant study attributes were recorded, coded, and tabulated for analysis. The effect estimate was defined as the absolute mean difference in cognitive developmental test score between breast-fed and formula-fed groups (breast-fed minus formula fed) for meta-analysis of results of matched disaggregated (28 unadjusted and 28 adjusted observations) and matched composite (11 unadjusted and 11 adjusted observations) categories. These comparisons were confined to combinations of test results providing a single score for cognitive development (or intelligence quotient; IQ) referenced to the norm to provide a mean of 100 points and an SD of 10–20 points (33). A second comparison estimated the weighted average difference between unadjusted and adjusted results by calculating the difference between these values for each observation (adjusted minus unadjusted result) and combining differences across observations. For meta-analysis of the total sample (32 unadjusted and 30 adjusted observations) the effect estimate was defined as the standardized mean difference (34) between breast-fed and formula-fed groups (breast-fed minus formula-fed means divided by the pooled SD of the estimate) to facilitate comparison of results across disparate test score metrics.

Other variables

Additional analyses estimated effects of breast-feeding compared with those of formula feeding on cognitive development after disaggregating sample results by age category, birth weight, and duration of breast-feeding exposure.

Age

We examined pooled effect estimates separately across different age classifications both to evaluate the stability of effects across developmental periods and because appropriate developmental testing during childhood is age dependent. We defined 4 age categories for separate pooling and presentation of results, based jointly on recommended age-appropriate boundaries for tests used in a sample of studies and on the available distribution of ages at assessment included in our final sample. These categories were 6–23 mo, 2–5 y, 6–9 y, and 10–15 y. We also estimated results by using more specific age categories but did not observe significant differences in findings.

Birth weight

Observations were placed in low- or normal birth weight categories. Results for low-birth-weight subjects were pooled across the 6 adjusted observations available in the matched disaggregated data subset. The definitions of authors were used to identify low birth weights as defined in **Table 1**; however, the study of Pollock (9) was not included in these analyses. Most studies presented full cohort results for subjects without further disaggregation by birth weight. Thus, in aggregate, the comparison category of 24 general observations was considered to be of normal birth weight.

Duration

Greater duration of breast-feeding may enhance its effect on cognitive development (1). To evaluate this, we pooled results separately across 5 breast-feeding duration intervals: 4–7, 8–11, 12–19, 20–27, and ≥28 wk. To obtain a substantial distribution of estimates across several exposure categories, both covariate-adjusted and unadjusted, duration-based estimates were included. Before results were combined, unadjusted values, were adjusted by subtracting the best available estimate of difference between adjusted and unadjusted values, which was defined as either the value for the effect of cofactors obtained for the overall comparison of adjusted and unadjusted results for the study (range: 2.09–2.53 points), or, if this value was unavailable, the weighted average covariate-adjustment effect obtained across all observations (because of heterogeneity, the random-effects average of 2.41 points was subtracted). After adjustment, results were pooled separately for each duration category.

RESULTS

Attributes of studies

The summary characteristics of 20 studies meeting initial criteria for inclusion are listed in Table 1. In some cases data from the same parent sample were used in ≥2 reports. These studies were included separately if they presented test results from new measurements of subjects or reported new results from a specific subset of the original sample. Most studies were conducted in the United Kingdom (10 reports) and the United States (5 reports), with others from Australia, Germany, New Zealand, and Spain. All studies included males and females. Although sex was frequently included as a covariate in analyses, insufficient information was reported to provide reliable estimates separately for males and females. The age at which cognitive evaluation took place ranged from 6 mo to 16 y. Five studies reported results separately for low-birth-weight children. Of the 20 studies, 18 used prospective designs.

Tests of cognitive development that were identified as appropriate for inclusion in the meta-analysis are also shown in Table 1. Fourteen distinct assessment procedures designed to provide an estimate of overall cognitive ability were used. The most commonly used measures were the Bayley Mental Development Index (12 observations), the Peabody Picture Vocabulary Test (6 observations), the General Cognitive Index of the McCarthy Scales of Children's Abilities (5 observations), the Wechsler Child Intelligence Scale (4 observations), and the Stanford-Binet Intelligence Scale (2 observations). No other test was used in more than one instance. Information on infant-feeding measures is presented in column 6. At a minimum, all studies classified subjects into categories representing a predominantly formula-fed or breast-fed experience. Information on exclusivity, duration, or other specifics of the subjects' feeding experience was also noted. Other childhood outcomes measured and additional sources of information we used are also shown in Table 1.

The extent to which key cofactors were assessed by previous investigators is given in **Table 2**. "Matched" studies were defined as reports that presented both unadjusted and cofactor-adjusted estimates of the effect of breast-feeding on cognitive development for the same sample; 12 studies met this criterion. The total number of covariates included in models comparing effects of breast-feeding and formula feeding on cognitive development are given; this number ranged from 1 to 12 in the full sample and from 5 to 12 in matched studies only, with a mean of 8 cofactors included in models in the latter category. The 10 studies that directly evaluated the effects of the duration of breast-feeding exposure on subjects' cognitive development are noted in the table. The extent to which key covariates were included in models across studies is displayed across columns 5–18. Cofactors that were well represented across studies included, in order of frequency, socioeconomic status (SES), sex, maternal education, birth weight, parity, gestational age, maternal intelligence quotient, and maternal smoking. Covariates that were infrequently evaluated in studies included race or ethnicity, parenting behaviors, childhood experiences, family size, and paternal characteristics. Each of these latter factors was evaluated in <5 studies.

