Beneficial Effects of a Polyunsaturated Fatty Acid on Infant Development: Evidence from the Inuit of Arctic Quebec

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Objectives To examine the relation of cord plasma docosahexaenoic acid (DHA) concentration to gestation length, birth size, growth, and infant visual acuity, cognitive, and motor development and the effects on growth and development associated with DHA intake from breast-feeding.

Study design DHA, other polyunsaturated fatty acids, and 3 environmental contaminants (polychlorinated biphenyls, mercury, and lead) were assessed in cord plasma and maternal plasma and milk in 109 Inuit infants in Arctic Quebec. Multiple regression was used to examine the relation of cord DHA and DHA from breast-feeding on growth and development at 6 and 11 months, after controlling for contaminant exposure and other potential confounders.

Results Higher cord DHA concentration was associated with longer gestation, better visual acuity and novelty preference on the Fagan Test at 6 months, and better Bayley Scale mental and psychomotor performance at 11 months. By contrast, DHA from breast-feeding was not related to any indicator of cognitive or motor development in this full-term sample.

Conclusions The association of higher cord DHA concentration with more optimal visual, cognitive, and motor development is consistent with the need for substantial increases in this critically important fatty acid during the third trimester spurt of synaptogenesis in brain and photoreceptor development. *(J Pediatr 2008;152:356-64)*

Docosahexaenoic acid (DHA; 22:6n-3) and arachidonic acid (AA; 20:4n-6) are essential long-chain polyunsaturated fatty acids (LCPUFAs) that are important in early central nervous system development. DHA is the only n-3 fatty acid found in significant quantities in brain, and AA is the most important of the n-6 fatty acids. The highest concentrations of DHA and AA are found in the gray matter of cerebral cortex,[1] particularly the membranes of neuronal synapses,[2] and DHA is also highly concentrated in the photoreceptor outer segment membranes of the retina.[3] DHA is critically important for vision and learning; AA is important for normal growth and is a precursor of the series 2 eicosanoids that induce labor.[4]

Because they compete for the same metabolic pathways, high dietary intake of DHA can result in decreased tissue AA. DHA accumulates preferentially in brain, particularly during the spurt of synaptogenesis and photoreceptor cell development that occurs during the third trimester of pregnancy. Because of the metabolic competition between these fatty acids, Martinez[5] suggests that the DHA/AA ratio may be useful for evaluating the degree of DHA enrichment. The capacity to synthesize DHA and AA is very limited until 16 weeks postpartum.[6] There is active transport across the placenta, as evidenced by greater DHA concentration in the fetus relative to the mother,[7] and after delivery significant amounts of preformed DHA and AA are transferred to the breast-feeding infant.

Several randomized clinical trials have reported increased length of gestation in response to DHA supplementation during pregnancy,[8-10] and several trials have linked DHA supplementation of infant formula to improved visual acuity.[6,11,12] Data on the beneficial effects of formula supplementation on cognitive and motor function assessed on

AA	Arachidonic acid	FTII	Fagan Test of Infant Intelligence
BSID-II	Bayley Scales of Infant Development, 2nd edition	LCPUFA	Long-chain polyunsaturated fatty acid
DHA	Docosahexaenoic acid	PCB	Polychlorinated biphenyl
		PUFA	Polyunsaturated fatty acid

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Supported by the National Institute of Environmental Health Sciences (R01 ES07902), Indian and Northern Affairs, Canada (Northern Contaminants Program), Health Canada, Hydro-Quebec (Environmental Child Health Initiative), and Joseph Young, Sr, Fund of the State of Michigan.

Submitted for publication Jan 4, 2007; last revision received Jun 11, 2007; accepted Jul 6, 2007.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2007.07.008

the Bayley Scales of Infant Development are inconsistent,[11,13-15] but 2 studies have reported more optimal performance on narrow-band tests focusing specifically on infant information processing and problem-solving that are predictive of childhood IQ.[16,17] Although studies on the role of LCPUFA in neurobehavioral development have focused primarily on the benefits of infant formula supplementation, the absolute accretion rates of n-3 polyunsaturated fatty acids (PUFAs) are greater in the prenatal period than postpartum.[18] One prenatal supplementation study, in which mothers were given fish oil during pregnancy, reported better performance on the K-ABC, an IQ-type test for preschool-age children.[19]

This study is among the first to examine the relation of prenatal and postnatal DHA status to development in infancy. The data were obtained in the context of a prospective longitudinal study of a cohort of Inuit infants in Arctic Quebec who were exposed to relatively large quantities of 2 environmental contaminants—polychlorinated biphenyls (PCBs) and methylmercury, which are prevalent in the fish and sea mammals that are staples of the Inuit diet.[20] Because these foods are also rich in LCPUFA,[21] the Inuit benefit from markedly higher levels of DHA intake both prenatally and from breast-feeding compared with most infants in Southern Canada and the United States. In this study, we examine the relation of cord plasma phospholipid DHA concentration to gestation length, birth size, postnatal growth, and several neurodevelopmental outcomes. Developmental effects associated with PUFA from breast-feeding are also examined.

