Journal of Exposure Analysis and Environmental Epidemiology (2005) 15, 423–430

www.nature.com/jea

Effects of breast feeding on neuropsychological development in a community with methylmercury exposure from seafood

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Breastfeeding has been associated with an advantage to infant neurobehavioral development, possibly in part due to essential nutrients in breast milk. However, breast milk may be contaminated by environmental neurotoxicants, such as methylmercury. In the Faroe Islands, where maternal consumption of pilot whale may cause transfer of marine toxicants into breast milk, a cohort of 1022 consecutive singleton births was generated during 1986–87. Methylmercury exposure was assessed from mercury concentrations in cord blood and in the hair of the child at age 12 months, and the duration of breastfeeding was recorded. At approximately 7 years of age, 917 (90%) of the children underwent detailed neurobehavioral examination. After adjustment for confounders, breastfeeding was associated with only marginally better neuropsychological performance on most tests. These associations were robust even after adjustment for cord-blood and hair mercury concentration at age 1 year. Thus, in this cohort of children with a relatively high prenatal toxicant exposure and potential exposure to neurotoxicants through breast milk, breastfeeding was associated with less benefits on neurobehavioral development than previously published studies though not associated with a deficit in neuropsychological performance at age 7. Although the advantage may be less, Faroese women can still safely breastfeed their children.
Journal of Exposure Analysis and Environmental Epidemiology (2005) **15,** 423–430. doi:10.1038/sj.jea.7500420; published online 26 January 2005

Keywords: *breast feeding, environmental pollution, neuropsychological tests, pre school child, food contamination, methylmercury compounds.*

Introduction

Breastfeeding is known to reduce the risk of a wide range of diseases, including both life-threatening and less serious ailments (Amin-Zaki et al., 1980; Rowland et al., 1984; Saarinen and Kajosaari, 1995; Gartner et al., 1997), and the World Health Organization has therefore extended its recommendation of the length that the infant should be breastfed exclusively from 4 to 6 months or longer (World Health Assembly Resolution 25, 2002). Breastfeeding is also associated with an advantage in subsequent mental development, as indicated by global neurological and cognitive development. Thus, a meta-analysis (Anderson et al., 1999) adjusted for appropriate key cofactors, such as maternal intelligence and birth weight, showed an adjusted benefit of 3.16 IQ points for breastfed compared with formula-fed children. The differences in IQ among breastfed and formula fed children were observed across all age categories from 6 months to 15 years of age, but children with low birth weight exhibited larger benefits (Anderson et al., 1999). Among the essential nutrients in human milk of particular importance for brain development, long-chain polyunsaturated fatty acids are thought to be of special relevance, especially docosahexaenoic and arachidonic acid (Carlson, 1999). For these fatty acids, seafood is an important source, and breastfeeding could therefore be particularly advantageous in fishing communities.

On the other hand, breast milk may be contaminated with marine pollutants (Jensen and Slorach, 1991), some of which are neurotoxic. The human brain is particularly sensitive to toxicity during gestation and infancy (Davidson and Dobbing, 1968), and some seafood contaminants, including methylmercury (Amin-Zaki et al., 1981), have been reported to cause toxic effects in breastfed infants. With essential nutrients and neurotoxicants originating from the same food items, the resultant effect of breastfeeding may be difficult to predict. An additional complication is that the toxicants may also have been transferred to the fetus through placenta *in utero*, thereby affecting both prenatal and postnatal development.

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Received 14 October 2003; accepted 6 December 2004; published online 26 January 2005

The population in the Faroe Islands has traditionally consumed pilot whale meat and blubber, which is shared in the communities where the whales are caught (Grandjean et al., 1992). This Nordic fishing community of about 45,000 inhabitants has large variations in whale meat consumption and is socially relatively homogeneous. In a birth cohort assembled in 1986–1987, the length of breastfeeding showed a positive association with the mercury concentration in hair at 12 months of age, thereby indicating that exposure took place through breast milk (Grandjean et al., 1994). Even so, breastfed children reached their developmental milestones (creeping, sitting, rising) before formula-fed children (Grandjean et al., 1995b), thus suggesting an overall beneficial effect of breast milk despite the contamination. However, when the same children (regardless of whether they were breastfed or not) were examined at age 7 years with a series of domain-specific neurobehavioral tests, worse performance on only a single test (reflecting attention) was associated with increased hair-mercury concentrations (which largely stems from breastfeeding) at age 12 months (Grandjean et al., 1999). On the other hand, performance on a test of language skills increased with increasing hair mercury level at age 12 months (Grandjean et al., 1999). Both domains are thought to be particularly sensitive to developmental methylmercury exposure, and this apparent paradox therefore calls for a more detailed evaluation of the effect of breastfeeding.

