0031-3998/06/6003-0334
PEDIATRIC RESEARCH

Vol. 60, No. 3, 2006
Printed in U.S.A.

Neurologic Condition of Healthy Term Infants at 18 Months: Positive Association With Venous Umbilical DHA Status and Negative Association With Umbilical *Trans*-fatty Acids

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ABSTRACT: Prenatal long-chain polyunsaturated fatty acids (LCPUFAs) and *trans*-fatty acids may affect neurodevelopment. In healthy term children, we determined relationships between relative fatty acid contents of umbilical arteries and veins and neurodevelopment at 18 mo. The study comprised a mixed group of 317 breast-fed, formula-fed, and LCPUFA formula–fed children. Study endpoints were the Hempel neurologic examination resulting in a neurologic classification and neurologic optimality score (NOS), and the Bayley Psychomotor Developmental Index (PDI) and Mental Developmental Index (MDI). Fifteen children showed minor neurologic dysfunction (MND). The umbilical vein *trans, trans*-18:2n-6 content was higher in children with MND than in the normal group. The NOS was significantly reduced in infants with an umbilical vein docosahexaenoic acid (DHA) content within the lowest quartile. Umbilical vein arachidonic acid (AA) was related to NOS in univariate statistics but not in multivariate analyses. The sum of *trans*-fatty acids and that of C18 *trans*-fatty acids showed a negative association with NOS in both univariate and multivariate analyses. No associations were found between AA, DHA and total *trans*-fatty acids with PDI or MDI. In conclusion, neonates with a relatively low DHA status and those with high *trans*-fatty acid levels have a less favorable neurologic condition at 18 mo. **(*Pediatr Res* 60: 334–339, 2006)**

Little is known about the effects of prenatal essential fatty acid and long-chain polyunsaturated fatty acid (LCPUFA) status on long-term neurodevelopmental outcome in healthy term infants. This is remarkable because there are many indications that LCPUFAs play an important role in the development and function of the nervous system (1,2). LCPUFAs, notably DHA, affect biochemical properties of cell membranes and may alter signal transduction, gene expression, and cell function in the nervous system (1,3,4). Rapid accretion of LCPUFAs takes place in the infant's nervous tissue during pre- and early postnatal life when infants do not seem to synthesize sufficient amounts of LCPUFAs from their precursors to cover their high demands (5,6). The exclusive source of LCPUFAs during the prenatal period is supplied from maternal stores and maternal diet, a supply that is reflected by the LCPUFA content of the umbilical vein (7). Two recent studies indicated that the umbilical cord content of DHA, AA, and EFA is related to neurologic condition at postnatal d 10–14 and at 3 mo (8,9). Two other studies found no relationship between neonatal fatty acid status and cognitive function at 4 and 7 y of age (10,11).

Koletzko (12) found that neonatal *trans*-fatty acid status is inversely correlated to birth weight in preterm infants. Little is known about the effects of *trans*-fatty acids on development and child health, but the available data indicate that *trans*-fatty acids may have adverse effects because of their negative association with LCPUFA status (13–15). A review by Larqué *et al.* (16) indicated that *trans*-fatty acid intake in adults averages 2–8 g/d (2.5% of total energy intake). This intake has been quite stable in the past decades due to a counterbalancing effect of more intake of hydrogenated oil and decreases in *trans*-fatty acid content in food (16). A report of the Dutch Ministry of Health, Welfare, and Sports indicated that adult intake of *trans*-fatty acids in The Netherlands in 2003 averaged 2.8 g/d (1.1% of total energy intake) (17). It is possible that *trans*-fatty acid exposure during early life may affect the infant's neurologic condition (16).

The primary aim of this study is to evaluate in healthy term infants, the relationship between the relative LCPUFA content in the umbilical wall, used as a proxy of prenatal LCPUFA status, and neurodevelopmental outcome at 18 mo of age. The secondary aim was to study the relationship between *trans*-fatty acid content in the umbilical wall and neurodevelopmental outcome at 18 mo.