Unadjusted and adjusted estimates

The results of meta-analysis for all matched observations are given in **Table 3**. Unadjusted and adjusted-pooled mean differences in cognitive developmental score between breast-fed and formula-fed children are reported by using fixed-effects estimation procedures. A positive value indicates an advantage in average developmental score for breast-fed compared with bottle-fed children. For purposes of sensitivity analysis, results are displayed separately in the table for all composite observations ($n = 11$) and all observations without aggregation ($n = 28$); results obtained

TABLE 1
Attributes of studies evaluating the effect of breast-feeding on cognitive development[1]

Study and location	Subject characteristics	Study type	Cognitive development assessments[2]	Breast-feeding attributes	Other childhood outcomes	Other data-collection methods
Hoefer and Hardy (1), United States[3]	383 M + F 7–13 y	P	Stanford-Binet Intelligence Scale Pinter-Patterson Performance	FF, BF ≤3 mo, BF 10–20 mo	Age of talking Percentage with IQ > 120 Percentage with IQ > 130 Stanford Educational Achievement Test results	Questionnaire: parent Interview: parent Medical records "Baby book" records
Dorner and Grychtolik (2), Germany	134 M + F 16 y	R	School mark averages (natural sciences and languages)	FF, BF, FF and BF	School mark averages (sports, behavior and conduct)	Teacher reports
Rodgers (3), United Kingdom[3]	2424 M + F subsample assessed: 8 y, 15 y	P	8 y: Picture Intelligence 15 y: Nonverbal ability Sentence completion	FF exclusively; BF exclusively; BF 1 mo, 2 mo, 3 mo, 4 mo, 5–7 mo, ≥8 mo	8 y: Word reading 15 y: Mathematics	Interview: mother Teacher reports
Silva et al (18), New Zealand	1037 M + F 3 y	P	Peabody Picture Vocabulary Test	BF <1 wk, BF 1–4 wk, BF 5–12 wk, BF 13–24 wk, BF 25–36 wk, BF 37–51 wk, BF >51 wk	Developmental experiences Age of attainment of developmental milestones Gross and fine motor coordination Verbal comprehension and expression Behavior problems	Interview: mother
Fergusson et al (4), New Zealand[3]	1037 M + F assessed: 3y, 5 y, 7 y	P	3 y: Peabody Picture Intelligence Test 5 y: Stanford-Binet Intelligence Scale 7 y: Wechsler Intelligence Scale	FF, BF <4 mo, BF ≥4 mo	3, 5, 7 y: Language development 5, 7 y: Articulation	Interview: mother
Ounsted et al (5), United Kingdom[3]	242 M + F 7.5 y	P	British Abilities Scales (10 subscales)	FF, BF, DNR	Holbom Reading Quotient	Not reported
Taylor and Wadsworth (6), United Kingdom	13135 M + F 5 y	P	English Picture Vocabulary Test	FF, BF <1 mo partial or exclusive BF 1–3 mo partial or exclusive BF >3 mo partial or exclusive	Copying Designs Score Child Behavior Score Percentage with speech problems	Interview: mother
Morley et al (7), United Kingdom[3]	771 M + F 18 mo LBW < 1850 g	P	Bayley Mental Development Index Developmental Profile II (academic scale IQ equivalent)	FF, BF, DNR	None	Interview: caregiver
Morrow-Tlucak et al (8), United States[3]	229 M + F Assessed: 6 mo, 1 y, 2 y	P	6 mo, 1 y, 2 y: Bayley Mental Development Index	FF, BF ≤4 mo, BF >4 mo	None	Questionnaire: mother Interview: mother HOME Instrument administration
Pollock (9), United Kingdom	8128 M + F 5 y LBW < 2537 g	P	English Picture Vocabulary Test	FF, BF partial or exclusive, during first 7 d postpartum	Copying Designs Test Human Figure Drawing Test	Not reported
Bauer et al (10), United States	50 M + F 3 y	P	McCarthy Scales of Children's Abilities General Cognitive Index	BF duration not further specified	None	Not reported
Doyle et al (11), Australia[3]	96 M + F Assessed: 2y, 5 y, 8 y LBW 500–1500 g	P	2 y: Bayley Mental Development Index 5 y: Wechsler Preschool and Primary Scale of Intelligence 8 y: Wechsler Intelligence Scale for Children Revised	FF exclusively BF, DNR	None	Not reported
Jacobson and Jacobson (19), United States[3]	323 M + F 4 y	P	McCarthy Scales of Children's Abilities General Cognitive Index Peabody Picture Vocabulary Test Revised	FF exclusively to BF exclusively (5 categories not further specified)	None	Interview: mother

(*Continued*)

TABLE 1 (*Continued*)

