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Attenuated growth of breast-fed children exposed to increased concentrations of methylmercury and polychlorinated biphenyls

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ABSTRACT

Breast-feeding has been linked to slowed postnatal growth. Although the basis for this "weanling's dilemma" is unclear, environmental contaminants in human milk may be of relevance. We studied a Faroese birth cohort of 182 singleton children, born at term in 1994–95. Concentrations of mercury in cord blood and of polychlorinated biphenyls in maternal milk were measured, and duration of breast-feeding was recorded. At 18 months, children who had been exclusively breast-fed for at least 6 months weighed 0.59 kg less [95% confidence interval (CI) = 0.03, 1.16 kg] and were 1.50 cm [95% CI = 0.52, 2.47 cm] shorter than those not breast-fed. However, calculated transfer of contaminants from human milk fully explained the attenuated growth. Irrespective of duration of breast-feeding, a doubling of the mercury concentration in cord blood was associated with a decrease in weight at 18 months by 0.19 kg (95% CI = 0.03, 0.35 kg) and in height by 0.26 cm (95% CI = –0.02, 0.55 cm). Weight and height at 42 months showed the same tendencies, but the main effect occurred before 18 months of age. Thus, in communities with increased contaminant exposures, risks associated with lactational transfer of toxicants to the infant must be considered when judging the benefits of prolonged breast-feeding.

Key words: body weight • eicosapentaenoic acid • diet • postnatal growth • prenatal exposure delayed effects

Because of substantial benefits of breast-feeding to the infant and the mother, international agencies recommend exclusive breast-feeding for 6 months, most recently confirmed at the 55th World Health Assembly in May 2002 (1). However, breast-feeding beyond a few months appears to be associated with attenuated growth of the infant (2–5). The reasons for

this "weanling's dilemma" are unclear (6,7), but caloric intake, nutritional deficiencies, and quality of complementary foods are important considerations (5). Of potential relevance, lipophilic environmental toxicants, including polychlorinated biphenyls (PCBs), are transferred through human milk in concentrations in considerable excess of those normally occurring in food (8). In addition, the infant's elimination of methylmercury may be suppressed because breast-feeding causes a delay in the colonization by demethylating bacteria of the gut, as demonstrated in a rodent model (9).

Prenatal exposure to methylmercury, PCB, and related contaminants has been linked to decreased birth weight (10–12), and some studies have also shown that prenatal PCB exposure was associated with delayed postnatal growth (13, 14). In addition, excess supply of eicosapentaenoic acid (EPA), a polyunsaturated fatty acid mainly originating from seafood, may also adversely affect birth weight (15) and postnatal growth (16).

In a prospectively followed Faroese birth cohort (15, 17), we have determined whether postnatal growth was associated with prenatal and lactational exposures to PCB and methylmercury originating from maternal seafood consumption. This cohort includes subjects with highly increased contaminant exposures: The average cord blood mercury concentration is about four times the recommended exposure limit recommended by the U.S. Environmental Protection Agency (18), and the average PCB concentration exceeds levels elsewhere in Europe by about the same factor (19).

MATERIALS AND METHODS

Participants and design

A cohort of 182 singleton term births was established from consecutive spontaneous births during a 12-month period in 1994–95 at the National Hospital in Tórshavn, Faroe Islands (15, 17). To obtain the widest possible range of contaminant exposures, the cohort was based on the primary hospital catchment area away from the capital area of Tórshavn, that is, the central and northwestern villages, where access to fish and whale is the easiest. Birth before the 36th week and congenital neurological disease were used as exclusion criteria. [Table 1](#) shows the major obstetric parameters for the 171 children examined at age 18 months.

As a measure of developmental methylmercury exposure, blood from the umbilical cord was analyzed for total mercury (15); in five cases without a cord blood sample, the result was estimated from the mercury concentration in maternal hair by using an average ratio of 210 (20). Methylmercury concentrations in milk were not assessed, because the relatively high concentration of inorganic mercury would require more complex speciation analysis (19). However, a previous study in the same population had shown that the cord blood mercury concentration was a strong predictor also of postnatal exposure to this substance, if the duration of breast-feeding was taken into account (21).

Major PCB congeners were determined in transition milk and were expressed in relation to the lipid concentration (15, 22). The total PCB concentration was calculated as the sum of congeners 138, 153, and 180 multiplied by 2.0 (19). In 12 cases without a milk sample, the result was estimated by recovery adjustment of the lipid-based concentration in maternal serum obtained at the 34th week of pregnancy (15, 23). As expected from the persistence of PCB in the body lipids, these two PCB

exposure biomarkers were closely associated ($r = 0.91$). When expressed on a lipid basis, the milk PCB concentration, therefore, also reflects the prenatal exposure level.