METHODS

Subjects. This study is part of a double-blind, randomized, controlled trial investigating the effect of LCPUFA supplementation on neurodevelopment of healthy term infants. Details of the study design have been described elsewhere (18). Briefly, mother-infant pairs were recruited during pregnancy

Received February 16, 2006; accepted April 19, 2006.
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The study was financially supported by Numico Research B.V.

DOI: 10.1203/01.pdr.0000233043.16674.1d

Abbreviations: AA, arachidonic acid; **DHA,** docosahexaenoic acid; **EFA,** essential fatty acid; **LCPUFA,** long-chain polyunsaturated fatty acid; **MDI,** mental developmental index; **MND,** minor neurologic dysfunction; **NOS,** neurologicoptimality score; **PDI,** psychomotor development index

checkup visits at various locations in and near Groningen at which time the parents provided written informed consent. Final enrollment in the study occurred in the neonatal period, at which time parents provided written informed consent. Enrollment occurred between February 1997 and October 1999. All infants were born at 37–42 wk of gestation and were of native West European origin. Excluded from the study were children with a congenital disorder interfering with adequate functioning in daily life, children from multiple births, children whose mother did not master the Dutch language or suffered from significant illness or disability, and children who were adopted and fostered. The study population comprised 474 infants. Three study groups were formed; two randomized formula groups and a breast-fed group (n = 159). The control formula group (n = 169) received a commercially available formula (Nutrilon Premium; Nutricia, Zoetermeer, The Netherlands) for 6 mo. The LCPUFA-supplemented formula group (n = 146) received the same formula enriched with 0.45% AA and 0.30% DHA for 2 mo. After 2 mo, the LCPUFA-supplemented group received control formula until the age of 6 mo. Breast-feeding was done as long as possible. If breast-fed infants required formula feeding as a supplement or when breast-feeding stopped, they received LCPUFA-supplemented formula until 2 mo and control formula from 2 to 6 mo. The parents and the examiners were unaware of the type of formula that the infants received. The study was approved by the Ethics Committee of the Groningen University Hospital (MEC 95/08/207).

Analysis of fatty acids of the umbilical vessels. Permission to collect umbilical cord tissue was granted for 317 infants, *i.e.* 67% of the original population (Fig. 1). The umbilical cord was immediately collected after parturition. Seven- to 10-cm samples were taken at the most proximal site of the placenta and stored in saline at 4°C according to established methods (19). Fatty acid methyl esters were determined by high-resolution capillary gas liquid chromatography as described by Dijck-Brouwer *et al.* (8) and Decsi *et al.* (20). Data were expressed as % by wt of fatty acids with chain lengths of 14 to 24 carbon atoms (19). The detection limit of *trans*-fatty acids was one molecule among 10,000, *i.e.* 0.01%. A typical chromatogram of *trans*-fatty acids detected in our laboratory has been published (21)

Neurologic assessments at 18 mo. Follow-up at the age of 18 mo consisted of two different neurodevelopmental assessments: the neurologic examination according to Hempel and the Bayley Scales of Infant Development (BSID). Follow-up for the various developmental outcome parameters in infants for whom information on fatty acid values in the umbilical cord was available is shown Figure 1. The social and perinatal background of the infants who were included in the present analyses, and the infants without assessments or fatty acid samples are shown in Table 1.

Each child was assessed neurologically using the technique described by Hempel (22). It measures in a standardized free-field situation motor functions (grasping, sitting, crawling, standing, and walking). In addition to the assessment of motor milestones, the quality of motor behavior is also assessed. In addition, muscle tone, reflexes and the function of the cranial nerves are assessed. Each toddler was classified as neurologically normal, showing signs of minor neurologic dysfunction (MND), or as definitely abnormal. The classification of definitely abnormal implies the presence of a distinct neurologic syndrome, which leads to severe limitations in function and social participation, such as cerebral palsy. MND implies the presence of a functional impairment that may be associated with some degree of disability. Examples are mild deviations in gross and fine motor function or mild abnormalities in muscle tone regulation or reflexes. After classification into distinct categories, we used the optimality concept to summarize the neurologic condition. The optimal range was defined from 57 items of the neurologic examination list. The NOS is the sum of the number of items with outcomes within the predefined optimal range (23,24).