Study and location	Subject characteristics	Study type	Cognitive development assessments[2]	Breast-feeding attributes	Other childhood outcomes	Other data-collection methods
Lucas et al (12), United Kingdom[3]	283 M + F Subsample 7.5–8 y LBW < 1850 g	P	Wechsler Intelligence Scale for Children Revised (Anglicized) Overall IQ assessed from 5 subscales	FF, BF successfully (determined within 72 h of delivery)	Wechsler Intelligence Scale for Children Revised Verbal Subscale Wechsler Intelligence Scale for Children Revised Performance Subscale	Not reported
Rogan and Gladen (13), United States[3]	855 M + F at baseline assessed: 6 mo, 1 y, 1.5 y, 2 y, 3 y, 4 y, 5 y	P	6 mo, 1 y, 1.5 y, 2 y: Bayley Mental Development Index 3 y, 4 y, 5 y: McCarthy Scales of Children's Abilities General Cognitive Index	FF exclusively BF ≤ 4wk and weaned ≤9 wk, BF ≤4 wk or 5–19 wk and weaned 9–19 wk, BF 5–19 wk or ≥20 wk and weaned 19–49 wk, BF ≥20 wk and weaned ≥50 wk	Bayley Psychomotor Index McCarthy Motor Scale McCarthy Scales of Children's Abilities Verbal, Quantitative, Perceptual-Performance, Memory Subscales Report card grades	Interview: mother Medical records Physical and developmental examinations Biological samples
Greene et al (22), United Kingdom	432 M + F 11–16 y	R	Primary Mental Abilities Test Intelligence Quotient Raven's Standard Progressive Matrices Test Intelligence Quotient	FF, BF as recorded on hospital consultation records BF 1–12 wk, >12 wk	Primary Mental Abilities Test Verbal, Numerical, and Reasoning Subscales	Hospital consultation records Health Visitor reports School health records
Lucas et al (14), United Kingdom	117 M + F subsample FF vs. BF donor breast milk 18 mo LBW < 1850 g	P	Bayley Mental Development Index (corrected for prematurity)	FF exclusively, BF exclusively with donor breast milk	Bayley Psychometer Development Index (corrected for prematurity)	History: clinical, social, demographic factors Physical examination Anthropometry Biological samples
Pollock (15), United Kingdom	3838 M + F subsample "clinically advantaged"[4] Assessed: 5 y, 10 y	P	5 y: English Picture Vocabulary Test 10 y: British Abilities Scales Total Score (overall cognitive and perceptual ability)	FF exclusively ≥3 mo BF exclusively ≥3 mo	5 y: Human Figure Drawing Copying Design Score 10 y: Pictorial Language Test Friendly Maths Test Edinburgh Reading Test Spelling Test British Abilities Scales Word Definition, Matrices, and Similarities Subscales	Questionnaire and interview: parents Medical records, medical examination, school testing
Temboury et al (16), Spain[3]	229 M + F 18–29 mo	P	Bayley Mental Development Index	FF from birth or BF ≤1mo BF for ≤3 mo	Bayley Psychomotor Development Index	Not reported
Florey et al (17), United Kingdom[3]	592 M + F 18 mo	P	Bayley Mental Development Index	FF, BF, DNR as recorded at hospital at discharge and on early Health Visitor record	Bayley Psychomotor Development Index	Interview: mother Medical records Health Visitor records

[1] LBW, low birth weight; FF, formula fed; BF, breast-fed; P, prospective study; R, retrospective study; DNR, duration not reported; IQ, intelligence quotient.
[2] Tests identified as appropriate for inclusion in the meta-analysis.
[3] Study reporting both unadjusted and covariate-adjusted (minimum of 5 covariates) findings.
[4] "Clinically advantaged" subsample defined in reference.

using random effects estimation procedures are reported below. The unadjusted pooled mean difference for the 11 composite observations was 5.32 points, indicating that on average, an incremental benefit of this magnitude was observed for breast-fed children across studies before adjustment for covariates. This unadjusted difference was significant but heterogeneous across studies. The counterpart unadjusted breast-fed advantage in cognitive development for all 28 observations of 4.97 points compared closely with the composite unadjusted value. When random-effects estimation procedures were used to account for heterogeneity between results, the pooled mean difference for the unadjusted composite observations was moderately elevated to 6.15 (95% CI: 4.68, 7.61) points, and the pooled mean difference for all observations increased to 5.64 (95% CI: 4.77, 6.52) points. Thus, all estimates established the average unadjusted benefit in cognitive development of breast-feeding compared with formula feeding at between 5 and 6 points.

After adjustment for covariates, the pooled mean increment in cognitive developmental score for breast-fed compared with formula-fed children across the 11 composite observations

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TABLE 2
Assessment of cofactors in studies on the effect of breast-feeding on cognitive development

Study	Matched report[1]	Number of cofactors[2]	Duration of breast-feeding	Sex	Maternal smoking	Maternal age	Maternal IQ[4]	Maternal education	Maternal training	Paternal education	Race or ethnicity	SES[5]	Family size	Birth order	Birth weight	Gestational age	Childhood experience
Hoefer and Hardy (1)	N	1	A[3]														
Dorner and Grychtolik (2)	N	3		A													
Rodgers (3)	Y	10	A	A			A	A		A		A	A	A	A		A
Silva et al (18)	N	4	A	A			A	A				A					A
Fergusson et al (4)	Y	7	A	A			A	A	A			A			A	A	A
Ounsted et al (5)	Y	8		A	A							A		A	A		
Taylor and Wadsworth (6)	Y	8	A	A	A	A						A		A	A		
Morley et al (7)	Y	10		A	A	A		A				A		A	A		
Morrow-Tlucak et al (8)	Y	8	A	A	A	A	A	A	A								
Pollock (9)	N	7		A		A		A				A	A		A	A	
Bauer et al (10)	N	3	A	A								A					
Doyle et al (11)	Y	6					A	A	A			A			A	A	
Jacobson and Jacobson (19)	Y	5	A				A	A	A			A					
Lucas et al (12)	Y	8		A		A		A			A	A		A	A	A	
Rogan and Gladen (13)	Y	9	A	A	A	A		A			A	A		A			
Greene et al (22)	N	7	A	A		A		A				A		A	A	A	
Lucas et al (14)	N	9		A				A				A			A	A	
Pollock (15)	N	9			A	A		A	A	A	A	A	A	A			
Temboury et al (16)	Y	12		A		A		A				A	A		A		
Florey et al (17)	Y	10		A	A	A		A				A			A	A	

[1] "Matched" denotes that numeric results are reported in the study for both unadjusted and cofactor-adjusted models; Y, yes; and N, no.
[2] Total number of cofactors evaluated in assessment of the effect of breast-feeding on cognitive development.
[3] A, assessed, ie, the cofactor was included in the assessment of the effect of breast-feeding on cognitive development.
[4] Socioeconomic status.
[5] Intelligence quotient.