METHODS

Participants

The sample consisted of 109 Inuit infants and their mothers, who participated in the Environmental Contaminants and Child Development Study in Nunavik—the northernmost portion of the Province of Quebec, which includes 14 coastal Inuit villages.[22] From November 1995 to March 2001, pregnant women from the 3 largest Hudson Bay villages were invited to participate in a study on environmental contaminants and infant development. Detailed informed consent was obtained following procedures approved by the Human Investigation Committees at Wayne State University and Laval University, and the study was approved by the Nunavik Nutrition and Health Committee and the Municipal Councils of the 3 villages. The data presented are from the 109 infants for whom cord plasma phospholipid LCPUFA concentrations are available. Maternal plasma LCPUFA concentrations are available for 91 of these infants; maternal milk LCPUFA concentrations are available for 67 of these infants.

Procedure

Information on demographic background, smoking and alcohol and drug use during pregnancy, and other maternal characteristics was obtained by maternal interview at mid-pregnancy and 1-month postpartum. Birth weight, length, and head circumference were obtained from hospital delivery records. Gestational age at delivery was determined from the medical examination performed by the midwife at the first prenatal visit or the Ballard Examination for Fetal Maturity. Infant growth, visual acuity, and cognitive and motor function were assessed at 6 and 11 months postpartum.

Biological Samples

A 30-mL blood sample was obtained from the umbilical cord after it was severed. A 12.5-mL blood sample was obtained from the mother at delivery or shortly thereafter (median, 2 days; interquartile range, 0-3 days; all cases except 6 within 2 months). A 10-mL milk sample was collected from breast-feeding mothers at the 1-month postnatal interview (median, 26.5 days; interquartile range, 13-50 days; all cases except 3 within 3 months). Postnatal LCPUFA intake from breast milk was assessed in terms of maternal LCPUFA plasma phospholipid concentration, weighted by weeks of exclusive breast-feeding. Maternal plasma was used to index maternal body burden rather than breast milk because it was available for more infants and because LCPUFAs are more stable in plasma than in milk, which can show substantial diurnal and day-to-day variations.[23]

Fatty acid compositions of plasma phospholipids and of total maternal milk lipids were determined with capillary gas-liquid chromatography at the University of Guelph Lipid Analytical Laboratory (B.J. Holub). A 200-μL aliquot of plasma was extracted after the addition of chloroform:methanol (2:1, vol/vol), in the presence of a known amount of internal standard (diheptadecanoyl phospholipid). Total phospholipids were isolated from the lipid extract with thin-layer chromatography using heptane:isopropyl ether:acetic acid (60:40:3, by vol) as the developing solvent. After transmethylation with BF_3/methanol, the fatty acid profile was determined with capillary gas-liquid chromatography. For milk samples, lipids were extracted according to the method of Bligh and Dyer[24] in the presence of the internal standard tridecanoin. Fatty acid methyl esters were prepared by using boron trichloride in methanol and heating the methylation tubes in a boiling water bath. The resulting fatty acid methyl esters were analyzed on a Varian 3400 gas-liquid chromatograph (Palo Alto, CA) with a 60-m DB-23 capillary column (0.32 mm internal diameter). Concentrations of DHA, AA, and the other LCPUFAs were expressed as percentages of the total area of all fatty acid peaks from C14:0 to C24:1 (percent weight). The methodologies for extracting PCBs, methylmercury, lead, and selenium were described elsewhere.[22] Because PCB 153, the most prevalent congener, was very highly correlated with the other congeners that were detected in at least 70% of the cord blood samples in this cohort (median $r = 0.9$; range, 0.71-0.98), we used it to represent PCB exposure in the analyses.[25]

Infant Visual, Cognitive, and Motor Assessments

The infants were assessed at 6 months with the Teller Visual Acuity Card Test[26] and the Fagan Test of Infant

Intelligence (FTII)[27] and at 11 months on the Teller, FTII, and the mental and psychomotor indices of the Bayley Scales of Infant Development, 2nd edition (BSID-II). The BSID is the most widely-used standardized test for assessing cognitive and motor development during infancy. Because of concerns that have been raised about the validity of the standardization of the BSID-II for at-risk and other atypical populations,[28] we analyzed the BSID raw scores, adjusted (residualized) for age in days. The Teller consists of a series of rectangular cards with a uniform gray background, on which a patch of black-and-white square-wave grating (vertical stripes) is imposed to the left or right of a central 4-mm peephole. The spatial frequency of the grating increases (ie, stripe width decreases) on successive cards from 0.23 to 38.0 cycles/cm in 0.5-octave steps. Acuity is defined as the narrowest grid for which the child shows a visual preference.