The BSID-II was used to assess mental and psychomotor development at the age of 18 mo (25). The Mental Developmental Index (MDI) and the Psychomotor Developmental Index (PDI) were scored based on the number of items that were successfully completed. Because the children were not exactly 18 mo of age at the time of the assessment, we converted the scores into age-normalized values, as derived from recently developed Dutch norms (26). The MDI assesses memory, problem solving, discrimination, classification, language, and social skills. The PDI measures control of gross and fine muscle groups, including walking, running, jumping, grasping, and imitation of hand movements.

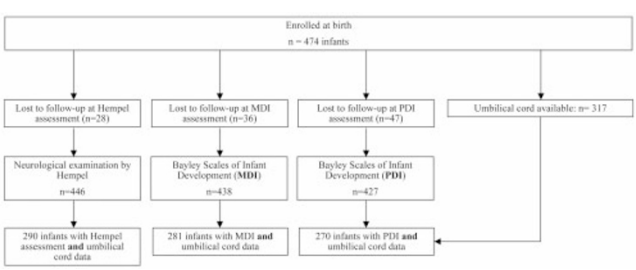

Figure 1. Flow diagram of infants included into the study and assessed at 18 mo of age. Total number of participants at enrollment: n = 474 {control formula group (n = 169), LCPUFA formula (n = 146), breast-feeding (n = 159)}.

Assessment of potential confounders. Detailed and standardized information on the infants' social and perinatal conditions was collected. For the latter, we used the 74 variables of the obstetric optimality score (OOS), which range from the parents' socioeconomic status and health condition to the infant's condition immediately after birth. The sum of the number of items having outcomes within a predefined optimal range forms the OOS score (27). We used the information obtained from the OOS both as raw data dichotomized into optimal and nonoptimal categories. Besides collecting information on the parent's level of education and occupation, social condition was also assessed by the Home Observation for Measurement of the Environment (HOME) inventory (28). The importance of taking into account the role of social factors in the analyses of the relationships between neonatal fatty acid status and developmental outcome is underlined by the fact that social economic characteristics and fatty acid status in the umbilical vein are related (Table 2) (17).

Statistics. The PDI and MDI had a normal distribution. The distribution of the NOS was skewed to the left. To achieve normality, we performed the following transformation: $-\ln(58.5 - \text{NOS})$. To calculate differences in fatty acid composition in umbilical vein and artery between the children with a normal neurologic condition and those with MND, we performed the Mann-Whitney test. The analyses focused on the relationship between the relative fatty acid contents of the umbilical wall (vein and artery) and the NOS and the Bayley MDI and PDI. Univariate nonparametric Spearman's correlations were used to calculate the correlations because most fatty acid data were nongaussian distributed. Subsequently, multivariate analyses were carried out by means of linear logistic regression analyses. This allowed elucidation of the relationship between the umbilical fatty acid content at birth and neurologic condition at 18 mo while correcting for potential confounders such as other umbilical fatty acids, type of postnatal feeding, the postnatal age of the infant at the time of follow-up assessment, paternal smoking, and the OOS. To calculate the effect of postnatal feeding, a dummy variable was created for the four following nutritional groups: LCPUFA formula, control formula, breast milk for ≤6 wk, breast milk >6 wk. p Values <0.05 were considered significant. Statistical analyses were performed using the statistical package for social sciences (SPSS 10; SPSS Inc., Chicago, IL).

RESULTS

Clinical neurologic classification. The umbilical fatty acids that were analyzed and related to neurodevelopmental outcome are presented in Table 3.

None of the participants of the study showed a definitely abnormal neurologic condition such as cerebral palsy. Two hundred ninety children had a normal neurologic condition (95% of the study population) and 15 children had MND. The differences in fatty acid composition of the umbilical vein and artery between the neurologically normal children and those with MND are shown in Table 4. Children with MND had a significantly lower 20:0 content in their umbilical veins and arteries than neurologically normal children. Furthermore, *trans, trans*-18:2n-6 content in the umbilical vein was higher in children with MND than those in the normal group.