TABLE 3
Results of meta-analysis: weighted mean difference in cognitive developmental score between breast-fed and formula-fed children: unadjusted and adjusted results compared for all matched composite observations and all matched observations[1]

Matched observations	Mean difference (breast-fed−formula fed)[2]	SE	95% CI	z^3	Q^4
Composite					
Unadjusted (n = 11)	5.32	0.4152	4.51, 6.14	12.82	23.20 (0.01)
Adjusted (n = 11)	3.16	0.416	2.35, 3.98	7.60	12.76 (0.2373)
Total					
Unadjusted (n = 28)	4.97	0.2455	4.49, 5.45	20.25	69.30 (<0.001)
Adjusted (n = 28)	2.89	0.2463	2.41, 3.37	11.74	27.54 (0.435)

[1] n is the number of observations (tests of hypothesis) in category.
[2] Fixed-effects estimate of the weighted mean difference in cognitive developmental score between groups. Positive values indicate greater mean score for breast-fed children relative to formula-fed children.
[3] Test of significance of weighted mean difference: $P < 0.001$.
[4] Test of homogeneity of weighted mean difference; associated P value in parentheses.

declined to 3.16 points. This adjusted difference was also significant and, in contrast with the unadjusted results, was homogeneous across studies. The counterpart-adjusted difference for all 28 observations of 2.89 points was similar in magnitude. When random-effects models were used, the pooled mean difference for 11 composite observations was modestly elevated to 3.49 (95% CI: 2.45, 4.53) points, and the counterpart value for all observations was 2.92 (95% CI: 2.42, 3.41) points. These alternative estimates indicate that after adjustment for covariates, breast-feeding conferred a consistent and significant incremental benefit of ≈3 points to children's cognitive development.

Adjusted mean differences and CIs for 11 studies (composite observations) that reported matched results, and the pooled estimate across studies, are shown in **Figure 1**. All 11 studies

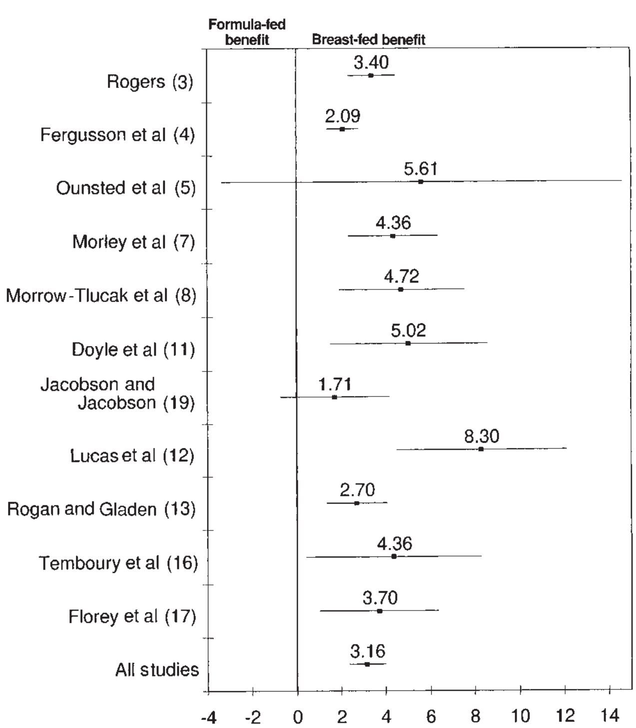

FIGURE 1. Effect of breast-feeding versus formula feeding on cognitive developmental score: covariate-adjusted mean differences for matched composite observations.

observed a benefit associated with breast-feeding after adjustment for covariates. This advantage was significant in 9 instances.

To specify the effects of covariate adjustment on observed benefits for breast-feeding as precisely as possible, differences between unadjusted and adjusted results were calculated for each study reporting both values (ie, matched observations) and the resulting differences were pooled by using fixed-effects models. Results addressing this question are given in **Table 4**. Results are reported separately for composite and for total observations. The pooled estimate indicates that covariate adjustment reduced the magnitude of the observed benefit in cognitive development obtained by breast-feeding by 2.11 points on average for 11 composite observations. The counterpart value for all 28 observations was closely comparable at −2.00 points. These pooled estimates were heterogeneous across studies. Random-effects models gave an estimated difference for composite observations of −2.41 points, and the value for all observations was −2.39 points.

Effect of age at measurement, birth weight, and duration of breast-feeding

Results, after disaggregating observations by age of subjects, birth-weight category, and duration of exposure to breast-feeding, are presented in **Tables 5–7**. The effect estimate reported is the adjusted mean differences in cognitive developmental score between breast-fed and formula-fed children. Results of estimates adjusted by age at measurement are presented in Table 5. Breast-fed children showed significant incremental benefits in developmental score in comparison with formula-fed children in each of the measured categories. The increment accruing from breast-feeding was observed in children measured as early as 6–23 mo of age (mean increment of 3.11 points). This benefit was stable across successive age categories. There is no evidence for an age-associated trend in the magnitude of the increment. The results suggest that a significant developmental augmentation attributable to breast-feeding is established early in the life course and persists at least through midadolescence.

The results of the meta-analysis by category of birth weight are presented in Table 6; they indicate that the benefit obtained from breast-feeding was most pronounced in children of low birth weight, although significant benefits were observed in both categories. An average adjusted benefit of 5.18 points was obtained for low-birth-weight children across the 6 available observations. This value was significant and homogeneous. The observed benefit for children in the low-birth-weight category was also significantly

TABLE 4

Results of meta-analysis: pooled difference between covariate-adjusted and unadjusted results for cognitive developmental score, comparing results for matched observations[1]

Matched observations	Pooled difference (adjusted − unadjusted)[2]	SE	95% CI	z^3	Q^4
Composite (n = 11)	−2.11	0.0204	−2.15, −2.07	103.95	1633.2
Total (n = 28)	−2.00	0.0117	−2.02, −1.97	170.54	7730.7

[1] n is the number of matched observations (studies reporting both unadjusted and adjusted results).