In the FTII, the infant is shown 2 identical target photos for a fixed period and is then shown the familiar target paired with a novel one. At 6 months, this test assesses "pre-explicit" recognition memory, a rudimentary form of declarative memory mediated by the medial temporal cortex,[29] which involves the construction of a memory trace of the visual stimulus, recall of information about the stimulus, and comparison of the memory trace with the visual input. Two measures are computed: novelty preference, defined as the proportion of looking time devoted to the novel stimulus, and average duration of the infant's visual fixations to the stimuli. These 2 measures reflect distinct aspects of information processing in infants.[30,31] Shorter visual fixations, which have been shown to correlate with faster habituation and shorter reaction times,[32] indicate more rapid encoding of the memory trace[33,34]; novelty preference reflects the strength of the dishabituation to the familiar stimulus.[35] In contrast to the BSID, which has a predictive validity during the first year for later childhood cognitive function that is generally poor (possibly because it confounds mental and sensorimotor function[36]), novelty preference and fixation duration, which focus more narrowly on memory and attention, are moderately predictive of childhood IQ scores,[35] particularly when assessed at 6 months of age.[37]

Control Variables

Eleven control variables were assessed for consideration as potential confounders of the relation of DHA intake to gestational age, somatic growth, and visual acuity: maternal age at delivery; parity; socioeconomic status; infant sex and age at assessment; maternal alcohol use (average ounces absolute alcohol/day), smoking (cigarettes/day), and frequent marijuana use (>4 times/month) during pregnancy; and cord PCB, mercury, and lead concentration. Six additional control variables were also considered as potential confounders of effects on cognitive and motor outcome: maternal years of education and performance on the Peabody Picture Vocabulary Test and the nonverbal Raven Progressive Matrices; the Home Observation for Measurement of the Environment, a semi-structured interview that assess quality of parental intellectual stimulation and emotional support; language of maternal interview (English or French versus Inuktituk), which reflects degree of assimilation to Western culture; and whether the infant was adopted. Adoption is common among the Inuit when the mother is either very young or not inclined to raise additional children; 9.2% of the infants in this sample were adopted. The intercorrelations of cord DHA, cord DHA/AA, and the 17 control variables, on which the multiple regression analyses are based, are shown in the Appendix (available at www.jpeds.com).

Data Analysis

All variables were checked for skewness. Only 1 variable was highly skewed (skewness >3.0), pregnancy alcohol use, and it was transformed by recoding all values >3 SDs higher than the mean to 1 point greater than the highest observed value.[38] Potential confounding influences were controlled statistically with multivariate analysis. On the basis of a Monte Carlo simulation study, Maldonado and Greenland[39] conclude that the inclusion of all control variables that are related to a given outcome at a P value <.20 is effective in protecting against confounding. They note, however, that the inclusion of a large number of control variables that only minimally confound the relation of exposure to a given outcome could result in a loss of precision. Greenland and Rothman[40] recommend a "change-in-estimate" approach that controls for all potential confounders, the inclusion of which alters the relation of exposure to outcome by at least 10%. Given these considerations, we adopted a 2-tier strategy. All control variables related to the outcome being examined at a P value <.20 were entered hierarchically in a multiple regression analysis, in which DHA intake was entered at the first step. The control variables were then entered individually using a forward selection approach,[40] with order of entry determined by the strength of the correlation of the control variable to the end point in question. Control variables were retained when their entry in the model altered the standardized regression coefficient for DHA intake by at least 10%.

Four prenatal DHA intake groups were constructed by dividing cord DHA concentration into quartiles. Dose-response relations were examined in analyses of covariance, in which each outcome found to be associated with prenatal DHA intake in the regression analyses was analyzed in relation to DHA group, after adjustment for potential confounders. Each outcome was also examined in a multiple regression analysis in relation to postnatal DHA intake from breast milk (assessed in terms of maternal plasma phospholipid DHA concentration multiplied by weeks of exclusive breast-feeding) and the potential confounders selected as aforementioned.

RESULTS

Comparisons with Other Cohorts

Table I shows the cord plasma phospholipid concentrations of DHA and AA by using the 2 metrics most commonly reported in the literature—percentage of total fatty

Table I. PUFA concentrations in cord and maternal plasma phospholipids and maternal milk

	Cord plasma phospholipids (*N* = 109)		Maternal plasma phospholipids (*N* = 91)		Maternal milk (*N* = 67)
	% of fatty acids	mg/L	% of fatty acids	mg/L	% of fatty acids
DHA	3.7 (1.1)	37.5 (22.3)	2.8 (1.6)	29.1 (23.6)	0.6 (0.6)
AA	9.3 (1.7)	92.4 (23.3)	4.0 (1.4)	41.4 (22.6)	0.3 (0.1)
DHA/AA	0.4 (0.1)	0.4 (0.1)	0.7 (0.3)	0.7 (0.3)	1.7 (1.5)

Values are mean (SD).

acids in plasma phospholipids and volume (mg/L)—and breast milk concentration as percentage of total fatty acids in the milk. Mean milk DHA concentration in this cohort is higher than the 0.1% to 0.5% range cited by Innis[4] for recent studies of women who follow a Western diet and substantially higher than the mean of 0.2% found for Caucasian women in Vancouver in 1998. Three-quarters of the women in this Inuit cohort exceed that level. By contrast, milk AA concentration is at the low end of the 0.3% to 0.7% range cited by Innis and less than the mean of 0.4% for Vancouver. Maternal milk DHA/AA ratio is markedly higher than the 0.5 to 1 range reported as typical values by Uauy et al.[41]

Mean cord DHA concentration in this cohort is 3-times higher than the mean of 1.2% reported for Southern Quebec,[42] and mean AA concentration is considerably lower (mean for Southern Quebec, 17.6%). The cord DHA concentration is more comparable with those reported in several European countries and Ecuador during the early 1990s by Otto et al,[43] which ranged from 37.1 mg/L in the Netherlands to 46.1 mg/L in England. Cord AA concentration is lower than in most of the countries studied by Otto et al (range, 97.5-128 mg/L), except for Finland (mean, 91.5 mg/L), where, as in Nunavik, fish is a substantial part of the daily diet. DHA concentration is lower than reported by Grandjean et al[44] for the Faroe Islands, where maternal plasma fatty acid DHA averaged 9.3%. These cross-national comparisons must be considered with caution, however, because chromatographic methods vary, and there is no international cross-laboratory comparison program.