NOS. The correlation between the fatty acid composition of the umbilical vein and NOS is shown in Table 5. Univariate analysis revealed that AA in the umbilical vein showed a significantly positive relationship with NOS. The association was mainly explained by the difference in NOS between infants with umbilical vein AA content at or below the 50th percentile and those with umbilical vein AA content above the 50th percentile (p = 0.02, Fig. 2). The Spearman rank correlation did not reveal a relationship between DHA content of the umbilical vein and NOS (Table 5). However, closer in-

Table 1. *Social and perinatal characteristics of the infants*

	Study group	No samples or no NOS available	*p*
No. of infants (%)	290 (61%)	184 (39%)	
Male gender (%)	55%	52%	NS
Birth weight, g (mean ± SD)	3547 ± 430	3533 ± 501	NS
Birth order: first born (%)	60%	40%	NS
Maternal age, yr (mean ± SD)	30 ± 4.2	30 ± 4.6	NS
Maternal education: higher education (%)	22%	20%	NS
Paternal education: higher education (%)	22%	26%	NS
Maternal smoking during pregnancy (%)	25%	36%	NS
Paternal smoking during pregnancy (%)	41%	53%	0.02
Maternal alcohol consumption during pregnancy (%)	13%	17%	NS
Obstetric optimality score (mean ± SD)	62 ± 3.7	61 ± 4.7	0.05

NS, not significant.

Table 2. *Relationship between venous umbilical LCPUFAs,* trans*-fatty acids, and social economic characteristics*

	AA		DHA		Total c18 *trans*-fatty acids		Total *trans*-fatty acids	
	Median	Range	Median	Range	Median	Range	Median	Range
Maternal education								
Low	16.51	11.1–19.9	4.29	2.82–6.76	0.176	0.04–1.14	0.696	0.27–1.62
High*	16.56	13.4–21.1	4.23	2.93–7.47	0.172	0.05–1.36	0.739	0.32–1.94
Paternal education								
Low	16.63	11.1–21.1	4.28	2.82–6.76	0.165	0.04–1.14	0.686	0.31–1.62
High*	16.28‡	13.1–19.8	4.26	3.07–7.47	0.200§	0.08–1.36	0.767§	0.27–1.94
Maternal profession								
Low	16.53	11.1–21.1	4.24	2.82–6.76	0.171	0.04–1.32	0.687	0.27–1.92
High†	16.48	13.4–19.8	4.40‡	3.14–7.47	0.177	0.05–1.36	0.739	0.33–1.94
Paternal profession								
Low	16.61	11.1–19.8	4.27	2.82–6.76	0.168	0.04–1.14	0.697	0.31–1.62
High†	16.31	13.4–21.1	4.27	3.07–7.47	0.191	0.05–1.36	0.714	0.27–1.94
Maternal smoking during pregnancy								
No	16.43	11.1–21.1	4.25	2.82–7.47	0.175	0.04–1.36	0.704	0.27–1.94
Yes	16.86‡	13.1–19.8	4.31	3.08–6.25	0.171	0.04–0.57	0.685	0.35–1.54
Paternal smoking during pregnancy								
No	16.48	14.1–21.1	4.24	2.82–7.47	0.177	0.04–1.36	0.718	0.27–1.94
Yes	16.54	11.7–19.9	4.27	2.76–6.25	0.161	0.04–0.57	0.685	0.33–1.54
Maternal alcohol use during pregnancy								
No	16.54	11.1–21.1	4.24	2.82–6.76	0.170	0.04–1.36	0.691	0.27–1.94
Yes	16.26	13.9–19.8	4.42	2.93–7.47	0.200‡	0.10–0.70	0.753	0.33–1.35

* University education or vocational college.
† Higher profession or independent middle class.
‡ $p < 0.05$.
§ $p < 0.01$.