[2] Fixed-effects estimate of the weighted average difference in cognitive development score between adjusted and unadjusted results. A negative value indicates reduction in the magnitude of difference in adjusted results in comparison with unadjusted results.

[3] Test of significance of weighted estimate: $P < 0.001$.

[4] Test of homogeneity of weighted estimate: $P < 0.001$.

higher than the average adjusted increment of 2.66 points observed for children in the normal-birth-weight category. However, the higher score noted for breast-fed children in the comparison category was also significant and homogeneous across observations.

Results of examining the duration of breast-feeding exposure are presented in Table 7. For each duration category, the value reported represents the weighted, adjusted mean difference in cognitive developmental score between breast-fed and formula-fed children. The results showed a pattern of gradual increase in the magnitude of the incremental benefit in cognitive development correlated with breast-feeding compared with formula-feeding as the duration of breast-feeding exposure increased from 8–11 wk (weighted mean benefit of 1.68 points) to ≥28 wk (weighted mean benefit of 2.91 points). Although a consistent pattern of increase in the weighted-mean estimates was evident, substantial overlap exists in CIs for these estimates. Also, a significant benefit for breast-feeding was obtained for the 4 longer-duration categories representing breast-feeding exposure >8 wk. Results were homogeneous across observations in 3 of 5 categories. Similar findings were obtained when random-effects models were estimated for these data (results not shown).

DISCUSSION

This meta-analysis of 20 controlled studies indicated that breast-feeding was associated with a 3.2-point higher cognitive development score than was formula feeding after adjustment for key cofactors. These results were homogeneous and significant ($P < 0.001$). Enhanced cognitive development of breast-fed compared with formula-fed children was manifested early in development and was sustained through childhood and adolescence. Increasing duration of breast-feeding was accompanied by a gradual increase in cognitive developmental benefit. Our analysis supports data reported in individual studies (3, 4, 8, 11, 13, 15).

Low-birth-weight infants derived greater benefits from breast-feeding than did normal-weight infants. Our analysis suggests that normal-birth-weight infants who are breast-fed rather than formula fed have a cognitive developmental advantage of 2.66 points ($P < 0.001$) whereas low-birth-weight infants have an advantage of 5.18 points ($P < 0.001$) compared with formula-fed infants matched for birth weight. These observations support the results of comparisons made in individual studies (7, 9, 11, 12, 14, 35).

Although our meta-analysis suggests that key cofactors contribute from 2.0 to 2.4 points to the difference in cognitive developmental score between breast-fed and formula-fed children, differences in measured and unmeasured cofactors between these 2 groups remain a major limitation of this analysis. Recently, investigators (Table 2) assessed between 3 and 12 covariates and adjusted, as far as possible, for these confounders. After adjustment for significant cofactors, 9 of 11 investigations (Figure 1) reported significantly higher cognitive deveolpment scores for breast-fed infants than for formula-fed infants. Because recognized covariates contributed to an estimated 2.11-point difference, it is unlikely but possible that heretofore unrecognized or inadequately assessed covariates, if adjusted for would negate the 3.16-point difference noted in the cognitive function for breast-fed compared with formula-fed children. Further studies, such as those of Lucas et al (14), may help answer this question.

Several additional factors support a specific value of breast-feeding with respect to cognitive function. First, breast-fed children appear to have a broad range of enhanced brain functions

TABLE 5

Results of meta-analysis: weighted mean difference in cognitive developmental score between breast-fed and formula-fed children by age at measurement[1]

Age category	Breast-fed	Formula fed	Mean difference (breast-fed − formula fed)[2]	95% CI	z^3	Q^4
6–23 mo (n = 7)	2283	1169	3.11	1.82, 4.39	4.75	4.68 (0.585)
2–5 y (n = 12)	3674	5166	2.53	1.86, 3.20	7.39	9.34 (0.590)
6–9 y (n = 5)	1575	1461	3.01	1.99, 4.03	5.78	10.28 (0.036)
10–15 y (n = 2)	1116	4120	3.19	1.89, 4.48	4.82	0.04 (0.837)

[1] n is the number of observations (tests of hypothesis) across all studies.

[2] Fixed-effects estimate of the weighted mean difference in cognitive developmental score between groups. Positive values indicate a greater mean score for breast-fed children relative to formula-fed children.

[3] Test of significance of weighted mean difference: $P < 0.001$.

[4] Test of homogeneity of weighted mean difference; associated P value in parentheses.

TABLE 6
Results of meta-analysis: weighted mean difference in cognitive developmental score between breast-fed and formula-fed children by birth weight category

Birth weight	Breast-fed	Formula fed	Mean difference (breast-fed − formula fed)[1]	SE	95% CI	z[2]	Q[3]
Normal or mixed[4] (n = 22)	8922	5778	2.66	0.2585	2.15, 3.17	10.29	15.57 (0.793)
Low (n = 6)	1294	751	5.18	0.8117	3.59, 6.77	6.38	3.23 (0.665)

[1] Fixed-effects estimate of the weighted mean difference in cognitive developmental score between groups. Postive values indicate greater mean scores for breast-fed children relative to formula-fed children.

[2] Test of significance of weighted mean difference: $P < 0.001$.

[3] Test of homogeneity of weighted mean difference; associated P value in parentheses.

[4] Some studies did not distinguish between low- and normal-birth-weight children when reporting results; in these instances the results were placed in the "normal or mixed" category.

compared with formula-fed children. In addition to improved performance on a variety of different tests of cognitive function, indicating a general enhancement of cognitive function rather than of very specific functions, breast-fed children, compared with formula-fed children, show more rapid maturation of visual function (36, 37) and may acquire motor skills at an earlier age (2, 35). It has also been suggested that breast-fed children have fewer emotional or behavioral problems (2, 6, 35) and fewer minor neurologic problems later in life (38, 39) than do formula-fed children. These observations suggest that breast-feeding specifically enhances global neurologic development. Second, the enhanced benefit observed for low-birth-weight infants again suggests that breast milk provides specific advantages to premature infants. Third, the "dose effect," or increasing benefit with duration of breast-feeding, also suggests that there are specific advantages related to increasing exposure to breast milk.