Breastfeeding may therefore be associated not only with beneficial but also with adverse effects in population exposed to contaminants excreted via human breast milk. This paper examines in greater detail the effect of breastfeeding on neurobehavioral performance of the child at age 7 years.

Methods

A cohort of 1022 singleton births was assembled during a 21-month period from 1986 to 1987 at the three Faroese hospitals (75.1% of all deliveries) (Grandjean et al., 1997). Cord blood for mercury analysis was obtained at delivery. The midwifes interviewed the mothers about complications in pregnancy and delivery, nutritional habits (frequency of dinners with fish or pilot whale), use of alcohol (never, occasionally or frequently) and smoking during pregnancy. Furthermore, information on parity, birth weight and length and gestational age of the baby at delivery was obtained.

As part of the Faroese health care system, district health nurses visit the family at home shortly after the delivery and several times thereafter, at longer intervals as time passes. The last scheduled visit is usually at about 12 months of age. At this visit, the district health nurses filled in a short questionnaire on milestone development, the total number of months of breastfeeding (i.e. exclusive and until complete weaning) at the time of the visit and the number of months of exclusive breastfeeding (i.e. the age at which other food was introduced). A hair sample was also collected from the child for mercury analysis. The nurses were unaware of the mercury exposure data. Because some district health nurse positions were not filled at the time of the study, the coverage was incomplete (Grandjean et al., 1994) and some parts of the capital were not visited. The methylmercury concentration in maternal hair at the time of delivery was slightly higher among the children visited than those not visited, probably because of a higher intake of whale in the smaller villages than in the capital with better coverage.

The children were invited for a clinical examination in 1993–1994 just before school entry. Seven children had died from causes unrelated to mercury exposure. A total of 917 of the eligible children (90.3%) completed the examinations. The child was accompanied to the examination by a parent (usually the mother), who filled in a self-administered questionnaire about current and past health and medical history. The questionnaire also queried the number of months of total and exclusively breastfeeding. Information on breastfeeding was thus obtained both from the district health nurses and the mother, the latter with a 7-year delay. The prior information from the district health nurse, when available, overruled the information obtained from the mother. As a measure of maternal intelligence, the mothers completed Raven's Progressive Matrices Test (Raven, 1958).

Neuropsychological Tests

The child was examined by a pediatrician, and a detailed neuropsychological test battery was administered. Neuropsychological tests were selected to include tasks that would be affected by the neuropathologic abnormalities previously described in prenatal and early postnatal mercury exposure. The tests also had to be acceptable for the children and their parents, painless, not too time consuming, and appropriate for 7-year-old Faroese children who had not yet begun school. Tests that were likely to provide high statistically sensitivity and with test versions standardized in Scandinavian countries were preferred. The specifics of test administration and scoring and overall results have been previously described (Grandjean et al., 1997). The battery included tests of fine manual motor speed and dexterity (NES Finger Tapping Test and NES Hand Eye Coordination Test); attention measures (NES Continuous Performance Test (CPT). Wechsler Intelligence Scale for Children-Revised. (WISC-R) and Digit Spans forward condition); executive function (WISC-R Similarities); visuospatial tasks (WISC-R Block Designs and Bender Visual Motor Gestalt Test scored by the Göttingen system); language (Boston Naming Test); and short-term memory (California Verbal Learning Test (Children) and Bender Visual Motor Gestalt Test, memory condition). Before performing the computer-based tests, the child was asked about familiarity with computer games (i.e., none, some, or much). All examinations were conducted by health professionals with no knowledge about exposure levels. However, different examiners for the computer-based tests in 1993 and 1994 (medical supervision was discontinued in 1994) required that the examination year be included in the analyses and also resulted in exclusion of the 1994 data for the NES CPT.

Mercury and PCB Exposure Data

Hair samples were collected from the children at age 12 months by the district health nurses. All analyses were conducted by cold-vapor atomic absorption techniques with acceptable total analytical imprecision, as determined by analysis of control materials (NTT + EHP). At the time of each birth, about 10 cm of the umbilical cord were also collected. For 435 children examined at age 7 in 1993, these specimens were used for analysis of major polychlorinated biphenyl (PCB) congeners by capillary gas chromatography with electron-capture detector, and the result was expressed in ng/g wet weight (Grandjean et al., 2001). This measure correlated very well with cord-blood PCB concentrations (Grandjean et al., 2001).

Statistical Analysis

The length of exclusive breastfeeding (categorized as 0–4; >4 months) was used as indicator of the early postnatal exposures whereas the total length of breastfeeding (until complete weaning (categorized as 0–6; >6 months or inserted as a continuous variable) was chosen as indicator of the cumulated exposure. These were both used as independent exposure variables; whose effect on the score in the neuropsychological tests (outcome variable) was determined.

