

Stereoacuity at age 3.5 y in children born full-term is associated with prenatal and postnatal dietary factors: a report from a population-based cohort study¹⁻³

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ABSTRACT

Background: Observational studies suggested that breast-feeding benefits the visual development of preterm children, which has been attributed to the presence of docosahexaenoic acid (DHA) in breast milk but not most formula milks. Randomized studies showed that preterm children require a dietary supply of DHA in the first few weeks of life for optimal visual development, but it is unclear whether full-term children experience similar benefits from breast milk or DHA supplements.

Objective: The objective of this study was to compare stereoacuity at age 3.5 y in healthy, full-term children who were breast-fed and in similar children who had not been breast-fed after adjustment for socioeconomic status and maternal diet.

Design: Prospectively collected data on maternal diet during pregnancy (including intake of oily fish), the child's diet, and the socioeconomic status of the family were examined. Stereoacuity at age 3.5 y was assessed.

Results: Children who had been breast-fed for 4 mo were more likely to achieve high-grade stereopsis, or stereoscopic vision, than were children who had not been breast-fed (adjusted odds ratio: 2.77; 95% CI: 1.54, 4.97). The mother's antenatal blood DHA content was associated with her intake of oily fish ($P < 0.0001$). Children whose mothers ate oily fish during pregnancy were also more likely to achieve high-grade stereopsis than were children whose mothers did not eat oily fish (adjusted odds ratio: 1.57; 95% CI: 1.00, 2.45).

Conclusions: The results of this study suggest that for full-term infants, breast-feeding is associated with enhanced stereopsis at age 3.5 y, as is a maternal DHA-rich antenatal diet, irrespective of later infant feeding practice. *Am J Clin Nutr* 2001;73:316-22.

KEY WORDS Stereoacuity, breast-feeding, docosahexaenoic acid, DHA, oily fish intake, visual development, antenatal diet, full-term children, preterm children

INTRODUCTION

There has been extensive research into the developmental consequences of various components of infant diet. Many studies that investigated the neurologic sequelae of breast-feeding compared with formula feeding used visual functions as outcomes because of the well-documented increases in visual functions in the first

years of life (1). For preterm infants, consistent results were shown by various studies: infants who were breast-fed had better visual acuity at 2-4 mo of age (2) and more advanced retinal development than did those who were formula fed (3). However, for full-term infants, the issue of whether visual function is affected by infant diet remains unresolved. Two observational studies that compared breast-fed with formula-fed infants showed differences in visual acuities between the feeding groups at 3 mo (4) and 9 mo (5) of age. Conversely, other observational studies showed that breast-fed full-term infants had better visual acuity at age 2 mo (6) or 4 mo (7, 8), or better stereoacuity at age 3.5 y (8), than did children who were fed nonsupplemented formula milks.

The benefits of breast-feeding compared with formula feeding have been attributed by many researchers to the presence of the long-chain polyunsaturated fatty acid called docosahexaenoic acid (DHA). DHA is an important structural component of photoreceptor and cortical neuronal membranes (9, 10). The richest source of DHA in adult diets is fish, particularly fish oil (11). Preformed DHA is present in breast milk but is not available in most commercial formula milks (12, 13).

In the observational studies that had conflicting results on breast-feeding compared with formula-feeding and the effects on visual development, potentially confounding factors included socioeconomic status (14) and variability in the infants' DHA status at birth, which is itself dependent on maternal diet in pregnancy (15, 16) and may affect the infant's later tissue DHA concentrations (17).

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²Supported by The Medical Research Council; the Wellcome Trust; The Ministry of Agriculture, Foods and Fisheries; the Departments of Health and the Environment; The South West Regional Health Authority; the National Eye Research Centre; Cow and Gate; and Milupa, all in the United Kingdom. The docosahexaenoic acid assays of maternal blood were carried out by Scotia Pharmaceuticals, Stirling, United Kingdom, at the instigation of DF Horrobin.

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Received November 29, 1999.

Accepted for publication July 28, 2000.