Relation between Cord and Maternal DHA and AA

There is a strong relation between the DHA concentrations in maternal and cord plasma phospholipids ($r = 0.6$, $P < .001$). The correlation of the DHA/AA ratio in maternal and cord plasma is even higher ($r = 0.72$, $P < 0.001$). In contrast, the maternal-to-cord plasma AA correlation is only 0.15. Mean cord plasma DHA concentration is significantly higher than maternal plasma DHA concentration ($t\ [91] = 6.68$, $P < .001$).

Relation of Prenatal DHA Intake to Developmental Outcome

The results of the multiple regression analyses examining the relation of cord plasma DHA concentration and DHA/AA ratio to infant developmental outcome are summarized in Table II. The pattern of correlations for the 2 DHA indicators is very similar across these developmental end points. Higher cord DHA concentration is associated with a longer period of gestation. The dose-response analysis (Figure) shows that most of the benefit occurs when the DHA concentration reaches 3% of fatty acids, with little additional benefit thereafter. The gestation length of the infants with cord DHA concentrations ≥3% averages 4.2 days longer than in infants with lower cord DHA levels ($t\ [107] = -1.97$, $P < .05$). The relation of cord DHA/AA to birth weight falls short of statistical significance after adjustment for confounders. Moreover, once gestational age is added to the regression analysis, the standardized regression coefficient for DHA/AA falls to 0.08, suggesting that any apparent beneficial effect of DHA on fetal growth is attributable to a longer period of gestation. Higher cord DHA/AA ratio is associated with better visual acuity at 6 months, although not at 11 months. Higher cord DHA and DHA/AA ratio are associated with greater novelty preference on the FTII at 6 months. Beneficial effects are also seen on the Bayley mental and psychomotor development indices at 11 months. The effects on FTII novelty preference and the BSID-II mental index are generally dose dependent (Figure), but the effect on 6-month acuity is seen only at the highest DHA concentrations (>4.3 %), and the effect on the psychomotor index is evident only in the 2 highest prenatal intake groups.

Relation of Postnatal DHA Intake from Breast Milk to Developmental Outcome

Of the infants who were not adopted, 87.7% were exclusively breast fed for at least 1 month, 55.6% for at least 3 months, and 33.3% for at least 9 months. Each of the 6- and 11-month outcomes listed in Table II was also examined in a multiple regression analysis in relation to postnatal DHA from breast-feeding (assessed in terms of maternal DHA plasma phospholipid concentration weighted by weeks of exclusive breast-feeding). Only 1 of these end points, 6-month visual acuity, is even marginally related to postnatal DHA intake ($r = 0.24$, $P < .06$; none of the control variables met criteria for inclusion in the analysis). When cord DHA and postnatal DHA intake are entered together in a multiple regression with 6-month acuity, neither effect is statistically significant, presumably because of multicollinearity.

Table II. Relation of prenatal DHA and DHA/AA ratio to developmental outcome

	N	Confounders and suppressors[b]	b ± (SE)[a] Step 1	b ± (SE)[a] Final model	r	β[c]
Gestational age (days)						
DHA	109	None	2.1 (0.8)	2.1 (0.8)	.23*	.23*
DHA/AA	91	SES	12.5 (6.9)	12.0 (6.9)	.19†	.17
Birth weight (g)						
DHA	109	Parity, sex	78.6 (38.3)	55.7 (38.8)	.19*	.14
DHA/AA	109	Parity	673.1 (296.6)	558.2 (295.3)	.21*	.19†
Birth length (cm)						
DHA	108	Sex	0.3 (0.1)	0.2 (0.1)	.19*	.13
DHA/AA	108	Sex, pregnancy smoking	1.5 (1.2)	1.1 (1.1)	.13	.09
Birth head circumference (cm)						
DHA	108	Parity, sex	0.1 (0.1)	0.1 (0.1)	.12	.04
DHA/AA	108	Parity, sex, pregnancy smoking	1.2 (0.1)	0.7 (0.1)	.13	.08
Visual acuity—6 months (cycles/degree)						
DHA	78	Pregnancy alcohol and smoking	0.3 (0.2)	0.4 (0.2)	.14	.17
DHA/AA	78	Pregnancy alcohol	4.3 (1.8)	5.0 (1.8)	.26*	.31‡
Visual acuity—11 months (cycles/degree)						
DHA	80	Infant age, SES, cord lead	−0.2 (0.3)	−0.3 (0.3)	−.08	−.1
DHA/AA	80	Infant age, SES, cord lead	−0.1 (2.2)	−1.0 (2.0)	−.01	−.05
Fagan novelty preference—6 months (%)						
DHA	76	HOME, maternal age, cord PCBs	1.2 (0.6)	1.6 (0.6)	.19†	.3‡
DHA/AA	85	Pregnancy smoking, maternal age, cord PCBs	8.2 (4.7)	12.4 (4.9)	.19†	.28*
Fagan novelty preference—11 months (%)						
DHA	84	Infant age, cord PCBs and mercury	−0.3 (0.6)	−0 (0.6)	−.05	−.0
DHA/AA	84	Infant age, cord PCBs and mercury	−5.5 (4.6)	−3.9 (4.5)	−.13	−.09
Fagan fixation duration—6 months (s)						
DHA	72	Maternal language and vocabulary, cord lead, maternal Raven and education, SES	−0 (0)	−0 (0)	−.06	−.06
DHA/AA	72	Maternal language and vocabulary, cord lead, maternal Raven and education, SES	0 (0.4)	−0.1 (0.3)	.01	−.03
Fagan fixation duration—11 months (s)						
DHA	76	Maternal Raven, HOME, cord lead, SES, cord mercury	−0 (0)	−0 (0)	−.06	−.07
DHA/AA	74	HOME, cord lead, SES, cord mercury	−0.2 (0.2)	−0.3 (0.2)	−.09	−.15
BSID-II Mental Development Index						
DHA	80	Cord mercury	0.7 (0.3)	0.6 (0.3)	.27*	.23*
DHA/AA	76	Cord mercury and PCBs, HOME	3.2 (2.5)	1.2 (2.6)	.15	.05
BSID-II Psychomotor Development Index						
DHA	80	Maternal vocabulary, pregnancy marijuana	0.5 (0.3)	0.5 (0.3)	.2†	.18
DHA/AA	80	Maternal vocabulary, pregnancy marijuana	4.7 (2.1)	4.6 (2.1)	.24*	.24*