Table 3. *Fatty acid composition (% by weight) of the umbilical wall of neurologically normal children and those with MND at 18 mo*

	Neurologically normal children ($n = 275$)		Children with MND ($n = 15$)		
	Median %	Range	Median %	Range	*p*
Vein					
20:0	0.43	0.09–2.65	0.36	0.18–0.44	0.006
Trans, *trans*-18:2n-6	0.07	0.00–0.25	0.10	0.03–0.16	0.04
Artery					
20:0	0.50	0.04–2.90	0.41	0.19–0.61	0.02

spection of the data indicated that infants with an umbilical vein DHA content within the lowest quartile had a significantly lower NOS than the other infants ($p = 0.02$, Fig. 2). Multivariate analysis could not confirm the positive association between raw AA or dichotomized AA data and NOS. This approach did, however, confirm the association between the presence of umbilical vein DHA content in the lowest quartile and a lower NOS ($p = 0.003$, standardized $\beta = 0.17$).

The sum of *trans*-fatty acids, the sum of C18 *trans*-fatty acids, and three individual *trans*-fatty acids of the umbilical vein showed significantly negative associations with NOS (Table 5, Fig. 2). The majority of these negative associations remained statistically significant in the multivariate analysis (Table 5). The negative association between the sum of *trans*-fatty acids and the NOS also remained statistically significant when we adjusted for DHA and AA content in the umbilical vein ($p = 0.028$, standardized $\beta = -0.52$) and when we repeated the analyses after exclusion of the breast-fed group ($p = 0.007$, rho $= -0.20$). The latter finding suggests that the association between *trans*-fatty acids and NOS may be attributed to prenatal and not postnatal *trans*-fatty acid exposure.

No associations between essential fatty acids, LCPUFAs, or *trans*-fatty acids in the umbilical artery and the NOS were found.

Table 4. *Relative fatty acid composition of the umbilical vein and artery*

	Vein				Artery			
Fatty acid	No.	Median % of weight	Range	% below detection limit	No.	Median % of weight	Range	% below detection limit
14:0	312	1.09	0.61–2.7	0	307	1.28	0.64–2.2	0
15:0	312	0.73	0.23–4.5	0	307	0.71	0.06–7.1	0
16:0	312	25.5	20.7–34.0	0	307	23.6	19.8–38.4	0
18:0	312	18.1	14.4–23.1	0	307	18.8	9.0–25.7	0
20:0	312	0.42	0.09–2.7	0	307	0.50	0.04–2.9	0
22:0	312	0.97	0.33–2.4	0	307	1.3	0.35–1.9	0
24:0	312	1.77	1.2–2.6	0	307	2.4	1.0–3.7	0
SAFAs	311	48.6	44.8–61.8		307	48.8	43.7–58.8	
18:3n-3	311	0.01	0.0–0.24	0	306	0.01	0.0–0.17	0
20:5n-3	311	0.01	0.0–0.14	6.8	306	0.02	0.0–0.17	4.9
22:5n-3	311	0.35	0.08–1.1	0	306	0.31	0.08–0.77	0
22:6n-3	311	4.3	2.8–7.5	0	306	4.4	1.4–7.1	0
Sum n-3	311	4.6	2.9–8.6		306	4.8	1.7–7.9	
18:2n-6	311	2.6	1.4–4.0	0	306	1.6	0.70–2.9	0
18:3n-6	311	0.044	0.0–0.38	0	306	0.07	0.0–0.74	0
20:2n-6	311	0.35	0.04–0.94	0	306	0.14	0.01–0.87	0
20:3n-6	311	2.2	0.89–3.8	0	306	1.5	0.73–2.8	0
20:4n-6	311	16.5	11.1–21.1	0	306	12.8	9.0–18.8	0
22:4n-6	311	5.2	2.3–8.5	0	306	3.0	1.5–5.6	0
22:5n-6	311	2.9	1.4–4.7	0	306	3.5	1.8–5.5	0
Sum n-6	311	30.1	19.0–35.0		306	23.3	15.7–31.4	
16:1n-7	311	0.53	0.22–1.1	0	306	0.52	0.07–1.1	0
18:1n-7	311	2.4	1.4–3.9	0	306	2.8	1.7–3.8	0
Sum n-7	311	2.9	1.8–4.4		306	3.3	2.0–4.4	
18:1n-9	311	8.8	6.8–11.2	0	306	11.5	7.9–16.4	0
20:1n-9	311	0.36	0.06–3.9	0	306	0.49	0.13–9.4	0
20:3n-9	311	0.33	0.02–2.6	0	306	2.6	0.46–5.8	0
22:1n-9	311	0.04	0.0–0.20	0	306	0.07	0.0–0.20	0
24:1n-9	311	3.7	2.4–5.7	0	306	3.9	2.3–5.6	0
Sum n-9	311	13.5	9.7–20.2		306	18.8	11.1–26.0	
TT18:2n-6	311	0.07	0.0–0.25	0	306	0.09	0.0–0.30	0.3
TC18:2n-6	311	0.01	0.0–0.17	13.8	306	0.02	0.0–0.20	13.7
CT18:2n-6	311	0.02	0.0–1.1	0.3	306	0.04	0.0–2.1	0.3
PT16:1n-7	311	0.50	0.11–1.2	0	306	0.42	0.06–1.1	0
PT18:1n-9/7	311	0.06	0.01–0.29	0	306	0.05	0.0–0.25	0
Sum trans	311	0.70	0.27–1.9		306	0.67	0.35–2.8	
C18 trans	311	0.17	0.04–1.4		306	0.22	0.04–2.3	
MUFAs	311	16.8	12.5–21.3		306	19.9	13.7–26.0	
LCPUFAs	311	32.2	20.2–36.5		306	28.8	20.7–34.1	