The present study was designed in collaboration with an ongoing, prospective population birth cohort study called the Avon Longitudinal Study of Pregnancy and Childhood (ALSPAC; 18). The ALSPAC cohort comprises children born in a geographically defined area between 1 April 1991 and 31 December 1992. Eighty-five percent (≈ 14000) of eligible children were recruited into the study during their mother's pregnancy and extensive data on them are available. Further details and a publication list are available on the ALSPAC World Wide Web site (19). The hypothesis under test was that for healthy children born at term, a history of breast-feeding would precede better stereoacuity development than would a history of feeding with formula foods that did not contain DHA, after control for socioeconomic factors and maternal diet in pregnancy (as a proxy for the infant's DHA status at birth). Stereoacuity was chosen as the visual outcome of interest because in the absence of a visual defect (eg, strabismus), it is a cortical phenomenon and might be expected to reflect differences between individuals in the maturity of the visual cortex.

SUBJECTS AND METHODS

The subjects were from a randomly selected subset of children born in the last 6 mo of the ALSPAC enrollment period. The children in this subset had been examined at regular intervals to provide more detailed information than was available for the main cohort. Stereoacuity was assessed at age 3.5 y with use of a new test (20) that became available during the study, so that approximately two-thirds of the randomly selected subset who attended were tested. Stereoacuity matures through 3 stages (peripheral, or poor; macular, or moderate; and foveal, or adult) (21) and the new test was designed to show which stage a child had reached. There were 2 possible scores at each level: 40 or 60 s/arc for foveal, 100 or 200 s/arc for macular, and 400 or 800 s/arc for peripheral. Children who had >800 s/arc were included in the peripheral group. The stereotests were carried out at one site only, by one orthoptist who was blind to the other data available for each child. In a repeatability study, the intraclass correlation coefficient for testing 261 children aged 3 y on 2 occasions 6 mo apart was 0.39 (95% CI: 0.28, 0.48). When the same categories as those used in the present analysis were used, 60% were in the same category, 25% had improved by one category, and 15% had reduced their scores by one category.

Socioeconomic data were collected via self-completed questionnaires during pregnancy. Maternal dietary information was also collected during pregnancy via a food-frequency questionnaire filled in by the mother at 32 wk gestation. The food-frequency questionnaire asked about the frequency of consumption of 43 different foods, including white fish (cod, haddock, plaice, and fish fingers) and oily fish (pilchards, sardines, mackerel, tuna, herring, kippers, trout, and salmon). For some of the mothers in the ALSPAC cohort, blood samples obtained by venipuncture at the enrollment clinic were available. These samples were collected in heparin-containing tubes, centrifuged at $1500 \times g$ for 15 min at 4°C to separate them into plasma and red or white cells, and then frozen at -20°C . The percentage of DHA as a proportion of the total fatty acid content of the red blood cell membrane phospholipids was measured by gas chromatography in the laboratory of Scotia Pharmaceuticals (Stirling, United Kingdom); the laboratory staff were blind to the results. These data were used to ascertain the extent to which the data from the questionnaires

reflected differences in the amount of DHA in the mothers' blood cells. Questionnaires asking about infant feeding practices were completed on behalf of the child at ages 4 wk and 6 mo and a detailed prospective dietary diary describing the child's intake over 24 h was completed when the children were aged 4 mo.

Further details of the questionnaires and their design are available on the ALSPAC Web site (19). The relevant questionnaires are "Your Pregnancy" (administered at 32 wk gestation), on maternal education, maternal diet during pregnancy, and maternal worries about financial matters; "Your Environment" (administered on enrollment between 8 and 28 wk), on type of housing; "Looking After the Baby," on maternal smoking at 8 mo after the birth; "My Young Baby Boy/My Young Baby Girl" at 4 wk and "My Son/My Daughter" at 6 mo, on infant feeding practices; and "My Three-Year-Old Son/Daughter," on the child's diet. During the study period, no formula milks supplemented with DHA were commercially available in the United Kingdom. Information on the child's postnatal diet at age ≤ 36 mo was collected via a food-frequency questionnaire completed by the mother. The study was carried out according to the guidelines of the Declaration of Helsinki.