For estimation of cumulated PCB after weaning, sufficient serum was obtained from 121 of the children at age 54 months and was analyzed for PCB congeners (24). Because of the persistence of PCB and the expected absence of PCB from baby food, the total PCB concentration (calculated as above) in serum was thought to reflect the combined transplacental and lactational transfer.

Among essential fatty acid concentrations measured in cord serum, EPA was previously found to be associated both with decreased birth weight and increased contaminant concentrations (15, 17). Fatty acid concentrations were therefore considered in the statistical analyses, with EPA as an obligatory covariate.

Clinical examinations were scheduled at 18 and 42 months of age, and the exact age (in days) was recorded. Body weight (in kilograms with one digit after the decimal point) and standing height (in centimeters) were measured by a pediatrician. The children were generally in good health, and no medical reasons for growth impairment were identified. Duration of exclusive and supplemental breast-feeding was recorded by interview of the mother 7 months after childbirth and at the clinical examinations (data were missing in one case). Of the cohort members, 171 (94%) were examined at age 18 months and 154 (85%) at age 42 months. The main reason for attrition was foreign residence.

Statistical analysis

Multiple regression analysis was used to determine the relative importance of relevant covariates as predictors of the outcome parameters. We took into account all parameters significantly associated with birth weight in this cohort (17) or otherwise known to affect postnatal growth (7, 25), that is, gestational age, birth weight, sex, parity, maternal weight and height, gestational diabetes, maternal smoking and alcohol use, and the child's age at examination (in days). Models were generated by using the anthropometric variables at 18 and 42 months as dependent variables, first with all covariates selected a priori. By backward elimination, covariates were kept in the model if the P value was <0.2 ; the robustness of the regression equations was tested by inclusion of removed covariates one by one. The possible impact of EPA on the final regression equation was assessed by including this parameter as an additional covariate, whereas the need to consider other polyunsaturated fatty acids was determined from bivariate analyses.

Duration of breast-feeding and the individual exposure parameters were then examined as additional independent variables. Contaminant concentrations showed skewed distributions and were logarithmically transformed to obtain an improved fit of the models. An estimated dose via breast-feeding was computed by multiplying the concentration of PCB in milk by the duration of exclusive breast-feeding. A similar proxy measure was generated by using the mercury concentration in cord blood. Because of necessary logarithmic transformation, duration of breast-feeding was adjusted to 0.1 for mothers who did not breast-feed or only partially nursed their children. The impact of lactational exposure was first considered alone, and significant associations were then explored by including a parameter that reflected the prenatal exposure. Likewise, attempts were made to separate the effects of methylmercury and PCB by including both in the same regression equation. Finally, the child's serum-PCB concentration at age 54 months was considered in separate analyses as a measure of total accumulated absorption.

RESULTS

Body weight and height at 18 months were clearly associated with several predictors. [Table 2](#) shows the results for parameters that remained significant in the multiple regression models. Catch-up growth in children of smoking mothers was statistically significant when birth size was taken into account. Thus, the ~200 g deficit in birth weight in children of smoking mothers was fully recovered by the age of 18 months. The same patterns were also apparent at 42 months.

Duration of breast-feeding varied substantially, but only 33 (18.2%) mothers breast-fed without supplements for the recommended 6 months. Thirteen mothers (7.2%) did not provide exclusive breast-feeding at all. Duration of breast-feeding was not associated with the indicators of prenatal contaminant exposures. After adjustment for confounders, duration of breast-feeding was negatively associated with body weight ([Fig. 1](#)) and height at 18 months. Regression analysis showed that children who had been exclusively breast-fed for at least 6 months as recommended by WHO weighed 0.59 kg less (95% confidence interval {CI}= 0.03, 1.16 kg) and were 1.50 cm (95% CI = 0.52, 2.47 cm) shorter at 18 months when compared with those not breast-fed. The findings at 42 months were similar, but these associations all but vanished if body size at 18 months was included as a covariate.

Especially the cord blood mercury concentration was negatively associated with the 18-month weight and height ([Table 3](#)). Despite the association between the two contaminants ($r = 0.34$), the PCB concentration level was generally a less important predictor, and inclusion of this variable changed the mercury associations only negligibly. The same was true for EPA, which itself remained significant after confounder adjustment. Bivariate analyses indicated that none of the other fatty acids measured in cord serum impacted on postnatal growth. Similar associations with the contaminants were observed at 42 months ([Table 3](#)), but they almost completely disappeared when adjusted for body size at 18 months.