First characteristics of mothers who breastfed exclusively for 0–4 months or for 0–6 months in total were compared to mothers who breastfed longer. Then to estimate the effect of breastfeeding on neuropsychological test score, simple linear regression analysis was performed. Exclusive breastfeeding was entered as a dichotomous variable (0–4 months; >4 months) and total number of months of breastfeeding was entered as a continuous variable in the regression analyses. Multiple linear regression equations were then developed taking into account the effect of potential confounders. A uniform set of confounders previously identified (Grandjean et al., 1997) was used in all analyses to ensure that related test outcomes were adjusted for the same covariates. These covariates were age (continuous variable) and sex of the child (boy; girl), child in daycare (yes; no), medical risk factors of the child for neurobehavioral dysfunction eg. '(yes; no), maternal Raven score (continuous variable), professional training of each parent (yes; no), paternal employment at time of examination (yes; no), and for the computer-assisted NES tests familiarity with computers (yes; some and none). The fit of the regression models was evaluated by testing the residuals for normality and by inspecting the residual plots. Most of the neurobehavioral test results approximated a Gaussian distribution, but to obtain a better fit of the models, the Block Design results were transformed to the square root of the score +1, and the number of missed responses on the CPT was converted to the natural logarithm to the score +1. Similarly, the mercury concentrations were logarithmically transformed and entered as continuous variables. Because complete data were not available for all children, especially with regard to the hair-mercury concentration at 1 year, regression analyses were repeated for similar subsets of data.

Results

Of the 917 children who participated, seven were excluded from the analyses because of a neurological diagnosis unrelated to mercury exposure (mainly suspected epilepsy), and the statistical analyses were therefore performed for 910 children. The mean age at examination was 6.7 years. Cord-blood mercury was available for 888 of the children, and hair mercury at age 1 year for 522 children.

Information on breastfeeding up to at age 1 year was obtained by the district health nurse for 572 children (62% of the cohort). At the 7-year examination, a total of 905 mothers answered the questions on duration of exclusive breastfeeding and 846 reported the total length of breastfeeding. Comparison between the data on number of months of exclusive breastfeeding and total duration from mother and health nurse showed an agreement within ±1 month for 74% and 56% of the cases, respectively.

All but 70 (7.7%) of the children were breastfed, and 61% were exclusively breastfed for 0–4 months. Only 5% were fully breastfed for more than 6 months, but the total duration of the breastfeeding period exceeded 6 months for 55% of the children. Table 1 shows the characteristics of women who breastfed exclusively for 0–4 months and those breastfed at least partially up to 6 months, both groups as compared to women who breastfed longer. Children who were breastfed longer had a significantly higher hair mercury concentration at age 1 year, but the duration of breastfeeding was unrelated to the cord-blood mercury concentration. Women who breastfed longer had a higher Raven score and school education (the same was true for the father), were more often professionally trained, less often smoked and more often drank alcohol (none of them more than occasionally) during pregnancy. Their children less often had one of the defined risk factors.

Children who were breastfed longer (both exclusively and in total) performed slightly better on most neuropsychological tests before confounder adjustment (Table 2). After adjustment with the uniform set of confounders, the positive effect of breastfeeding was reduced (Table 2), although breastfeed children still performed slightly better on most tests. Children who were breastfed exclusively for more than

Table 1. Characteristics of women who breastfed their children exclusively for 0–4 months and in total for up to 6 months, as compared to women who breastfed for a longer time period.