Values are percentage by weight. SAFAs, saturated fatty acids; MUFAs, monounsaturated fatty acids.

Bayley Scales of Infant Development. Neither univariate nor multivariate analyses revealed significant associations between AA, DHA, and total *trans*-fatty acids in the umbilical walls of artery or vein and the Bayley PDI and MDI (Fig. 2).

DISCUSSION

The present study indicated that, in healthy term infants, a DHA content in the umbilical vein within the lowest quartile and a higher content of venous *trans*-fatty acids were associated with a less optimal neurologic condition at 18 mo. This effect was found with the Hempel technique but could not be demonstrated with psychomotor or mental development indices of the Bayley scales. This underscores the notion that the Hempel technique is a more sensitive instrument to assess possibly subtle effects of early nutritional condition on brain function than the Bayley scales, which are designed to detect major developmental delays (23).

Our study indicates that low prenatal venous umbilical DHA content is associated with a less optimal neurologic condition at 18 mo. In the same study cohort as in the present study, we previously found that DHA and AA content in the umbilical vein was associated with a more optimal neurologic condition on postnatal d 10–14 (8). In addition, we found that neonatal AA content in the umbilical artery was related to a better neurologic condition at 3 mo, whereas DHA affected neurologic condition at 3 mo to a marginal extent (9).

At 18 mo of age, we found the opposite: neonatal DHA content of the umbilical cord showed a significant correlation with neurologic optimality, whereas neonatal umbilical AA content only had a marginal effect on neurologic outcome. Taken together these findings suggest that both neonatal AA and DHA status might affect neurologic development to a limited extent. This could explain why previous studies produced conflicting results. Two studies that evaluated cognitive function in similarly large populations of full-term infants could not establish a relationship between neonatal LCPUFA status and cognitive function at 4 and 7 y (10,11). On the other hand, two supplementation studies with DHA during pregnancy found that a higher neonatal DHA status was positively associated with more mature electroencephalographic scores

Table 5. *Correlations between the fatty acid composition (% by weight) of the umbilical vein and the NOS at 18 mo*