The recent study of LeLorier et al (40) cautions against overinterpreting findings of meta-analyses. Appropriately conducted research syntheses must carefully specify criteria for study selection and quality assessment, explore sources of variation in results, and evaluate sensitivity of findings to different statistical models for pooling results (41, 42). Our meta-analysis pooled results of nonrandomized studies that were selected on the basis of their relative uniformity in addressing the research question of interest, and classified according to their extent of statistical control of the relation. We excluded one study (14) because it used a design that differed significantly from that of the other studies. We explored variation within and between various subsets of the sample of studies, grouped according to more or less restrictive criteria. We also examined differences between the results when alternative statistical models for pooling studies were applied to the data. Our pooled estimates were robust to different aggregations of data and to application of different statistical models for meta-analysis. This gives us confidence in the reliability of the findings as a summary of the current state of research knowledge but in no way implies that additional study of the research question is not warranted.

If breast-feeding is accompanied by more rapid or better development of neurologic function, it may be because breast milk provides nutrients required for rapid development of the immature brain. Human breast milk may support neurologic development by providing long-chain polyunsaturated fatty acids (LCPUFAs) such as docosahexaenoic acid (DHA; 22:6n−3) and arachidonic acid (AA; 20:4n−6). Structural lipid comprises 60% of the human brain, and DHA and AA are major lipid components (43–45). Premature infants are denied the intrauterine supply of DHA and AA and, having no fat stores of these basic LCPUFAs, do not have adequate DHA and AA for retinal and cortical brain development (36, 37, 46–48). Breast milk provides these critical LCPUFAs, whereas formulas available in the United States do not provide DHA or AA (37, 48). In 1979, Sanders and Naismith (49) noted that blood DHA concentrations were higher in breast-fed than in formula-fed infants. Research in primates (50) and humans (45, 51, 52) indicates that breast-fed infants have higher brain concentrations of DHA than do formula-fed infants studied after accidental death. Makrides et al (52) also noted that the DHA content of the brain cortex of infants increased significantly with duration of breast-feeding. Furthermore, erythrocyte DHA was significantly correlated with brain cortex DHA content in human infants (52), as reported previously in animal studies (53).

Crawford (44) hypothesized that DHA and AA are the vital components of human breast milk that support development of the newborn brain. Extensive animal (54), primate (55) and human (48, 56) research supports this hypothesis. Bjerve et al (57) docu-

TABLE 7
Results of meta-analysis: weighted mean difference in cognitive developmental score between breast-fed and formula-fed children by duration of breast-feeding exposure[1]

Duration of breast-feeding	Study reference number	Subjects by feeding status: Breast-fed	Subjects by feeding status: Formula fed	Mean difference (breast-fed − formula fed)[2]	95% CI	z[3]	Q[4]
4–7 wk	1,3,6,22	2609	8413	−0.02	−0.71, 0.67	0.06 (0.951)	4.98 (0.419)
8–11 wk	3,4,6,8,13	3070	10198	1.68	1.12, 2.25	5.84 (<0.001)	14.03 (0.448)
12–19 wk	3,6,13,22	2458	9569	2.15	1.41, 2.88	5.72 (<0.001)	18.77 (0.016)
20–27 wk	1,3,4,8	1232	2767	2.78	1.94, 3.61	6.50 (<0.001)	7.20 (0.516)
≥28 wk	1,3,13	2910	1840	2.91	1.73, 4.09	4.82 (<0.001)	17.50 (0.041)

[1] All available observations were included in the meta-analysis; the estimated effect of covariates has been subtracted from unadjusted observations.

[2] Fixed-effects estimate of the weighted mean difference in cognitive development score between groups. Positive values indicate a greater mean score for breast-fed children relative to formula-fed children; negative values indicate the opposite result.

[3] Test of significance of weighted mean difference; associated P value in parentheses.

[4] Test of homogeneity of weighted mean difference; associated P value in parentheses.

mented that serum DHA concentrations are positively and significantly correlated with results of Bayley mental and psychomotor development scales. Furthermore, several studies documented that DHA concentrations in serum and erthyrocytes are significantly lower in formula-fed than in breast-fed infants (48, 53, 58, 59). Early studies in primates (55) and more recent studies in human infants (36, 48, 60) showed that breast-fed infants score higher on visual acuity tests than do formula-fed infants, and this performance correlates with concentrations of DHA in erythrocytes.

The advantages associated with a 3- to 5-point higher level of cognitive function or IQ score are controversial. The available scientific data suggest that cognitive function is positively and significantly correlated with educational achievement (61), job performance (62), occupational achievement (63), and income (64), and inversely related to delinquency rates (65). An IQ increase of 3 points (one-fifth of an SD) from 100 to 103 would elevate an individual from the 50th to the 58th percentile of the population and would potentially be associated with higher educational achievement, occupational achievement, and social adjustment.

In conclusion, this meta-analysis of controlled studies indicates that breast-feeding is associated with a 3.16-point higher score for cognitive development compared with formula feeding after adjustment for significant covariates. This difference between breast-fed and formula-fed children was observed as early as 6 mo and was sustained through 15 y of age, the last time of reliable measurement. Longer duration of breast-feeding was accompanied by greater differences in cognitive development between breast-fed and formula-fed children. Whereas normal-weight infants showed a 2.66-point difference, low-birth-weight infants showed a 5.18-point difference in IQ compared with weight-matched, formula-fed infants. These studies suggest that nutrients present in breast milk may have a significant effect on neurologic development in premature and term infants.