Variable percent with characteristic	Number (%)	Months of exclusively breastfeeding (%)		Total months of breast feeding (until weaning) (%)	
		0–4 months	>4 months	0–6 months	>6 months
Maternal age (years), mean (SD)	909	27.1 (5.6)	27.9 (5.1)*	27.0 (5.6)	27.7 (5.3)*
Parity >0	609 (76.9)	66.1	68.2	64.3	68.5
Maternal Raven score mean (SD)	848	44.1 (8.5)	46.3 (7.4)**	43.4 (8.6)	46.4 (7.3)**
Maternal hair mercury at delivery (transformed by logarithm) mean (SD)	907	0.64 (0.34)	0.62 (0.35)	0.64 (0.36)	0.62 (0.33)
Cord-blood mercury (transformed by logarithm) mean (SD)	888	1.37 (0.36)	1.34 (0.39)	1.35 (0.38)	1.38 (0.36)
Foreign residence at age 7 years	101 (11.2)	9.8	13.4	11.1	11.5
Mother Faroese	865 (95.5)	96.2	94.3	96.5	94.5
Father Faroese	856 (94.5)	94.8	94.0	95.0	93.9
Mother's school education >7 years	788 (87.0)	85.4	89.5*	85.0	88.5*
Father's school education >7 years	633 (69.9)	65.3	77.0**	64.9	73.4**
Mother's professional training	420 (46.4)	42.3	52.8**	40.2	51.9**
Father's professional training	637 (70.3)	68.1	73.9*	68.2	72.2
Mother employed at time of examination	503 (55.5)	54.2	57.7	55.9	54.8
Father employed at time of examination	758 (83.7)	86.1	82.1	83.5	83.6
Maternal smoking during pregnancy	361 (39.7)	45.5	30.7**	49.1	31.7**
Maternal alcohol intake during pregnancy (occasional only)	217 (23.9)	21.3	27.9*	23.8	23.7
Sex of the child (boys)	453 (50.2)	48.3	53.2	51.5	49.3
Birthweight <2500 g	13 (1.4)	1.4	1.4	1.5	1.2
Length of gestation <37 weeks	28 (3.1)	4.1	1.4*	3.5	2.5
Neonatal jaundice according to district health nurse	120 (21.0)	21.3	20.3	20.4	21.5
Skull trauma	36 (4.0)	4.9	2.6	5.8	2.5*
Meningitis in childhood	10 (1.1)	1.3	0.9	0.5	1.6
History of seizures	54 (6.0)	6.9	4.5	7.8	4.1*
At least one risk factor[a]	130 (14.3)	16.8	10.4**	17.2	11.2**
Child lives with parents	816 (89.7)	88.6	91.3	88.5	91.2
Child in day care	474 (52.1)	49.5	56.1*	51.0	52.6
Younger siblings	517 (56.8)	55.5	58.9	53.0	60.5*
Older siblings	599 (65.8)	64.7	67.6	64.0	67.7
Examination in 1993	436 (47.9)	51.0	43.1*	50.5	45.2
Preferred hand					
Right	820 (90.6)	89.1	92.9	88.6	92.8
Left	81 (9.0)	10.5	6.5	11.1	6.8
None	4 (0.4)	0.4	0.6**	0.3	0.4
Familiarity with computer games					
None	292 (32.3)	33.4	30.5	34.3	29.7
Some	369 (40.8)	41.0	40.4	40.7	41.4
A lot much	244 (27.0)	25.6	29.1	25.0	28.9
Age of child at examination (years), mean (SD)	910	6.8 (0.3)	6.9 (0.3)	6.8 (0.3)	6.9 (0.3)
Mean hair mercury at age 1 year (transformed by logarithm) (nmol/g)	522	0.67 (0.31)	0.91 (0.31)**	0.61 (0.29)	0.88 (0.31)**

[a]Low birth weight, small-for date, history of head trauma and meningitis combined to one risk parameter.
SD = standard deviation.
*χ^2-test comparing children breastfed for a shorter duration with children breastfed longer significant at 5% level.
**χ^2-test comparing children breastfed for a shorter duration with children breastfed longer significant at 1% level. For continuous variables, a t-test was used.

Table 2. Mean and standard deviation score for neuropsychological test results acquired at age 7 among 905 Faroese children.

Test administered at age 7[a]	Number	Mean (standard deviation)	Test results for children breastfeed exclusively for more than 4 months compared to children breastfed for 0–4 months		Increase in test score for each months of increase in breastfeeding (until weaning)	
			Unadjusted *B*	Adjusted *B* and 95% CI[b]	Unadjusted *B*	Adjusted *B* and 95% CI[b]
NES 2 Finger Tapping (maximum taps in 15 s)						
Preferred hand	901	42.9 (6.1)	0.58	0.19 (−0.63; 1.01)	0.07*	0.04 (−0.01; 0.01)
Other hand	901	41.2 (6.0)	0.37	−0.21 (−0.99; 0.57)	0.05	0.01 (−0.04; 0.07)
Both hands	895	55.5 (12.2)	0.24	−0.96 (−2.60; 0.69)	−0.02	−0.09 (−0.20; 0.02)
NES 2 hand–eye coordination (average of best 2 trials)						
Error score	897	2.6 (0.3)	−0.03*	0.006 (−0.10; 0.12)	−0.003*	−0.001 (−0.004; 0.001)
NES 2 continuous performance test						
Misses responses[c]	888	3.8 (1.1)	−0.10*	0.006 (−0.05; 0.03)	−0.007	−0.001 (−0.008; 0.007)
Reaction time (ms)	900	750 (76.5)	1.49	8.08 (−2.00; 18.16)	−0.13	0.26 (−0.41; 0.53)
Wechsler Intelligence Scale for Children — Revised						
Digit spans	889	3.8 (1.5)	0.24*	0.07 (−0.14; 0.27)	0.01	0.005 (−0.009; 0.02)
Similarities	746	7.4 (3.9)	0.61*	0.35 (−0.22; 0.92)	0.01	0.01 (−0.03; 0.05)
Block designs[d]	903	1.7 (0.8)	0.29**	0.17* (−0.24; −0.06)	0.01*	0.004 (−0.007; 0.01)
Bender visual motor gestalt test						
Errors on copying	895	29.4 (5.3)	−0.51	0.04 (−0.65; 0.74)	−0.07**	−0.04 (−0.09; 0.003)
Recall	841	3.0 (1.6)	0.11	0.03 (−0.20; 0.26)	0.0002	−0.003 (−0.02; 0.01)
Boston naming test						
No cues	866	25.0 (5.5)	1.58**	0.79* (0.06; 1.51)	0.08**	0.05* (0.003; 0.10)
With cues	865	27.5 (5.5)	1.74**	0.81* (0.10; 1.53)	0.08**	0.05* (0.01; 0.09)
California verbal learning test — children						
Learning	879	4.1 (2.6)	1.25*	0.08 (−1.12; 1.29)	0.05	−0.003 (−0.08; 0.08)
Immediate recall	867	4.4 (2.9)	0.30	0.11 (−0.26; 0.47)	0.01	0.003 (−0.02; 0.03)
Delayed recall	837	10.4 (2.1)	0.32	0.007 (−0.40; 0.42)	0.009	−0.003 (−0.03; 0.02)
Recognition	830	25.0 (5.5)	0.16	0.04 (−0.55; 0.05)	0.009	0.007 (−0.01; 0.03)