	NOS			
	Univariate analysis		Multivariate analysis	
	Spearman's rho	*p*	Standardized coefficient (β)	*p*
Vein				
Saturated	—	NS	—	NS
Monounsaturated	—	NS	—	NS
Omega-6				
20:4n-6	0.13	0.03	—	NS
Omega-3				
22:6n-3	—	NS	—	NS
Total *trans*-fatty acids	−0.23	<0.0005	−0.52	0.03
C18 *trans*-fatty acids	−0.19	0.0001	−0.16	0.02
Trans-18:1n-9 or 7	−0.12	0.04	—	NS
Trans,*cis*-18:2n-6	−0.21	<0.005	−0.20	0.001
Trans-16:1n-7	−0.12	0.048	−0.14	0.02

Factors that played an additional significant role in at least one of the multivariate models were education of the father, HOME score, weight of gravida before pregnancy, uncertain or unreliable date of last menstrual period, breast-feeding for more than 6 wk, and age of assessment at 18 mo. Allocation into control formula or LCPUFA-supplemented formula group and primi- *versus* multiparity did not affect NOS significantly.

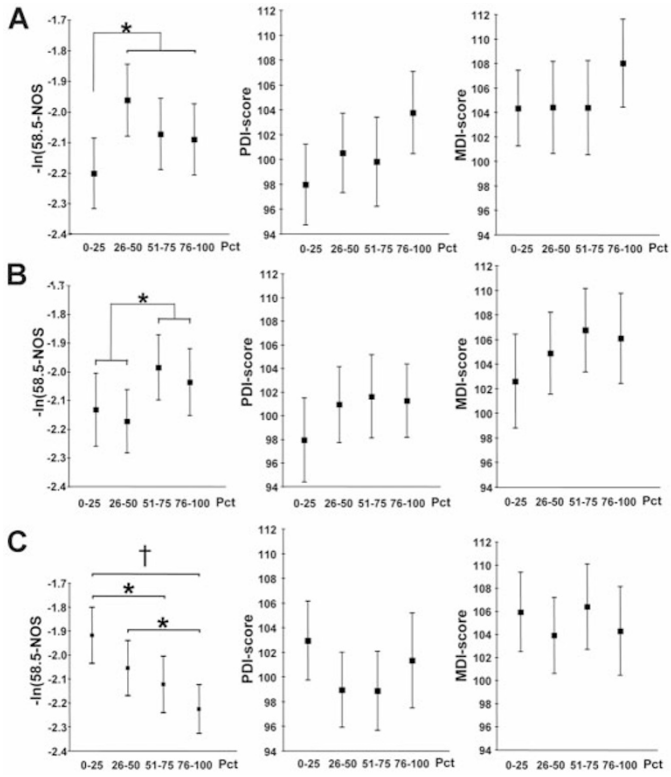

Figure 2. Relationships between umbilical vein content of DHA (*A*), AA (*B*) and the sum of *trans*-fatty acids (*C*) expressed in quartiles and NOS and PDI and MDI scores. The NOS is expressed in the transformed NOS, which was used to achieve gaussian distribution. Note that a higher −ln(58.5 − NOS) value means a better NOS. The *squares* denote mean values, the *vertical bars* the 95% confidence interval of the mean. *Asterisks* denote statistically significant differences between groups in the univariate analyses (Mann-Whitney *U* test): $*p < 0.05$, $\dagger p < 0.001$.

on the second day of life and latencies to visual evoked potentials recorded to pattern-reversal stimuli at 10 wk and 6 mo (29,30). Previous studies indicated that postnatal supplementation with DHA affects neurologic condition during early infancy, but not neurodevelopmental outcome at 1–3 y (24,31,32). In the present population, we also did not find an effect of breast-feeding or LCPUFA-enriched formula on neurologic condition at 18 mo (24). The present study demonstrated that the association of prenatal DHA with neurodevelopmental outcome was not restricted to early infancy, but was still demonstrable at the age of 18 mo (8,30,33). Although the association was relatively small, it remained present when we took into account the effect of postnatal LCPUFA supplementation. This suggests that in terms of neurologic health prenatal DHA status is more important than postnatal DHA status. This underscores the notion that we should pay attention to the essential fatty acid status of pregnant women, in particular of multiparous women (34,35).