REFERENCES

1. Hoefer C, Hardy MC. Later development of breast fed and artificially fed infants. J Am Med Assoc 1929;92:615–20.
2. Dorner G, Grychtolik H. Long-lasting ill-effects of neonatal qualitative and/or quantitative dysnutrition in the human. Endokrinologie 1978;71:81–8.
3. Rodgers B. Feeding in infancy and later ability and attainment: a longitudinal study. Dev Med Child Neurol 1978;20:421–6.
4. Fergusson DM, Beautrais AL, Silva PA. Breast-feeding and cognitive development in the first seven years of life. Soc Sci Med 1982; 16:1705–8.
5. Ounsted M, Moar V, Cockburn J, Redman C. Factors associated with intellectual ability of children born to women with high risk pregnancies. Br Med J 1984;288:1038–41.
6. Taylor B, Wadsworth J. Breast feeding and child development at five years. Dev Med Child Neurol 1984;26:73–80.
7. Morley R, Cole TJ, Powell R, Lucas A. Mother's choice to provide breast milk and developmental outcome. Arch Dis Child 1988; 63:1382–5.
8. Morrow-Tlucak M, Haude RH, Ernhart CB. Breastfeeding and cognitive development in the first 2 years of life. Soc Sci Med 1988; 26:635–9.
9. Pollock JI. Mother's choice to provide breast milk and developmental outcome. Arch Dis Child 1989;64:763–4.
10. Bauer G, Ewald ES, Hoffman J, Dubanoski R. Breast feeding and cognitive development in three-year-old children. Arch Dis Child 1991;64:763–4.
11. Doyle LW, Rickards AL, Kelly EA, Ford GW, Callanan C. Breast-feeding and intelligence. Lancet 1992;339:744–5 (letter).
12. Lucas A, Morley R, Cole TJ, Lister G, Lesson-Payne C. Breast milk and subsequent intelligence quotient in children born preterm. Lancet 1992;339:261–4.
13. Rogan WJ, Gladen BC. Breast-feeding and cognitive development. Early Hum Dev 1993;31:181–93.
14. Lucas A, Morley R, Cole TJ, Gore SM. A randomised multicentre study of human milk versus formula and later development in preterm infants. Arch Dis Child 1994;70:F141–6.
15. Pollock JI. Long-term associations with infant feedings in a clinically advantaged population of babies. Dev Med Child Neurol 1994;36:429–40.
16. Temboury MC, Otero A, Polanco I, Arribas E. Influence of breast-feeding on the infant's intellectual development. J Pediatr Gastroenterol Nutr 1994;18:32–6.
17. Florey CV, Leech AM, Blackhall A. Infant feeding and mental and motor development at 18 months of age in first born singletons. Int J Epidemiol 1995;24:S21–6.
18. Silva PA, Buckfield P, Spears GF. Some maternal and child developmental characteristics associated with breast feeding: a report from the Dunedin Multidisciplinary Child Developmental Study. Aust Paediatr J 1978;14:265–8.
19. Jacobson SW, Jacobson JL. Breastfeeding and intelligence. Lancet 1992;339:926.
20. Statement of the Standing Committee on Nutrition of the British Paediatric Association. Is breast feeding beneficial in the UK? Arch Dis Child 1994;71:376–80.
21. White HD. Scientific communication and literature retrieval. In: Cooper H, Hedges LV, eds. The handbook of research synthesis. New York: Russell Sage Foundation, 1994:41–55.
22. Greene LC, Lucas A, Livingstone MBE, Erasmus PS, Harland G, Baker BA. Relationship between early diet and subsequent cognitive performance during childhood. Biochem Soc Trans 1995;23:376S (abstr).
23. Wolraich ML, Wilson DB, White JW. The effect of sugar on behavior or cognition in children: a meta-analysis. JAMA 1995;274: 1617–21.
24. Friedenreich CM. Methods of pooled analyses of epidemiologic studies. Epidemiology 1993;4:295–302.
25. Mosteller F, Colditz GA. Understanding research synthesis (meta-analysis). Annu Rev Public Health 1996;17:1–23.
26. Johnstone BM, Leino EV, Ager CR, Ferrer H, Fillmore KM. Determinants of life-course variation in the frequency of alcohol consumption: meta-analysis of studies from the Collaborative Alcohol-Related Longitudinal Project. J Stud Alcohol 1996;57: 494–506.
27. Greenland S. Quantitative methods in review of epidemiologic literature. Epidemiol Rev 1987;9:1–30.
28. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res 1997;2:121–45.
29. Colditz GA, Burdick E, Mosteller F. Heterogeneity in meta-analysis of data from epidemiologic studies: a commentary. Am J Epidemiol 1995;142:371–82.
30. Laird NM, Mosteller F. Some statistical methods for combining experimental results. Int J Technol Assess Health Care 1990;6: 5–30.
31. Hasselblad V, Mosteller F, Littenberg B, et al. A survey of current problems in meta-analysis: discussion from the Agency for Health Care Policy and Research inter-PORT Work Group on Literature Review/Meta-Analysis. Med Care 1995;33:202–20.
32. Shadish WR, Haddock CK. Combining estimates of effect size. In: Cooper H, Hedges LV, eds. The handbook of research synthesis. New York: Russell Sage Foundation, 1994:261–84.
33. Sattler JM. Assessment of children. 3rd ed. San Diego: Jerome M Sattler, Publisher, Inc, 1992.
34. Hedges LV, Olkin I. Statistical methods for meta-analysis. New York: Academic Press, 1985.