Regression coefficients (unstandardized *B*) for test scores for children breastfed longer than 4 months (as compared to children breastfed 0–4 months) and the increase in test scores per month of total duration of breastfeeding (until weaning) with 95% confidence intervals (95% CI).

*$P<0.05$; **$P<0.01$.

[a]Higher test results represent a better performance, except for error scores, missed responses and reaction time.

[b]Adjusted for sex of the child, mother and father professionally trained, father employed at examination, Raven score, child ''risk score'', child in day care, age of the child at examination, examination year and in NES test computer familiarities according to categorization from Table 1.

[c]Transformed by the natural logarithm to the score +1.

[d]Transformed to the square root of the score +1.

4 months had significantly better scores on the Boston Naming Test and also scored significantly better on the WISC-R Block Designs. Children who were breastfed longer in total also scored higher on the Boston Naming Test. As an interesting reverse tendency, children who were breastfed longer had a longer (although not statistically significant) reaction time on the NES2 Continuous Performance test.

The tasks that showed apparent associations with breastfeeding in the adjusted model in Table 2 or were *a priori* expected to be affected (because they were related to hair mercury concentration at 1 year of age) were then examined more closely. Table 3 shows the adjusted test results for Boston Naming Test Block Design, NES 2 Hand-eye Coordination error score and NES 2 Continuous Performance Test reaction time for the 510 children from whom cord-blood and hair mercury at age 1 were available. A stronger effect of breastfeeding might be expected after adjustment for cord-blood mercury and child-hair mercury, due to their negative effect on neuropsychological performance. However, the results were only negligibly affected, apart from the Boston Naming Test. Fewer results were significant in the reduced dataset, and breastfed children still had a longer (although still insignificant) reaction time on the NES2 Continuous Performance test. As previously reported (Grandjean et al., 1999), higher hair mercury at age 1 was associated with increase in test scores, but the regression coefficients for hair mercury at age 1 were clearly reduced after inclusion of breastfeeding (Table 3).

Table 3. Adjusted neuropsychological test scores acquired at age 7 for 510 Faeroese children with available information about cord-blood and child-hair mercury at age 1 year.

Test administered at age 7[a]	B for hair mercury (logarithmically transformed) at age 1 adjusted for[b,c]	Test results for children breastfeed exclusively for more than 4 months compared to children breastfed 0–4 months			Increase in test score for each months of increase in breastfeeding (until weaning)		
		Adjusted B^b	Adjusted B^d	Adjusted B^e	Adjusted B^b	Adjusted B^d	Adjusted B^e
NES 2 hand-eye coordination							
Error score	0.003/−0.003	0.01	0.01	0.02	−0.003	−0.004	−0.003
NES 2 continuous performance test							
Reaction time	24.57*/22.53*	9.30	8.81	5.20	0.57	−0.22	−0.1
Wechsler intelligence scale for children — revised							
Block designs[f]	0.12/0.04	0.18	0.18	0.15	0.02*	0.02*	0.02*
Boston naming test							
No cues	0.44/0.25	0.46	0.49	0.21	0.05	0.05	0.01
With cues	0.56/0.38	0.47	0.50	0.17	0.03	0.1	−0.02

Regression coefficients (unstandardized B) for children breastfed exclusively longer than 4 months (compared to children breastfed only 0–4 months) and the change in test scores per month of total duration of breastfeeding. For comparison, the regression coefficients for hair mercury at age 1 year before and after adjustment for breastfeeding are also shown.
*$P<0.05$.
[a]Higher test results represent a better performance, except for error scores, missed responses and reaction time.
[b]Adjusted for sex of the child, mother and father professionally trained, father employed at examination, Raven score, child "risk score", child in day care, age of the child at examination, examination year and in NES test computer familiarities according to categorisation from Table 1.
[c]Adjusted as for the above (b) and breastfeeding for 0–4 months or longer than 4 months.
[d]Adjusted for (b) plus mercury concentration in the hair of the child at age 1 year (logarithmically transformed).
[e]Adjusted for (b) plus mercury concentration in the hair of the child at age 1 year (logarithmically transformed) and mercury concentration in cord blood (logarithmically transformed).
[f]Transformed to the square root of the score +1.