The statistical analysis of the main research question was carried out with use of the Mantel-Haenszel chi-square test for trend followed by forward stepwise logistic regression using SPSS for WINDOWS (version 7.5; SPSS Inc, Chicago). In logistic regression analyses, the outcome must be dichotomous (rather than ordinal, as our stereopsis data were) and so was defined as foveal (or high-grade) compared with nonfoveal. The breast-feeding history was inputted to the model first; the other variables were then inputted and were retained only if they significantly improved the fit of the model to the data. Multiple regression was used to explore relations between potential explanatory variables and the mother's DHA concentration. Analysis of variance (ANOVA) was used to compare DHA concentrations between groups of women according to frequency of intake of oily fish. Where the data were available, the child's stereotest scores were compared with the mother's DHA concentrations with use of a nonparametric test for correlation (Spearman's). A two-tailed P value of <0.05 was considered to be significant.

RESULTS

Subjects

Six hundred forty-one children aged ≈ 3.5 y ($\bar{x} \pm \text{SD}$: 43.2 ± 0.6 mo) were assessed with the new stereoacuity test, of whom 55 (8.6%) were excluded from the analysis because of a strabismus, reduced vision, or high refractive error, which would be expected to reduce stereoacuity. Sixty-nine children (10.7%) were excluded because of missing dietary data and 66 children (10.3%) could not comply with the test (ie, refused to wear the goggles or did not know the names of the items pictured). A further 16 whose gestation period was <37 wk were excluded. Of the remaining 435 full-term children with complete data sets, foveal stereoacuity was achieved by 150 (34.5%), macular stereoacuity by 229 (52.6%), and peripheral stereoacuity by 56 (12.9%). The distribution of the individual scores is shown in **Figure 1**. The children who could not comply with the test were similar to those who did comply with respect to all variables used in the analysis, except that the noncompliers were significantly more likely to live in public housing ($P = 0.004$) and to have older siblings ($P = 0.04$) than were the compliers.

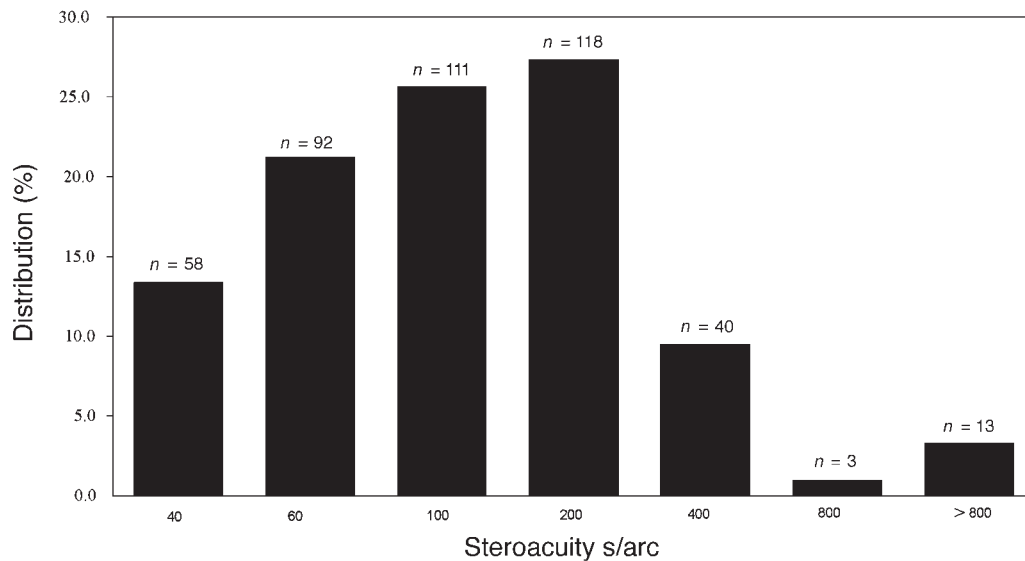


FIGURE 1. Distribution of stereoacuity in children aged 3.5 y.