The effect of lactational exposure alone was examined by using the product terms of contaminant concentrations and the duration of exclusive breast-feeding ([Table 3](#)). Lactational exposure to both mercury and PCB showed significant negative effects on both weight and height at 18 months. Mercury remained significant when both contaminant parameters were included. A mercury effect on weight was also significant at 42 months but again vanished if adjusted for the 18-month weight. The prenatal and the calculated lactational exposure levels were clearly not independent, with correlation coefficients of 0.59 and 0.47 for the pairs of mercury and PCB parameters, respectively.

Weight at 18 months was therefore examined in detail by multiple regression analyses. To reduce collinearity problems, three different equations were developed ([Table 4](#)). Model 1 suggested that both breast-feeding ($P = 0.05$) and prenatal methylmercury exposure ($P = 0.02$) may reduce body weight. The regression coefficient of -0.63 for the mercury effect indicates that a doubled exposure is associated with a decrease in weight by 0.19 kg (95% CI = 0.03, 0.35 kg). Similarly, height at 18 months was reduced by 0.26 cm (95% CI = -0.02 , 0.55 cm) when mercury exposure was doubled.

The negative effect of breast-feeding as such was completely abolished ($P = 0.88$) by adjustment for lactational mercury exposure ($P = 0.02$) ([Table 4](#), Model 2), but the results did not allow determination of the relative impact of the highly associated indicators of prenatal ($P = 0.41$) and lactational ($P = 0.10$) mercury exposure (Model 3). Mercury exposure remained statistically

significant after adjustment for PCB. Again, regression results at age 42 months were similar if not adjusted for body size at 18 months.

The lipid-based PCB concentration in serum at age 54 months was used as a proxy variable for accumulated lactational exposure. This parameter showed a significant negative association with weight and height at age 42 months. Because a heavier child with more body fat would also have a greater distribution volume for lipophilic PCB, the ponderal index was included as a covariate in addition to the confounders previously identified. This adjustment much reduced the regression coefficients, but they remained significant (both at $P = 0.008$), and a doubled PCB exposure level was associated with a decrease in 42-month weight by 0.30 kg (95% CI = 0.07, 0.55 kg) and in height by 0.63 cm (95% CI = 0.13, 1.12 cm). Again, these associations almost disappeared when adjusted for weight or height at 18 months. Adjustment for EPA did not affect any of the associations observed.

DISCUSSION

This study involves a wide concentration range of the contaminants and durations of breast-feeding. Although allowance must be made for the limited size of the cohort, the Faroese population is rather homogenous (15, 17, 26), and nutritional deficiencies or other serious confounding in regard to infant growth patterns would be unlikely in this Western, industrialized community.

In this prospective cohort study of term births, the environmental contaminants did not seem to affect birth weight, perhaps due to the impact of the well-known prolonged gestation caused by docosahexaenoic acid from seafood (17). The postnatal follow-up data replicated the expected (27, 28) catch-up growth of children of smoking mothers. Although maternal alcohol intake during pregnancy may affect postnatal growth (29, 30), this population of mostly non-drinking mothers ([Table 1](#)) did not show any such association.

The contaminant exposure biomarkers must be interpreted in light of the time of sample collection and the known fate of the chemicals in the body (31, 32). The biological half-life of methylmercury in the human body is probably ~45 days in adults (33), but it may be substantially longer in breast-fed infants (9, 21). Half-lives of the most prevalent PCB congeners are thought to be several years (34). Accordingly, PCB concentrations in maternal serum and milk correlated well, although sampled several weeks apart. Thus, the biomarker for developmental PCB exposure would be less likely to be affected by short-term changes in maternal intake levels. However, the accumulated dose in the infant will be affected by the postnatal expansion of the lipid compartment during growth (32). Such dilution will render the serum concentration a biased marker of the dose received. As expected, the association between this exposure biomarker and body weight and height was substantially reduced when adjusted for the body mass index. However, for the methylmercury biomarkers, no such confounding is known, and any random imprecisions, especially related to the calculation of lactational exposure levels, would likely bias the regression results toward the null hypothesis.

A different source of bias in this type of study relates to the possible differences in nutrients between human milk and complementary foods and related caloric intakes (5,7). Thus, the term "weanling's dilemma" was originally introduced because human milk was thought to constitute an insufficient source of nutrients after 3–4 months, while complementary foods in many developing countries were considered unsafe (6). However, as human milk is now thought to provide sufficient amounts of

nutrients (5), the present study suggests that a "weanling's dilemma" rather involves a choice between a suboptimal supply of nutrients from supplements and an optimal nutrition coupled with concomitant exposure to environmental pollutants in breast milk.