[a]Raw regression coefficient ± (standard error).
[b]Listed in order of entry into the model.
[c]Standardized regression coefficient.
*$P < .05$.
†$P < .1$.
‡$P < .01$.

The results of regression analyses relating prenatal and postnatal DHA intake to postnatal somatic growth are summarized in Table III. Birth size (weight, length, or head circumference), cord plasma DHA, and maternal plasma DHA weighted by weeks of breast-feeding were entered in the first step of each regression, and the results designated as $\beta_{\text{Step 1}}$ in the table show the effects on growth from birth through 6 and 11 months before adjustment for potential

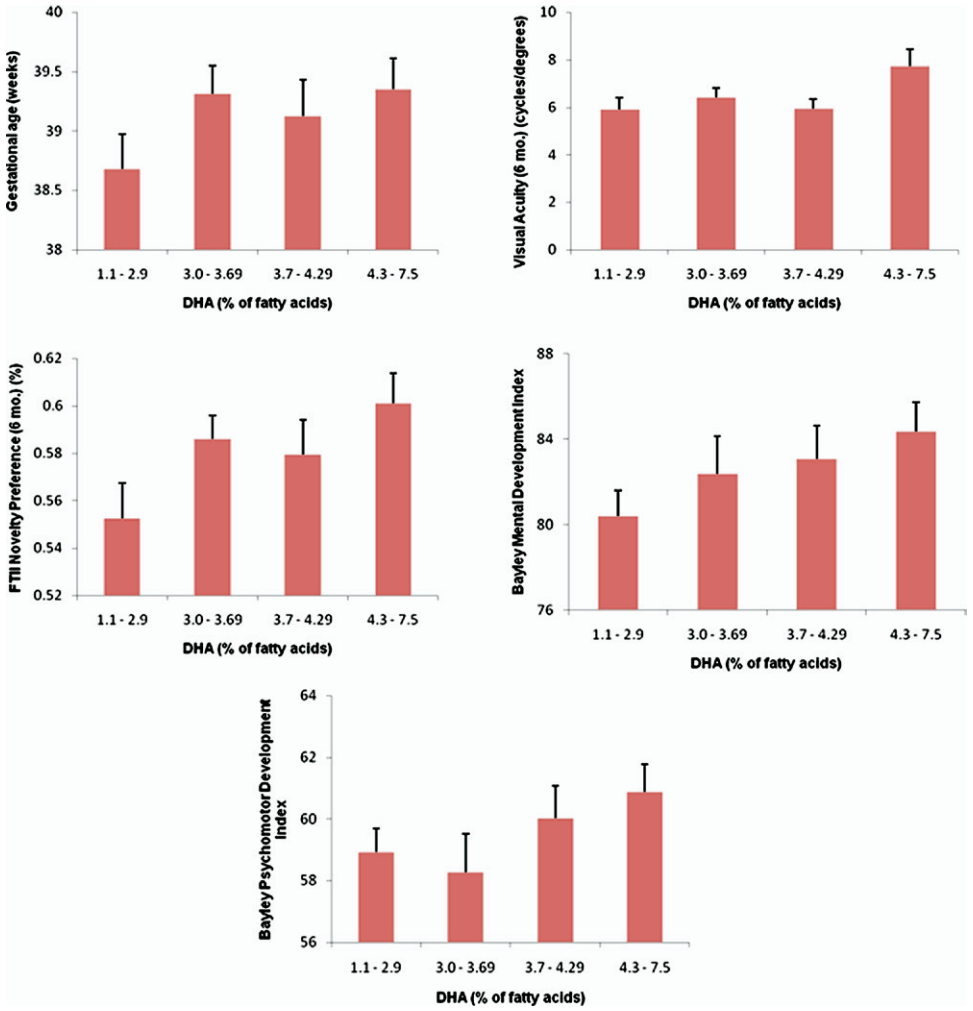

Figure. Relation of cord plasma phospholipid DHA concentration to developmental outcome. Outcome measures are adjusted for the potential confounders listed in Table II.