For 4733 of the mothers in the main ALSPAC cohort, red blood cell DHA percentages and responses to the dietary questionnaire were available. A multiple regression analysis was performed by using percentage of DHA as a proportion of the total fatty acids in the phospholipids in the maternal red blood cells as the outcome and including all the dietary and socioeconomic variables listed in **Table 1** as potential explanatory or confounding variables. The only variable significantly associated with the maternal red cell DHA percentage was whether or not the mother ate oily fish. Higher mean percentages of DHA were present in the erythrocytes of women who answered that they did eat oily fish than in those who answered that they did not ($F = 8.22$, $df = 1$, $P = 0.004$). The DHA concentrations in the subgroup of women participating in the present study were compared with DHA concentrations in the whole sample with respect to the frequency of consumption of oily fish (**Figure 2**). Overall, the mean DHA concentrations were higher in the subgroup of women who participated in the stereoacuity study than in the whole sample (2.71% compared with 2.36%; $t = 3.35$, $df = 1$, $P = 0.001$). There was evidence of a dose-response effect in that the percentages of DHA increased with the frequency of consumption of oily fish (ANOVA; $F = 25.1$, $df = 2$, $P < 0.0001$).

Stereoacuity

The results of univariate analyses comparing stereoacuity at age 3.5 y with the dietary and socioeconomic variables are shown in **Table 1**. Breast-feeding, greater maternal age, and consumption of oily fish by the mother antenatally or by the child up to the age of 3.5 y were all associated with an increased likelihood of the child having foveal stereoacuity. However, these variables were interrelated and so multiple logistic regression analysis was used to determine which factors might be independently associated with the child's stereoacuity. All the variables in **Table 1** were inputted to the model; the results are summarized in **Table 2**. The variable most associated with an increased likelihood of foveal as opposed to worse-than-foveal stereoacuity was breast-feeding. This was true both for the <4-mo category

(adjusted odds ratio: 2.92; 95% CI: 1.58, 5.43) and for the ≥ 4 -mo category (adjusted odds ratio: 2.77; 95% CI: 1.54, 4.97), compared with a diet without breast milk. The only other variable retained in the model was whether the mother ate oily fish. The mothers who ate oily fish at least once every 2 wk during pregnancy were more likely to have children who achieved foveal stereoacuity than were the mothers who never ate oily fish (adjusted odds ratio: 1.57; 95% CI: 1.00, 2.45). There was no statistical evidence of interaction between the effects on stereoacuity of whether or not the mother ate oily fish or of breast-feeding compared with formula feeding. When only the children whose mothers never breast-fed ($n = 101$) were selected, foveal stereoacuity in the children ($n = 20$) was still more likely if the mothers ate oily fish during pregnancy than if they did not, although the difference was not significant (adjusted odds ratio: 1.26; 95% CI: 0.47, 3.35). The univariate associations that were initially observed between stereoacuity and both maternal age and the child eating oily fish (**Table 1**) were not significant in the logistic regression results, suggesting that these associations were explained by the other variables.

There was no evidence of a dose-response effect for the duration of breast-feeding (1–6 mo) on the level of stereoacuity achieved. However, for the relatively few mothers ($n = 154$) for whom DHA percentages and their child's stereoacuity were available, there was a correlation between the child's stereoacuity score and the mother's antenatal DHA concentration (Spearman's $r = -0.176$, $0.01 < P < 0.05$). The mean values and ranges of the DHA concentrations for each of the 3 grades of stereoacuity are shown in **Table 3** and illustrate the association of better stereoacuity with higher maternal DHA.

DISCUSSION

The results of this study support the hypothesis that, for full-term children, breast-feeding allows better development of stereoacuity than does formula feeding, independent of the family's socioeconomic status and the maternal diet in pregnancy.