Poisoning episodes have documented adverse effects on postnatal growth associated with developmental PCB exposure (35, 36), but the contaminant mixtures involved in these incidents differed from those commonly occurring in human milk (8). Other studies reported somewhat inconsistent effects of PCB on postnatal growth (13, 14, 37); concomitant exposures to methylmercury and fatty acids were not considered. Experimental studies have shown a negative effect of developmental PCB exposure on postnatal growth in primates (38, 39) and rodents (40, 41). Decreased postnatal weight gain has also been reported in rats in relation to maternal methylmercury exposure (42,43). Unfortunately, this evidence does not allow a clear separation of the impacts of prenatal and postnatal exposures.

Intrauterine contaminant exposures could possibly determine postnatal growth through prenatal programming as suggested by long-term consequences of intrauterine growth retardation (44). Also, birth weight remains an important predictor for height throughout childhood (45). In the present study in a population with a high average birth weight, possible effects of contaminants on prenatal growth could have been blurred by the effects of essential fatty acids from seafood (17). Thus, the cord serum EPA concentration showed a negative effect on birth weight (17), and it remained an independent predictor also of growth during the postnatal follow-up. This finding is in accordance with observations from clinical trials using milk substitutes with an increased EPA concentration (16).

A slight, negative effect on body weight alone does not necessarily suggest systemic toxicity, and breast-feeding is indeed thought to protect against development of obesity (46). In addition, nursing may well confer an advantage for growth during the first few months, although most data suggest that continued breast-feeding has a negative effect that may also affect height (5, 7). Previous studies in this field were conducted in countries where human milk contaminants must have included PCB and pesticides (8), but the association has been attributed to differences in the risk of malnutrition, possible confounding due to social deprivation, and perhaps in some cases a reverse causation (5, 7). The present study conducted in a relatively homogeneous industrialized society without nutritional deficiencies suggests that the list of possible causal factors should include human milk contaminants.

Exposures to seafood contaminants is a worldwide concern, and exposures similar to or in excess of those recorded in the Faroes have been published from other communities with high seafood or freshwater fish intakes (18, 37). The present study indicates that postnatal growth may be adversely affected by exposure to methylmercury and PCB, which originate from maternal seafood diets. It also suggests that the previously observed decreased growth in breast-fed infants could be at least partially explained by environmental contaminants excreted by the mother into breast milk. Effects on weight and height were most clear at age 18 months, but a lasting effect was suggested by the similar associations that were apparent two years later. Although such effects may have been detectable only because the present study included subjects with substantially increased exposures, the safe margin for populations with lower exposures would seem to be rather slim.

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Table 1**Characteristics of 171 children from the birth cohort included in postnatal follow-up^a**

Variable	
Maternal age in years	28.1 ± 5.8
Previous births (none /one/at least two in %)	28.7 / 28.1 / 43.2
Smoking during pregnancy (no/yes in %)	67.3 / 32.7
Alcohol consumption (never/ever in %)	87.1 / 12.9
Gestational age in weeks	39.6 ± 1.3
Mercury concentration in cord blood in µg/l ^c	20.3 (1.9-102)
ΣPCB ^b concentration in maternal milk in µg/g lipid ^c	1.52 (0.07-18.5)
Eicosapentaenoic acid concentration in cord serum phospholipids in % ^c	0.63 ± 0.28
Birth weight in g	3678 ± 486
Length at 2 weeks in cm	54.8 ± 2.1
Duration of exclusive breast-feeding in months	3.5 ± 2.0
Duration of total breast-feeding in months	7.8 ± 5.7
ΣPCB concentration in serum from age 54 months in µg/g lipid ^c	0.98 (0.10-7.1)
Age at 18-month examination in months	18.0 ± 0.3
Body weight at 18 months in kg	12.0 ± 1.4
Height at 18 months in cm	82.0 ± 2.6
Age at 42-month examination in months	41.6 ± 1.0
Body weight at 42 months in kg	16.4 ± 1.8
Height at 42 months in cm	100.3 ± 3.6

^aData in given as mean ± SD unless otherwise indicated. ^bSum of the major polychlorinated biphenyl congeners 138, 153, and 180 multiplied by 2.0. ^cGeometric mean; range in parenthesis

Table 2**Body weight and height at age 18 months according to main predictors studied^a**