Additional analyses also employed other stratifications. The analyses were repeated for the children where the information on breastfeeding was available from the district health nurse only ($N=572$), but this stratification did not affect the findings. Furthermore, they were repeated for children examined in 1993 only and for each gender separately though without any difference in the trends. The 70 children who were not breastfed at all generally performed less well on most tests. Children with a high cord-blood mercury concentration (above 40 μg/l) might also have been exposed to very high mercury concentrations when breastfed, but the breastfed children in this group did not perform any worse on any neuropsychological test. Furthermore, the analyses were performed on the subset of data from 1993, when cord-tissue PCB was measured, but inclusion of this covariate barely changed the regression coefficients for the breastfeeding variable.

Discussion

In this cohort of children with a relatively high prenatal mercury exposure and exposure through breast milk, as indicated in hair mercury concentrations at age 1, breastfeeding was not associated with reduction in neuropsychological performance at age 7 years. On the other hand, breastfed children did not perform significantly better, as observed in previous studies in populations exposed to less contaminant (Anderson et al., 1999).

The advantages of breastfeeding in regard to the child's subsequent mental development have previously been considered only in light of the possible adverse effects of contaminants in few studies. In the Seychelles, a community with large fish intake as well, breastfed children preformed slightly better than formula-fed infants (Myers et al., 1997). A study on a different cohort from the Faroe Islands found a reduction in height and weight at age 18 months among children exclusively breastfeed for more than 6 months compared to children breastfed shorter (Grandjean et al., 2003). However, no neuropsychological test results were included at that time. Also, while most previous studies used IQ as outcome measure of global intelligence, many different functional domains of the human brain can be affected by contaminants. By using domain-related tests, we found that visuospatial performance and language best reflected the beneficial effects of breastfeeding. Both these brain functions are known also to be affected by exposure to methylmercury (Grandjean et al., 1997). At least in regard to visuospatial function and language, the adverse effects of methylmercury, therefore, appeared to be overruled by the beneficial effects of breastfeeding. Adjustment for prenatal exposures to methylmercury and PCB did not affect the regression coefficient for breastfeeding, but the apparent adverse effect of mercury at age 1 year was attenuated when breastfeeding was introduced in the regression equation.

This study focuses on methylmercury, because this pollutant is found in seafood and freshwater fish throughout the world (WHO, 1990). It has an almost complete absorption from the gut and passes the placental barrier easily (Reynolds and Pitkin, 1975); it can also be transferred to the infant through breast milk (Amin-Zaki et al., 1980). Clinical data from Iraq (Amin-Zaki et al., 1974, 1980) suggest that postnatal exposure via breast milk contributed to or caused several cases of methylmercury intoxication. However, the exact contribution of exposure from milk, as compared to transplacental exposure, is unclear from the published data, partly because some congenital cases of methylmercury poisoning were not diagnosed until 3 months after birth. In Iraq, no detailed information on duration of breastfeeding was obtained. In addition, the persistence of methylmercury and the continuing maternal exposure through intake of contaminated food make both pre- and postnatal exposures of babies likely in breastfed children. Infants may not have the capacity to eliminate methylmercury because of the lack of demethylating bacteria in the gut (Rowland, 1988; Rowland et al., 1984). The exact timing of this colonization is unknown, and considerable interindividual variation may exist.

The mercury concentration in hair has been used in the past as the most convenient exposure parameter, though potentially associated with substantial imprecision (Grandjean et al., 2002). For example, exogenous mercury vapor may bind to the hair surface, and mercury concentration may also be affected by factors, such as hair treatment (Yamamoto and Suzuki, 1978; Yasutake et al., 2003) The distance of the hair sample from the root indicates the time period represented by the analysis. The proximal 2-cm segment of hair samples obtained at age 12 months therefore reflects the mercury exposure during the second half-year of the child's life, when approximately half of the children were still breastfed. In contrast, the cord-blood concentration reflects the exposure of the fetus. Because the biological half-life of methylmercury in blood is thought to be up to 2 months (Bakir et al., 1973), this exposure biomarker mainly reflects third-trimester exposures.