The association between venous umbilical DHA content and NOS was not a linear one, but showed a threshold effect. Animal studies suggest that low DHA status results in deviant behavior. n-3 LCPUFA–deficient rhesus monkeys showed more stereotyped motor behavior than control animals fed a matched control diet abundant in n-3 fatty acids (36). In rats, low brain content of DHA induces altered dopaminergic function and behavior (37).

Surprisingly, we found that the venous umbilical *trans*-fatty acid content was more prominently associated with neurodevelopmental outcome at 18 mo than LCPUFA content, an association that was statistically independent of DHA and AA content of the umbilical vein. This negative association remained statistically significant when we excluded the breast-fed infants from the analyses to evaluate whether the association still persists without potential postnatal *trans*-fatty supply *via* breast-feeding. Before addressing the putative biologic mechanisms underlying this finding, we emphasize that we cannot exclude that a certain but small amount of all *trans*-fatty acids present were not analyzed, *e.g.* the longer chain *trans*-fatty acids. Thus, we found a negative correlation between the lion's share of *trans*-fatty acids and neurologic condition at 18 mo. Because *trans*-fatty acids cannot be synthesized *de novo*, the content of *trans*-fatty acids in the umbilical wall reflects maternal dietary intake of *trans*-fatty acids. *Trans*-fatty acid can potentially alter numerous cell membrane properties when incorporated in membranes (38); however, no significant *in vivo* incorporation of *trans*-fatty acids in the neuronal membranes takes place (16). Despite the minor effects of *trans*-fatty acids on the fatty acid composition of neuronal membranes, high *trans*-fatty diets do induce dopaminergic alterations in the brains of pigs and rats (39,40). The biochemical mechanisms are not yet clear, but it seems unlikely that the biochemical effects of *trans*-fatty acids are mediated by neuronal membrane function. It has been shown that fatty acids can alter gene transcription that impacts lipid, carbohydrate, and protein metabolism as well as cell growth and differentiation *via* several transcription factors in the cytoplasm and cell nucleus (4). It could be that some specific *trans*-fatty acids such as conjugated *trans*-fatty acids by means of interaction with peroxisome proliferator–activated receptors (PPARs) might induce unfavorable neuronal func-

tion. To our knowledge, no data are available on the effects of *trans*-fatty acids on neurodevelopmental outcome (14,16). Such knowledge is urgently needed as it is possible that humans are more vulnerable to early *trans*-fatty acid exposure than animals. This is suggested by the finding that *trans*-fatty acids do not affect birth weight, growth, and longevity in animals (14,41), whereas in human preterm infants, *trans*-fatty acids are negatively correlated to birth weight (12).

Besides the direct potential harmful effects of *trans*-fatty acids on neurodevelopment, we originally assumed that *trans*-fatty acids could also be indicators of the presence of less favorable dietary constituents in general, which in turn could be associated with a lower socioeconomic status. However, our data indicated that higher *trans*-fatty content to a limited extent was even related to a higher social class as indicated by the father's profession (Table 2). A recent report of the Dutch Ministry of Health, Welfare, and Sports indicated that the intake of *trans*-fatty acids among Dutch young adults was not related to socioeconomic characteristics (17). These findings do not exclude the possibility that a higher *trans*-fatty acid intake may be associated with an unhealthy diet or lifestyle. To illustrate the point, the consumption of a diet rich in *trans*-fatty acid content has been associated with bakery products, confectionery, and snacks (42).

In conclusion neonatal DHA status, used as a proxy of maternal supply during pregnancy, has a small but statistically significant beneficial effect on neurologic condition at 18 mo. In addition, neonatal *trans*-fatty acid status has a substantial negative effect on neurologic condition at 18 mo. The latter finding might support a plea for the removal of the industrially produced *trans*-fatty acids from our diet.

Acknowledgments. We gratefully acknowledge the statistical advice of Dr. M. R. Fokkema.

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