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Maternal fish and other seafood intakes during pregnancy and child neurodevelopment at age 4 years

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Abstract

Objective: To analyse the relationship between maternal intakes of fish and other seafood during pregnancy and child neurodevelopment at age 4 years. Although pregnant women are advised to limit seafood intakes because of possible neurotoxin contamination, several studies suggest that overall maternal seafood intakes are associated with improved child neurodevelopment, perhaps because of higher DHA intakes.

Design: The study uses data from a prospective birth cohort study. Maternal seafood intakes were assessed using a semi-quantitative FFQ administered shortly after delivery. Multivariate linear regression was used to estimate associations between seafood consumption and scores on the McCarthy Scales of Children's Abilities (MCSA). Analyses were stratified by breast-feeding duration as breast milk is a source of DHA during the postnatal phase of the brain growth spurt.

Setting: Menorca, Spain, 1997–2001.

Subjects: Full-term children (n 392) with data on maternal diet in pregnancy, breast-feeding duration and neurodevelopment at age 4 years.

Results: Among children breast-fed for <6 months, maternal fish intakes of >2–3 times/week were associated with significantly higher scores on several MCSA subscales compared with intakes ≤1 time/week. There was no association among children breast-fed for longer periods. Maternal intakes of other seafood (shellfish/squid) were, however, inversely associated with scores on several subscales, regardless of breast-feeding duration.

Conclusions: The study suggests that moderately high intakes of fish, but not other seafood, during pregnancy may be beneficial for neurodevelopment among children breast-fed for <6 months. Further research in other populations with high seafood intakes and data on additional potential confounders are needed to confirm this finding.

Keywords
Child development
Fish
Pregnancy
Diet

Numerous studies suggest that deficiencies of key micronutrients during the brain growth spurt, which occurs in the last trimester of pregnancy and the first 2 years of life, may have lasting effects on neurodevelopment[1–9]. Among these nutrients, there is evidence that several long-chain PUFA, particularly the n-3 fatty acid DHA, may be essential for optimal brain function. DHA is not widely distributed in the diet but is predominantly concentrated in fish, with, on average, lower levels in other types of seafood[10–12]. It has been hypothesized that higher DHA levels may at least partly explain the positive associations between maternal fish consumption during pregnancy and measures of child development reported in several studies[13–16]. Maternal supplies strongly influence offspring levels of this nutrient during this period[2,17]. DHA is actively transported across the placenta[18] and is supplied through breast milk during the postnatal stage of the brain growth spurt[19]. Levels are substantially higher in the plasma of pregnant women who eat fish frequently or are supplemented with fish oils[20,21].

On the other hand, seafood is also a common source of neurotoxic contaminants such as methylmercury (MeHg)[22,23]. Pregnant women must therefore weigh the potential risks as well as the benefits of fetal exposure to substances found in seafood[24]. Umbilical cord MeHg or maternal hair Hg have been associated with poorer offspring performance in developmental tests in several[14,25],

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though not all[15,22] studies. Because of the potential risks, US and UK government agencies have issued advice that pregnant women limit seafood intakes to 340 g or about 3 servings per week[26,27]. To date, few studies have examined relationships between seafood consumption in pregnancy and child neurodevelopment, and these studies have not reported adverse effects of exceeding this threshold[13–15]. The present study examines relationships between consumption of fish and other seafood in pregnancy and children's performance in cognitive and motor skills tests at age 4 years using data from a longitudinal cohort study conducted in the Spanish Mediterranean island of Menorca, a setting where seafood consumption is common[28,29].

Methods

Details on the design and data collection methods have been given previously[30,31]. Briefly, 482 (95 % participation) pregnant women were recruited from prenatal clinics in Menorca over 12 months in 1997–8. Mothers provided signed informed consent, and the study was approved by the ethics committee of the Institut Municipal d'Investigació Mèdica. At recruitment, interviewers collected data from mothers including maternal age, education, parity, smoking habits and pre-pregnancy weight. Maternal height was measured by trained staff. Mothers reported usual diet during the course of pregnancy using an FFQ administered by interviewers 3 months after delivery[29,32]. Infant height, weight and gestational age were obtained at birth; information on feeding practices including breast-feeding was collected in follow-up surveys at 6 and 14 months. Measures of child neurodevelopment, dietary intakes and physical activity patterns were collected at age 4 years.

The analysis sample (n 392) excluded preterm children (<37 weeks' gestation, n 23), who have known differences in intellectual development compared with term births[33,34], as well as those without developmental test/schooling (n 64) or breast-feeding duration (n 3) data. Multivariate analyses also excluded subjects missing data on maternal education or weeks of gestation (n 18). Children without test scores were somewhat less likely to have mothers with post-secondary education ($P = 0{\cdot}08$), although there were no differences in fathers' education ($P = 0{\cdot}99$). There were no other differences among those with and without testing data in terms of child (sex, birth weight, gestational age, breast-feeding duration, fish consumption at age 4 years) or other maternal (fish consumption in pregnancy, age, parity, obesity, smoking during pregnancy) characteristics.