TABLE 1

Results of univariate chi-square analyses of the distributions of the 3 grades of stereoacuity according to maternal and child factors

	Foveal stereo (<i>n</i> = 150; 34.5%)	Macular stereo (<i>n</i> = 236; 52.6%)	Peripheral stereo (<i>n</i> = 57; 12.9%)	<i>P</i>
	%			
Breast-feeding				
Never (24.9%)	19.2	64.4	16.3	0.002 ¹
Stopped by 4 mo (31.2%)	40.8	49.2	10.0	
Still at 4 mo (43.9%)	40.0	49.2	10.8	
Child's sex				
Male (52.1%)	31.8	53.2	15.0	0.097
Female (47.9%)	38.6	51.5	9.9	
Maternal education				
Secondary (12.4%)	32.1	58.5	9.4	0.066 ¹
Vocational (9.6%)	29.3	51.2	19.5	
O level (32.2%)	30.4	53.6	15.9	
A level (27.3%)	36.8	53.0	10.3	
Degree (18.5%)	44.3	46.8	8.9	
Maternal age				
<25 y (15.6%)	22.2	58.8	19.1	0.017 ¹
25–29 y (40.5%)	34.7	53.4	11.9	
≥30 y (43.9%)	38.7	49.7	11.5	
Housing tenure ²				
Owner-occupied (83.8%)	36.5	51.8	11.6	0.486
Public housing (8.8%)	24.3	56.8	18.9	
Rented (7.4%)	35.5	54.8	9.7	
Financial difficulties ²				
None (34.9%)	37.4	49.0	13.6	0.400 ¹
Some (38.7%)	37.4	51.5	11.0	
Many (25.7%)	29.7	57.0	13.2	
Maternal smoking ²				
No (81.4%)	35.1	52.9	12.0	0.839
Yes (18.6%)	34.6	51.3	14.1	
Number of older siblings in household				
0 (49.9%)	32.2	53.6	14.2	0.312 ¹
1 (33.1%)	39.3	47.1	13.6	
≥2 (17.0%)	33.3	58.3	8.3	
Child has paid child care				
No (23.4%)	35.3	55.9	8.8	0.396
Yes (76.6%)	34.2	51.7	14.1	
Mother has had paid job since child's birth				
No (49.1%)	36.7	52.2	11.1	0.561
Yes (50.9%)	33.5	52.6	14.0	
Mother is a vegetarian ³				
No (94.6%)	34.3	53.0	12.8	0.419
Yes (5.4%)	43.5	52.2	4.3	
Mother eats any fish ³				
No (22.8%)	36.4	54.5	9.1	0.046
Yes (77.2%)	33.9	52.1	14.0	
Mother eats white fish ³				
No (17.4%)	29.6	53.5	16.9	0.274
Yes (82.6%)	36.7	51.2	12.1	
Mother eats oily fish ³				
No (38.8%)	27.5	57.5	15.6	0.012
Yes (61.2%)	40.1	48.0	11.9	
Mother eats shellfish ³				
No (75.6%)	34.8	51.0	14.2	0.582
Yes (24.4%)	36.0	54.6	10.0	
Child eats oily fish (at 36 mo)				
No (56.0%)	33.3	50.7	16.3	0.039
Yes (44.0%)	38.2	54.5	7.3	

¹Chi-square for trend.²When the child was aged 8 mo.³At 32 wk gestation.