confounders. The control variables were then entered hierarchically following the procedure aforementioned. In contrast to the effects seen on visual acuity and cognitive outcome in Table II, cord DHA concentration is not related to any of the measures of postnatal growth. However, the postnatal DHA intake measure is associated with slower weight gain through 11 months, with an effect on 6-month weight gain that falls short of statistical significance. The relation of DHA intake from breast-feeding to 11-month weight gain was examined in an additional regression analysis, in which 11-month weight (adjusted for birth weight and the control variables listed in Table III) was examined in relation to each of the components of DHA breast-feeding intake: maternal DHA and weeks of breast-feeding. Breast milk intake and maternal DHA body burden are independently related to 11-month weight gain ($\beta = -0.43$, $P < .001$, and $\beta = -0.27$, $P < .05$, respectively), suggesting that higher DHA concentration in breast milk contributes to slower 11-month weight gain over and above the reduction in weight gain generally observed in breast-fed children.

DISCUSSION

The DHA and AA concentrations in blood plasma phospholipids and breast milk in this cohort are similar to those seen in Finland, another society in which fish is a substantial part of the diet. DHA concentrations are markedly higher than in other North American samples, and AA concentrations are lower. This higher ratio of DHA to AA may reflect the competition of these PUFAs for the same metabolic pathways.[4] The DHA concentrations are similar to those found by Otto et al[43] in 4 European countries and Ecuador, although not as high as those attained in a Norwegian fish oil supplementation study.[1] Our finding that DHA concentration is significantly higher in cord plasma than in maternal plasma provides additional support for preferential placental uptake of DHA from the mother during the third trimester spurt of synaptogenesis in brain and photoreceptor development.[7] The strong correlation between cord and maternal DHA concentration, which is consistent with data from 5 other populations,[43] provides additional evidence of the fetus' strong dependence on the mother for an adequate

Table III. Relation of prenatal DHA and DHA from breast milk to postnatal growth

		Prenatal DHA			DHA from breast milk		
	N	*r*	$\beta_{\text{Step 1}}$	$\beta_{\text{final step}}$	*r*	$\beta_{\text{Step 1}}$	$\beta_{\text{final step}}$
6 months							
Weight[a]	73	−.08	−.03	−.16	−.26*	−.27*	−.22†
Height[b]	71	.07	−.03	.03	−.05	−.07	−.06
Head circumference[c]	74	−.02	−.04	−.14	−.13	−.14	−.09
12 months							
Weight[d]	63	−.08	.04	−.18	−.48§	−.52§	−.38‡
Height[e]	62	.03	.07	−.1	−.16	−.19	−.07
Head circumference[f]	67	−.0	.01	−.18†	−.17	−.27*	−.14

$\beta_{\text{Step 1}}$ shows relation of DHA to 6- or 12-month size, controlling for the corresponding birth size measure (eg, 6-month weight, controlling for birthweight).
$\beta_{\text{final step}}$ shows relation after controlling for birth size and the control variables that are listed below in the order of their entry into the model.
[a]Control variables: sex, cord PCBs.
[b]Control variables: sex, SES, infant age at assessment, cord mercury.
[c]Control variables: sex, cord PCBs, infant age at assessment, pregnancy alcohol.
[d]Control variables: cord PCBs, sex, infant age at assessment, cord lead.
[e]Control variables: infant age at assessment, sex, SES, cord PCBs, pregnancy smoking.
[f]Control variables: sex, cord PCBs, infant age at assessment.
*$P < .05$.
†$P < .1$.
‡$P < .01$.
§$P < .001$.

supply of DHA. The very weak cord-maternal AA correlation indicates much less dependence on the mother for AA, a pattern that Otto et al[43] attribute to the substantially greater availability of AA in most contemporary maternal diets.

Our data are consistent with prior studies indicating beneficial effects of DHA on length of gestation.[44,45] Two Danish studies[8,9] reported average increases in gestation length of 4 days and 8.5 days, respectively, in women who were given supplements of fish oil containing DHA and eicosapentaenoic acid (EPA; 20:5n-3) during pregnancy. Smuts et al[10] reported a 6-day increase in gestation length in mothers who ate DHA-enriched eggs during pregnancy in an economically disadvantaged U.S. sample. The 4.2-day increment in gestation length in our naturally occurring, correlational study is comparable with that seen in the randomized controlled food supplementation trials. As in earlier studies,[10,46] there is also some suggestion of a positive association between cord DHA concentration and increased fetal growth, but, as reported elsewhere, this association appears to be primarily caused by the effect of DHA in prolonging the period of gestation.[1,8]