	<i>n</i>	Weight (kg)	<i>P</i> ^b	Height (cm)	<i>P</i> ^b
Sex			0.0005		0.0006
Boy	88	12.34 (1.41)		82.65 (2.44)	
Girl	83	11.60 (1.26)		81.30 (2.61)	
Birth weight (g)			<0.0001		<0.0001
2500–2999	11	10.69 (1.07)		79.36 (2.25)	
3000–3499	46	11.58 (1.52)		81.02 (2.89)	
3500–3999	65	12.31 (1.28)		82.60 (2.11)	
4000–4499	37	12.15 (1.11)		82.38 (2.40)	
≥4500	12	12.38 (1.57)		83.67 (2.15)	
Maternal height (cm)			<0.0001		<0.0001
≤155	11	11.04 (0.62)		79.82 (2.60)	
156–160	41	11.54 (1.35)		81.26 (2.42)	
161–165	55	11.88 (1.30)		81.51 (2.45)	
166–170	42	12.40 (1.27)		82.98 (1.99)	
>170	21	12.79 (1.62)		83.86 (2.87)	
Maternal smoking during pregnancy			0.22		0.28
Yes	115	11.89 (1.43)		81.84 (2.78)	
No	56	12.16 (1.28)		82.30 (2.20)	
Concentration of eicosapentaenoic acid in cord serum phospholipids (%)			0.0051		0.052
≤0.43	37	12.34 (1.49)		82.11 (3.02)	
0.44–0.58	38	12.19 (1.47)		82.71 (2.19)	
0.59–0.77	37	11.80 (1.24)		81.46 (2.56)	
≥0.78	34	11.61 (1.43)		81.32 (2.86)	

^aData are mean (SD). ^bAnalysis of variance (categorical predictors) and regression analysis (continuous variables).

Table 3

Adjusted change (95% confidence interval) in weight and height at ages 18 months and 42 months at a 10-fold increased exposure to mercury and PCB prenatally and via breast-feeding^a

	Mercury	PCB
Prenatal		
Age 18 months (<i>n</i> = 171)		
Weight (kg)	−0.63 (−1.17, −0.09)	−0.31 (−0.88, 0.25)
Height (cm)	−0.88 (−1.85, 0.09)	−0.75 (−1.74, 0.25)
Age 42 months (<i>n</i> = 154)		
Weight (kg)	−0.80 (−1.56, −0.04)	−0.03 (−0.79, 0.73)
Height (cm)	−0.97 (−2.42, 0.49)	−0.71 (−2.08, 0.82)
Lactational		
Age 18 months (<i>n</i> = 171)		
Weight (kg)	−0.45 (−0.77, −0.12)	−0.43 (−0.79, −0.06)
Height (cm)	−0.73 (−1.30, −0.16)	−0.88 (−1.52, −0.24)
Age 42 months (<i>n</i> = 154)		
Weight (kg)	−0.46 (−0.88, −0.03)	−0.27 (−0.74, 0.20)
Height (cm)	−0.34 (−1.16, 0.48)	−0.33 (−1.24, 0.57)

^aResults are calculated as regression coefficients adjusted for birth weight, sex, maternal height, smoking, and age (in days) at the 42-month examination. Prenatal exposure indicators are the mercury concentration in cord blood and the lipid-based Σ PCB concentration in maternal milk. Lactational exposures are calculated as the same parameters multiplied by duration of exclusive breast-feeding.

Table 4

Adjusted change (95% confidence interval) in weight (kg) at age 18 months per month of exclusive breast-feeding and 10-fold increase in methylmercury exposure^a

Variable	Model 1	Model 2	Model 3
Duration of breast-feeding (mo)	−0.09 (−0.19, −0.00)	−0.01 (−0.14, 0.12)	
Prenatal mercury exposure ^b	−0.63 (−1.16, −0.09)		−0.28 (−0.96, 0.39)
Mercury from breast-feeding ^c		−0.43 (−0.87, 0.02)	−0.34 (−0.75, 0.06)

^aResults are adjusted for sex, birth weight, maternal height, and smoking during pregnancy.

^bCord blood mercury concentration.

^cCord blood mercury concentration multiplied by duration of exclusive breast-feeding.

Fig. 1

Figure 1. Mean (SEM) weight at 18 months of age adjusted to average birth weight and maternal height, boy and nonsmoking mother, in relation to duration of exclusive breast-feeding (P for trend = 0.04). Also shown is the regression line after adjustment also for lactational methylmercury exposure (P for trend = 0.88).