Among its most important strengths, this prospective study is one of the largest so far which aimed at separating the effects of prenatal and postnatal exposures to contaminants. The very high participation rate suggests that any selection bias would be limited and unlikely to affect the relationship observed between breastfeeding and neurobehavioral performance (Grandjean et al., 1992). Although multiple comparisons were done, almost all associations with the neuropsychological results pointed in the same direction. We obtained information about both prenatal and postnatal mercury exposure, but it may still be difficult to differentiate between these, because very few children (8%) were not breastfed, and most children were therefore exposed to mercury both pre- and postnatally. However, the non-breastfed children performed less well on all tests. The regression analyses were performed after adjustment for hair and/or cord-blood mercury concentrations, but these factors could be intermediary in the relation between breastfeeding and neuropsychological performance. Nevertheless, adjustment for mercury exposures barely changed the associations.

The information on breastfeeding was recorded by the district health nurse who had visited the family during first year and again from the mother when the child was 7 years. In the latter case, recall bias may have been present. Nevertheless, the agreement between these two sources of information was good although only 56% of mothers and district health nurses agreed within 1 month about the total duration of breastfeeding. The difference was probably due to the length of the recall for the mothers of approximately 6 years. However, the agreement within 2 months between the mothers and the district health nurses was 76%. In repeated analyses of the subset with data from the district health nurse no change in the findings were observed.

Several genetic, social and environmental factors may affect neurobehavioral function and covariates suspected of being relevant in the Faroese society were considered in the regression analyses. The maternal Raven score was the most important confounder strongly associated with length of breastfeeding, although it seemed to be only weakly associated with seafood habits. Confounding therefore appeared to be of limited importance in this study, as would be expected for a relatively homogeneous community where the methylmercury exposure depends on the local availability of whale meat (Grandjean et al., 1997) more than on socio-economic factors.

Prenatal exposure and exposure through breast milk to other contaminants such as PCBs have also been linked to adverse effects on the nervous system (although the potential confounding due to methylmercury exposure was not determined in these studies) (Jacobson et al., 1990; Gladen and Rogan, 1991). Whale blubber has high concentrations of organochlorine compounds (Borrell, 1993) and the PCB concentration in breast milk is therefore high in the Faroes compared to other Scandinavian countries (Grandjean et al., 1995a). In our study adjusting for PCB did not affect the associations described above.

In conclusion, in this cohort of children with a relatively high prenatal mercury exposure and potential exposure through breast milk, breastfeeding was not associated with any deficit in neuropsychological performance at age 7. On the other hand, breastfeeding appeared not as beneficial as previously reported by other investigators in non exposed populations. At least in regard to neurotoxic risks, the women can still be advised to breastfeed their children even in this community with relatively high exposures to pollutants. However, newly published results have found a negative effect of breastfeeding on early postnatal growth in children with high exposure to methylmercury, and it therefore remains to be determined whether breastfeeding should be limited at high contamination levels.

Acknowledgements

This work was supported by grants from the US National Institute of Environmental Health Sciences (ES06112), the European Commission (Environmental Research Programme), the Danish Medical Research Council (Grant No. SV1736), and the Dannin Foundation.

References

Amin-Zaki L., Elhassani S.B., Majeed M.A., Clarkson T.W., Doherty R.A., and Greenwood M.R. Studies of infants postnatally exposed to methylmercury. *J Pediatr* 1974: 85: 81–84.

Amin-Zaki L., Elhassani S.B., Majeed M.A., Clarkson T.W., Doherty R.A., and Greenwood M.R. Methylmercury poisoning in mothers and their suckling infant. *Dev Toxicol Environ Sci* 1980: 8: 75–78.

Amin-Zaki L., Majeed M.A., Greenwood M.R., Elhassani S.B., Clarkson T.W., and Doherty R.A. Methylmercury poisoning in the Iraqi suckling infant: a longitudinal study over five years. *J Appl Toxicol* 1981: 1: 210–214.

Anderson J.W., Johnstone B.M., and Remley D.T. Breast-feeding and cognitive development: a meta-analysis. *Am J Clin Nutr* 1999: 70: 525–535.

Bakir F., Damluji S.F., Amin-Zaki L., Murtadha M., Khalidi A., Alrawi N.Y., Tikriti S., Dhahir H.I., Clarkson T.W., Smith J.C., and Doherty R.A. Methylmercury poisoning in Iraq — interuniversity report. *Science* 1973: 181: 230–241.

Borrell A. Pcb and Ddts in blubber of cetaceans from the Northeastern North-Atlantic. *Mar Pollut Bull* 1993: 26: 146–151.

Carlson S.E. Long-chain polyunsaturated fatty acids and the development of human infants. *Acta Paediatr Suppl* 1999: 88: 72–77.

Davidson A.N., and Dobbing J, (Eds.). Vulnerable periods in developing brain. *Applied Neurochemistry*. Davis, Philadelphia, 1968, pp. 287–316.

Gartner L.M., Black L.S., Eaton A.P., Lawrence R.A., Naylor A.J., Neifert M.E., Ohare D., Schanler R.J., Georgieff M., Piovanetti Y., and Queenan J. Breastfeeding and the use of human milk. *Pediatrics* 1997: 100: 1035–1039.