Most of the beneficial effect on gestation length is evident once cord DHA concentration reaches 3% of fatty acids, with no apparent additional benefit at higher concentrations (Figure). This pattern is consistent with data from a large Norwegian survey, in which most of the benefit to gestation length was seen at the lower end of the distribution for omega-3 fatty acid intake estimated from fish consumption.[46] Similarly, Olsen et al[45] found a stronger association between maternal omega-3 erythrocyte concentration and gestation length in a Danish sample in which low-to-moderate quantities of fish were consumed during pregnancy than in the Faroe Islands, where LCPUFA intake is substantially higher throughout the population. The conclusion that the beneficial effect on gestation length occurs primarily at the lower end of the distribution is further buttressed by the clinical trial of Smuts et al,[10] in which the 6-day gestation length benefit was seen in an LCPUFA-deficient, inner-city U.S. sample, even though the absolute quantities of DHA ingested by the women who were given supplements were relatively modest. For mechanism, it has been suggested that DHA may prolong gestation by decreasing the synthesis of 2 prostaglandins, E_2 and $F_{2\alpha}$, which are derived from AA and required for labor and delivery,[47] by competing with and reducing the availability of AA in membrane phospholipids, by retroconversion to EPA, which produces less potent prostaglandins, or both.[48]

The association of a higher DHA/AA ratio in cord plasma with better 6-month visual acuity is consistent with the importance of DHA for retinal development, with a report by Malcolm et al[49] linking higher cord DHA concentration with more optimal visual function assessed with visual-evoked potentials at 11 and 15 months postpartum, and with findings from numerous formula supplementation studies.[11,50,51] Our finding that this benefit is seen only in the infants with the highest levels of prenatal intake (Figure) is consistent with the formula supplementation literature, in which most studies that used low-dose supplementation found either transitory effects[52] or no benefit.[53-55]

This study, which is the first to examine the effects of naturally occurring variability in prenatal DHA intake on cognitive and motor development, complements findings from maternal dietary supplementation studies about the beneficial effects of increased maternal DHA intake during pregnancy. Better performance on the BSID-II psychomotor development index has been reported in some formula supplementation studies, but not others.[11,13-15,56] DHA may be particularly beneficial in this Inuit population, in which the

infants' average psychomotor development score (93.1) is less than the U.S. norm of 100. For BSID-II mental development, although only 1 formula supplementation study reported positive findings,[11,13-15] our data provide the first evidence of beneficial effects from greater third trimester DHA availability.

Cord plasma DHA was also associated with better performance on the FTII novelty preference measure. This finding is consistent with a report by O'Connor et al[11] that linked LCPUFA formula supplementation to improved FTII novelty preference and with data from Colombo et al[36] that linked higher maternal blood DHA concentration to more rapid development of infant visual information processing during the first postpartum year. The effect on the FTII is important because the predictive validity of 6-month novelty preference for childhood IQ is well established.[57] Additional evidence for the long-term impact of early DHA intake on cognitive function comes from the study aforementioned that linked fish oil supplementation in pregnancy to better cognitive performance in preschool-age children.[19] In contrast to 2 formula supplementation studies,[16,58] we did not find an association of prenatal DHA intake with FTII fixation duration.

Prenatal DHA intake in this Inuit sample, whose diet includes both traditional native food high in LCPUFA and imported Western pre-prepared foods, ranged from very low levels similar to those commonly found in Southern Canada and the United States to higher levels comparable with those found in Europe in the early 1990s. Within this range, we found that higher cord plasma DHA concentration and a higher DHA/AA ratio are more optimal for infant visual, cognitive, and motor development, as would be predicted from the need for substantial increases in DHA during the third trimester spurt of synaptogenesis in brain and photoreceptor development.

The association of breast-feeding duration with decreased weight gain through 11 months is consistent with the observation that breast-fed children generally gain weight more slowly. The finding that maternal DHA body burden is associated with reduced weight gain, even after controlling for breast milk intake, suggests that a higher DHA concentration in breast milk may contribute additionally to limiting weight gain during the first year. It should be noted that, in contrast to some formula supplementation studies that found decreased length, head circumference, or both,[54,59-61] only weight was affected here. The relation of postnatal DHA to 6-month visual acuity fell short of statistical significance. Because of multicollinearity, it was not possible to determine the degree to which the beneficial effects on 6-month acuity are attributable primarily to pre- or postnatal DHA intake.

Although DHA formula supplementation studies have documented beneficial effects on infant cognitive and motor development, we found no benefits on these end points in relation to postnatal DHA intake via breast-feeding in this sample of full-term infants. The absence of associations with postnatal intake could be caused by less precise measurement than was available for prenatal intake. The maternal body burden component of the postnatal measure was based on a blood sample obtained at a single point shortly after delivery, and the month-to-month stability of DHA plasma phospholipids can vary with changes in the diet. These considerations notwithstanding, it seems likely that the beneficial effects of third trimester DHA intake will be more important than postnatal intake for full-term infants because of the importance of an adequate supply of DHA during the critical third trimester brain growth spurt. In light of our finding relating prenatal DHA to better performance on the 6-month FTII and the well-documented predictive validity of that measure for childhood IQ, it will be of particular interest to examine the degree to which the beneficial effects of increased third trimester DHA intake continue to be evident at school age.