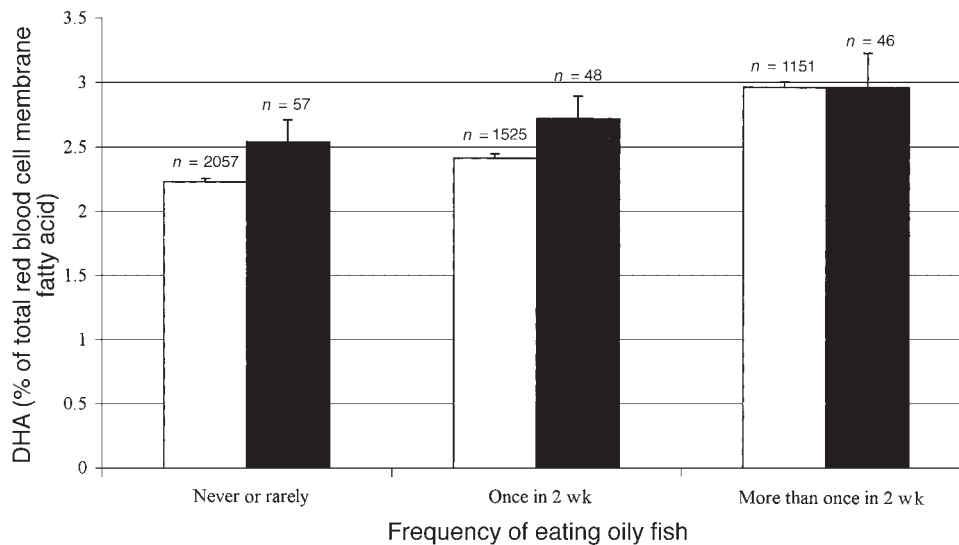


FIGURE 2. Docosahexaenoic acid concentrations by frequency of consumption of oily fish in the mothers of children in the main ALSPAC cohort (□) and in the subset of mothers of children for whom stereovision data were available (■).

There are many differences in composition between breast milk and formula milk that could be responsible for this observation. The additional finding that the inclusion of oily fish in the mother's diet during pregnancy was significantly associated with foveal stereoacuity, even after adjustment for all other factors, suggests that factors in the maternal antenatal diet may also be independently relevant for development of the visual system. If so, it would be expected that a relation between frequency of intake of oily fish and the likelihood of high-grade stereopsis would be present for children who were never breast-fed as well as for those who were breast-fed. Our subanalysis suggested that this was the case (adjusted odds ratio: 1.26; 95% CI: 0.47, 3.35), but this result was not significant, which is consistent with the greatly reduced numbers.

The association between the mother's DHA concentrations and her frequency of consumption of oily fish is consistent with the suggestion that the DHA in oily fish may be responsible for the effect on stereoacuity. The association with stereoacuity was specific to the question about oily fish, which may be because oily fish has ≈ 10 times more DHA than does white fish or shellfish (22). The human fetus can synthesize DHA precursors from 18 to 22 wk gestation (23) and preterm human infants have the capacity to synthesize DHA from essential fatty acids (24). However, both preterm (2, 25–28) and full-term (6, 29) infants who are fed formula milks that lack preformed DHA have lower concentrations of DHA in plasma and red blood cells than do breast-fed or DHA-supplemented infants. Cortical tissues in breast-fed infants also have higher amounts of DHA than do those in formula-fed infants (30, 31). These data suggest that the synthetic capacity of preterm and full-term infants may not be able to meet the demand for DHA in early development. If so, it would be expected that additional supplies of DHA in breast milk or from the mother's diet via the placenta antenatally might be associated with improved neurologic outcomes in full-term children, as seen in this study.

There is already consistent evidence that DHA supplements in formula milks lead to better visual acuity in preterm infants, but there is controversy about the effect of DHA supplements for

children born at term on visual acuity. Several randomized controlled trials in preterm infants showed that infants who are fed with DHA-supplemented formula foods have higher visual acuities at age 2 or 4 mo, or both, than do infants who are fed nonsupplemented foods (2, 32, 33). One randomized controlled trial that compared the outcome of feeding full-term infants with DHA-supplemented milks or nonsupplemented milks showed no differences in visual acuity at 2, 4, 6, 9, or 12 mo of age (34). However, other similar randomized controlled trials showed enhanced visual functions in DHA-supplemented groups of full-term children at ages 16 and 30 wk (35) or at ages 6, 17, and 52 wk (29). The discrepancies between the results of these randomized studies in children born at term may be due to differences in the DHA or linolenic acid content of the formula milks used, to variations in visual-acuity testing procedures, or to inadequate sample sizes in the studies that showed no effect. The analysis presented in this article had too few mothers with the relevant data to test fully the post hoc hypothesis that maternal DHA status in pregnancy affects stereoacuity in the child at age 3.5 y, and further data and studies are necessary. However, the correlation between higher maternal DHA concentrations and better stereoacuity scores in the children might suggest that increased maternal DHA concentrations in pregnancy could allow increased transfer of DHA from the mother to the fetus, with subsequent developmental benefits.