Gladen B.C., and Rogan W.J. Effects of perinatal polychlorinated-biphenyls and dichlorodiphenyl dichloroethene on later development. *J Pediatr* 1991: 119: 58–63.

Grandjean P., Budtz-Jorgensen E., Steuerwald U., Heinzow B., Needham L.L., Jorgensen P.J., and Weihe P. Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls. *FASEB J* 2003: 17: U443–U457.

Grandjean P., Budtz-Jorgensen E., White R.F., Jorgensen P.J., Weihe P., Debes F., and Keiding N. Methylmercury exposure biomarkers as indicators of neurotoxicity in children aged 7 years. *Am J Epidemiol* 1999: 150: 301–305.

Grandjean P., Jorgensen P.J., and Weihe P. Human-milk as a source of methylmercury exposure in infants. *Environ Health Perspect* 1994: 102: 74–77.

Grandjean P., Jørgensen P.J., and Weihe P. Validity of mercury exposure biomarkers. In: Wilson S.H., Suk W.A. (Eds.). *Biomarkers of Environmentally Associated Disease*. CRC Press/Lewis Publishers, Boca Raton, FL, 2002, pp. 235–247.

Grandjean P., Weihe P., Burse V.W., Needham L.L., Storr-Hansen E., Heinzow B., Debes F., Murata K., Simonsen H., Ellefsen P., Budtz-Jorgensen E., Keiding N., and White R.F. Neurobehavioral deficits associated with PCB in 7-year-old children prenatally exposed to seafood neurotoxicants. *Neurotoxicol Teratol* 2001: 23: 305–317.

Grandjean P., Weihe P., Jørgensen P.J., Clarkson T., Cernichiari E., and Viderø T. Impact of maternal seafood diet on fetal exposure to mercury, selenium, and lead. *Arch Environ Health* 1992: 47: 185–195.

Grandjean P., Weihe P., Needham L.L., Burse V.W., Patterson D.G., Sampson E.J., Jorgensen P.J., and Vahter M. Relation of a seafood diet to mercury, selenium, arsenic, and polychlorinated biphenyl and other organochlorine concentrations in human milk. *Environ Res* 1995a: 71: 29–38.

Grandjean P., Weihe P., and White R.F. Milestone development in infants exposed to methylmercury from human-milk. *Neurotoxicology* 1995b: 16: 27–33.

Grandjean P., Weihe P., White R.F., Debes F., Araki S., Yokoyama K., Murata K., Sorensen N., Dahl R., and Jorgensen P.J. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. *Neurotoxicol Teratol* 1997: 19: 417–428.

Jacobson J.L., Jacobson S.W., and Humphrey H.E.B. Effects of *in utero* exposure to polychlorinated-biphenyls and related contaminants on cognitive-functioning in young-children. *J Pediatr* 1990: 116: 38–45.

Jensen A.A., and Slorach S.A. *Chemical Contaminants in Human Milk*. CRC Press, Boston, MA, 1991, p. 298.

Myers G.J., Davidson P.W., Shamlaye C.F., Axtell C.D., Cernichiari E., Choisy O., Choi A., Cox C., and Clarkson T.W. Effects of prenatal methylmercury exposure from a high fish diet on developmental milestones in the Seychelles Child Development Study. *Neurotoxicology* 1997: 18: 819–829.

Raven J. *Standard Progressive Matrices*. HK Levis, London, 1958.

Reynolds W.A., and Pitkin R.M. Transplacental passage of methylmercury and its uptake by primate fetal tissues. *Proc Soc Exp Biol Med* 1975: 148: 523–526.

Rowland I.R. Factors affecting metabolic-activity of the intestinal microflora. *Drug Metab Rev* 1988: 19: 243–261.

Rowland I.R., Robinson R.D., and Doherty R.A. Effects of diet on mercury metabolism and excretion in mice given methylmercury — role of gut flora. *Arch Environ Health* 1984: 39: 401–408.

Saarinen U.M., and Kajosaari M. Breast-feeding as prophylaxis against atopic disease — prospective follow-up-study until 17 years old. *Lancet* 1995: 346: 1065–1069.

World Health Assembly Resolution 25. *Infant and Young Child Nutrition*. World Health Organization, Geneva, 2002.

WHO. *Methylmercury (Environmental Health Criteria 101)*. World Health Organization, Geneva, 1990.

Yamamoto R., and Suzuki T. Effects of artificial hair-waving on hair mercury values. *Int Arch Occup Environ Health* 1978: 42: 1–9.

Yasutake A., Matsumoto M., Yamaguchi M., and Hachiya N. Current hair mercury levels in Japanese: survey in five districts. *Tohuku J Exp Med* 2003: 199: 161–169.