We thank the Nunavik Nutrition and Health Committee, Municipal Councils of Puvirnituq, Inukjuak, and Kuujjuarapik, Pauktuutit Inuit Women's Association, and Nunalituqait Ikaluqatigiitut for their support. We also appreciate the contributions of Edna Lachance, Christine Bouffard, Karine Poitras, Carole Vezina, and Jocelyne Gagnon, who collected the data in the field, and Neil Dodge and Jocelyne Gagnon, who assisted in the data analysis.

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Appendix Table. Intercorrelations of cord DHA, cord DHA/AA, and control variables

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1. Cord DHA	—																			
2. Cord DHA/AA ratio	.83§ (109)	—																		
3. Maternal age	.23* (109)	.17† (109)	—																	
4. Parity	.19* (109)	.17† (109)	.73§ (109)	—																
5. Sex[a]	.18† (109)	.14 (109)	.17† (109)	.15 (109)	—															
6. Age at 6-month assessment	−.1 (87)	−.08 (87)	−.06 (87)	−.05 (87)	−.12 (87)	—														
7. Age at 11-month assessment	.26* (78)	.25* (78)	.05 (78)	.06 (78)	.01 (78)	.12 (74)	—													
8. SES	−.08 (91)	−.14 (91)	−.02 (91)	−.03 (91)	.06 (91)	−.05 (87)	.08 (78)	—												
9. Pregnancy alcohol use	.16 (105)	.12 (105)	.11 (105)	.01 (105)	−.11 (105)	−.01 (.87)	.23* (78)	.02 (91)	—											
10. Pregnancy cigarette use	.06 (109)	.09 (109)	.14 (109)	.14 (109)	.13 (109)	.16 (87)	.27* (78)	−.02 (91)	.14 (105)											
11. Pregnancy marijuana use[b]	.08 (109)	.08 (109)	.01 (109)	−.12 (109)	−.06 (109)	.07 (87)	.05 (78)	−.19† (91)	.12 (105)	−.05 (109)	—									
12. Cord PCBs	.22* (108)	.23* (108)	.27‡ (108)	.13 (108)	.05 (108)	.1 (86)	.09 (78)	.02 (90)	.08 (104)	.14 (108)	.01 (108)	—								
13. Cord mercury	.30‡ (105)	.33‡ (105)	.05 (105)	.15 (105)	−.02 (105)	.06 (85)	.13 (77)	−.19† (89)	−.03 (101)	.01 (105)	−.01 (105)	.21* (105)	—							
14. Cord lead	.08 (105)	.12 (105)	.45§ (105)	.34§ (105)	.1 (105)	.09 (85)	.06 (77)	−.03 (89)	−.01 (101)	.15 (105)	.02 (105)	.14 (105)	.18† (105)	—						
15. Maternal education	.01 (.91)	−.11 (91)	.11 (91)	.06 (91)	.12 (91)	−.1 (87)	.04 (78)	.31‡ (91)	−.05 (91)	.07 (91)	−.19† (91)	−.07 (90)	.06 (89)	−.12 (89)	—					
16. Maternal vocabulary	.19† (88)	.12 (88)	.19† (88)	.17 (.88)	−.05 (88)	−.08 (85)	.1 (76)	.2† (88)	.18† (88)	.05 (88)	−.03 (88)	.13 (87)	−.11 (86)	−.38§ (86)	.38§ (88)	—				
17. Maternal Raven	.18† (88)	.04 (88)	−.18† (88)	−.12 (88)	.13 (88)	−.07 (84)	.13 (77)	.3‡ (88)	.12 (88)	.01 (88)	−.05 (88)	−.06 (87)	−.03 (86)	−.29‡ (86)	.39§ (88)	.35‡ (86)	—			
18. HOME	.1 (82)	.13 (82)	.14 (82)	.24* (82)	.06 (82)	.08 (78)	.16 (73)	.16 (82)	.15 (82)	.26* (82)	−.13 (82)	.17 (81)	−.11 (80)	−.01 (80)	.16 (82)	.38‡ (79)	.04 (80)	—		
19. Maternal language[c]	−.08 (91)	−.08 (91)	−.2† (91)	−.12 (91)	.06 (91)	.05 (87)	−.19† (78)	−.03 (91)	−.08 (91)	−.19† (91)	.03 (91)	−.11 (90)	.06 (89)	.2† (89)	−.27* (91)	−.38§ (88)	−.07 (88)	−.43§ (82)	—	
20. Child adopted[d]	−.03 (91)	−.01 (91)	−.13 (91)	−.01 (91)	−.11 (91)	.17 (87)	.35‡ (78)	−.07 (91)	.03 (91)	.05 (91)	.20† (91)	.1 (90)	.05 (89)	−.05 (89)	−.38§ (91)	.16 (88)	−.13 (88)	.03 (82)	−.05 (91)	—

SES, Socioeconomic status; *Raven*, ; *HOME,* Home Observation for Measurement of the Environment.
[a]1 = female, 2 = male.
[b]≥4 days/month; 0 = no, 1 = yes.
[c]1 = English or French, 2 = Inuktituk.
[d]0 = no, 1 = yes.
*$P < .05$.
†$P < .1$.
‡$P < .01$.
§$P < .001$.