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35. Lucas A, Morley R, Cole TJ, et al. Early diet in preterm babies and developmental status in infancy. Arch Dis Child 1989;64:1570–8.
36. Birch EE, Birch DG, Hoffman DR, Uauy R. Dietary essential fatty acid supply and visual acuity development. Invest Ophthalmol Vis Sci 1992;32:3242–53.
37. Carlson SE, Werkman SH, Rhodes PG, Tolley EA. Visual-acuity development in healthy preterm infants: effect of marine-oil supplementation. Am J Clin Nutr 1993;58:35–42.
38. Menkes JH. Early feeding history of children with learning disorders. Dev Med Child Neurol 1977;19:169–71.
39. Lanting CI, Fidler V, Huisman M, Touwen BLC, Boersma ER. Neurological differences between 9-year-old children fed breast-milk or formula-milk as babies. Lancet 1994;344:1319–22.
40. LeLorier J, Gregoire G, Benhaddad A, Lapierre J, Derderian F. Discrepancies between meta-analyses and subsequent large randomized, controlled trials. N Engl J Med 1997;337:536–42.
41. Draper D, Gaver DP Jr, Goel PK, et al. Combining information: statistical issues and opportunities for research. Report of the National Research Council, Panel on Statistical Issues and Opportunities for Research in the Combination of Information. Washington, DC: National Academy Press, 1992.
42. Bailar JC. The promise and problems of meta-analysis. N Engl J Med 1997;337:559–61.
43. Neuringer M, Connor WE. Omega-3 fatty acids in the brain and retina: evidence for their essentiality. Nutr Rev 1986;44:285–94.
44. Crawford MA. The role of essential fatty acids in neural development: implications for perinatal nutrition. Am J Clin Nutr 1993;57(suppl):703S–10S.
45. Farguharson J, Jamieson EC, Abbasi KA, Patrick WJA, Logan RW, Cockburn F. Effects of diet on fatty acid composition of the major phospholipids of infant cerebral cortex. Arch Dis Child 1995;72:198–203.
46. Farguharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Effect of diet on infant subcutaneous tissue triglyceride fatty acids. Arch Dis Child 1993;69:589–93.
47. Foreman-van Drongelen MHP, van Houwelingen AC, Kester AD, Hasaart THM, Blanco CE, Hornstra G. Long-chain polyunsaturated fatty acids in preterm infants: status at birth and its influence on postnatal levels. J Pediatr 1995;126:611–8.
48. Birch DG, Birch EE, Hoffman DR, Uauy RD. Retinal development in very-low-birth-weight infants fed diets differing in omega-3 fatty acids. Invest Ophthalmol Vis Sci 1992;33:2365–76.
49. Sanders TAB, Naismith DJ. A comparison of the influence of breast-feeding and bottle-feeding on the fatty acid composition of the erythrocytes. Br J Nutr 1979;41:619–23.
50. Connor WE, Neuringer M, Lin DS. Dietary effects on brain fatty acid composition: the reversibility of omega-3 fatty acid deficiency and turnover of docosahexaenoic acid in the brain, erythrocyte, and plasma of rhesus monkeys. J Lipid Res 1990;31:237–47.
51. Farguharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Infant cerebral cortex phospholipid fatty acid composition and diet. Lancet 1992;340:810–3.
52. Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Fatty acid composition of brain, retina, and erythrocytes in breast- and formula-fed infants. Am J Clin Nutr 1994;60:189–94.
53. Carlson SE, Carver JD, House SA. High fat diets varying in ratios of polyunsaturated to saturated fatty acid and linoleic and linolenic acid: a comparison of rat neural and red cell membrane phospholipids. J Nutr 1986;116:718–25.
54. Clandinin MT, Jumpsen J, Suh M. Relationship between fatty acid accretion, membrane composition, and biological function. J Pediatr 1994;125:S25–32.
55. Neuringer M, Connor WE, Van Patten C, Barstad L. Dietary omega-3 fatty acid deficiency and visual loss in infant rhesus monkeys. J Clin Invest 1984;73:272–6.
56. Makrides M, Neuman M, Simmer K, Pater J, Gibson R. Are long-chain polyunsaturated fatty acids essential nutrients in infancy? Lancet 1995;345:1463–8.
57. Bjerve KS, Brubakk AM, Fougner KJ, Johnsen H, Midthjell K, Vik T. Omega-3 fatty acids: essential fatty acids with important biological effects,and serum phospholipid fatty acids as markers of dietary omega-3 fatty acid intake. Am J Clin Nutr 1993;57(suppl):801S–6S.
58. Uauy R, Birch DG, Birch EE, Tyson JE, Hoffman DR. Effect of dietary omega-3 fatty acids on retinal function of very-low-birth-weight neonates. Pediatr Res 1990;28:485–92.
59. Clandinin MT, Parrott A, Van Aerde JE, Hervada AR, Lien E. Feeding preterm infants a formula containing C20 and C22 fatty acids simulates plasma phospholipid fatty acid composition of infants fed human milk. Early Hum Dev 1992;31:41–51.
60. Makrides M, Simmer K, Goggin M, Gibson RA. Erythrocyte docosahexaenoic acid correlates with the visual response of healthy, term infants. Pediatr Res 1993;33:425–7.
61. Taubman P, Wales T. Mental ability and higher education attainment in the 20th century. New York: McGraw-Hill, 1972.
62. Hunter JE. Cognitive ability, cognitive aptitudes, job knowledge, and job performance. J Vocat Behav 1986;29:340–62.
63. McCall RB. Childhood IQs as predictors of adult educational and occupational status. Science 1977;197:482–3.
64. Bender WJ. Final report of WJ Bender, Chairman of the Admissions and Scholarship Committee and Dean of Admissions and Financial Aids, 1952–1960. Cambridge, MA: Harvard University, 1960.
65. Moffitt TE, Gabriella WF, Mednick SA, Schulsinger F. Socioeconomic status, IQ, and delinquency. J Abnorm Psychol 1981;90:152–6.