TABLE 2

Results of adjusted logistic regression showing factors independently associated with stereoacuity

Explanatory variable	Adjusted odds ratio (95% CI)
Breast-feeding	
Never	1.00 Reference
<4 mo	2.92 (1.58, 5.43)
≥ 4 mo	2.77 (1.54, 4.97)
Maternal oily fish consumption	
No	1.00 Reference
Yes	1.57 (1.00, 2.45)


TABLE 3

Maternal docosahexaenoic concentrations in pregnancy, according to the level of stereoacuity of the child at age 3.5 y¹

Type of stereoacuity		95% CI
Foveal (<i>n</i> = 57)	2.96 ± 1.44 (1.06–7.96)	2.57, 3.34
Macular (<i>n</i> = 79)	2.68 ± 1.45 (0.69–7.45)	2.36, 3.01
Peripheral (<i>n</i> = 18)	2.07 ± 1.33 (0.57–5.34)	1.41, 2.73

¹Expressed as percentage of total red blood cell membrane fatty acid.

The ability to control for socioeconomic variables and maternal diet (as a proxy for DHA status at birth) and the use of stereoacuity as the outcome may explain why an effect of breast-feeding on visual development in full-term children was seen in this study but not in some earlier studies. Stereoacuity is a central phenomenon that may better reflect the maturity of the visual system in young children than does visual acuity. However, as with other observational studies, these results may have been affected by confounding variables that were unknown and thus not accounted for, and the observation of an association gives no proof of causality. DHA concentrations are correlated with other markers of a healthy lifestyle (36) that might themselves affect visual function. The DHA concentrations of the women in the present study were higher than were those in the whole ALSPAC cohort, which may be due to socioeconomic or health-awareness factors. Other nutrients that are present in oily fish, such as eicosapentanoic acid and fat-soluble vitamins, could also have had effects on development. Stereopsis testing for a child aged 3.5 y is difficult and the repeatability of the test was only moderately reliable, as shown by the intraclass correlation coefficient of 0.39. This study used proxy measures for prenatal (maternal intake of oily fish) and postnatal (breast- or bottle feeding) DHA availability because, for most of the children, insufficient data were available for comparison of maternal DHA concentrations in pregnancy, or DHA concentrations in the infant, directly with the child's stereoacuity. However, the use of the question on consumption of oily fish as an indicator of maternal DHA status is supported by the correlation between the frequency of intake of oily fish with the amount of DHA in the maternal red blood cell membranes (Figure 1). The effects of maternal fish intake on breast-milk DHA content are well described (12, 13, 37).

Further work within ALSPAC will repeat these analyses in a much larger sample with use of both direct and proxy measures of DHA and neurologic outcomes (including stereoacuity) measured at 7–8 y, when testing is likely to be more accurate. However, the findings described in this article support current efforts to investigate the neurologic benefits of breast-feeding for full-term and preterm infants. They also suggest for the first time an association between maternal diet during pregnancy and a child's visual status at age 3.5 y. Further research is needed to determine whether a child's DHA status at birth is the mechanism by which this is achieved and, if so, whether there is a minimum DHA requirement for mothers during pregnancy for optimal neurologic development. 

We are grateful to all the women and children who took part in this study and to the midwives for their help in recruiting them. The ALSPAC team includes interviewers, computer and laboratory technicians, clerical workers, research assistants, volunteers, managers, receptionists, nurses, psychologists, and the orthoptists who carried out the examinations. The ALSPAC study is part of the World Health Organization-initiated European Longitudinal Study of Pregnancy and Childhood.

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