Study variables

Developmental tests

To assess neurodevelopment, the Spanish version of the McCarthy Scales of Children's Abilities (MCSA) tests was administered by two trained psychologists, as previously described[31]. The global cognitive scale and five subscales (perceptive-performance, memory, verbal, quantitative and motor) were used to assess children's abilities. Scores were previously standardized to a mean of 100 with a standard deviation of 15 points to increase comparability across scales.

Seafood consumption

Maternal seafood consumption was estimated from an interviewer-administered, semi-quantitative, forty-two-item FFQ that included questions about fish, octopus/squid and shellfish consumption. Shellfish and squid were analysed separately from fish, as these types of seafood have, on average, a lower DHA content[12]. Intakes were converted to weekly amounts based on reported consumption per day (×7), week, month (×7/30) or year (×7/365) and categorized based on distribution patterns in the data. Fish intake frequencies were categorized as ≤1 time/week, >1 to 2 times/week, >2 to 3 times/week and >3 times/week, the last exceeding recommended maximum seafood intake levels. Other seafood (squid and shellfish) intake frequencies were categorized as ≤0·5 time/week, >0·5 to 1 time/week and >1 time/week. Overall seafood intakes were categorized roughly in quartiles as ≤1·5 times/week, ≥1·5 to 2 times/week, >2 to 3 times/week and >3 times/week. Children's seafood consumption at age 4 years, reported by mothers using the same questionnaire, was classified using the same methods and intake categories.

Covariates

The primary covariates included: (i) maternal education and parity; (ii) child sex, birth weight and weeks of gestation; (iii) breast-feeding duration; and (iv) child age at test administration, current trimester/grade and psychologist administering the test. Models simultaneously adjusted for maternal intakes of fish and other seafood, as well as child seafood consumption at age 4 years. Other potential covariates were excluded for parsimony, as they did not confound associations between maternal fish consumption and child development, including maternal age, pre-pregnancy overweight/obesity ($\mathrm{BMI} \geq 25{\cdot}0\,\mathrm{kg/m^2}$), smoking during pregnancy, social class based on occupation, child overweight at 4 years (Centers for Disease Control and Prevention/WHO reference[35]), as well as other aspects of maternal diet in pregnancy (dietary supplement, meat, fruit, vegetable, alcohol and coffee intakes) and children's current diets (meat, fruit and vegetable intakes). Confounding was defined as a change-in-estimate ≥10 % for maternal fish intake variables.

Statistical analysis

Standardized test scores and other sample characteristics were described across maternal fish consumption categories using means and proportions with χ^2 or ANOVA tests. Interactions between maternal fish intakes and breast-feeding duration were assessed, as breast milk is an alternative source of DHA. Descriptive analyses were also conducted stratified by breast-feeding duration since interactions with breast-feeding duration were significant (multivariate-adjusted $P<0·05$ using weeks continuously or greater than/equal to *v.* less than the recommended 6 months for general cognitive, memory and numeric scores; $P<0·10$ for perceptual-performance and verbal scores). Multivariate linear regression was used to examine associations between maternal fish and other seafood intakes and performance on the MCSA global and sub-tests, adjusting for the covariates listed above. Coefficients represent the mean difference in standardized test scores compared with children whose mothers reported intakes in the referent category. Separate models were run to examine effects of overall maternal seafood intakes *v.* fish and other types of seafood, examined independently. To improve comparability with overall seafood intakes, fish intakes were categorized using the same groups as all types of seafood in some models; results were meaningfully unchanged.

In supplementary models, we confirmed that results were similar after excluding children who were never breast-fed (17·1 %), omitting non-consumers (3·3 %) or women with the highest fish intakes (>4 times/week, *n* 7), separating shellfish and squid intakes; separately categorizing subjects with other seafood intakes >2 times/week (*n* 21) or >3 times/week (*n* 6); excluding overweight and obese mothers (18·8 %) or women with higher education (15·3 %); and excluding potentially influential observations based on change in β (not shown). Stratifying by maternal education also yielded similar results among women with higher, secondary and primary education or less (not shown). Adjusting for the usual type of fish consumed (white fish (59·8 %) *v.* oily fish) did not affect findings (not shown). We also examined the effects of adjusting for cord blood levels of several contaminants potentially associated with neurodevelopment: DDT (2,2-bis(*p*-chlorophenyl)-1,1,1-trichloroethane), DDE (2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene) and polychlorinated biphenyls (PCB; the sum of congeners 25, 52 101, 118, 138, 153 and 180)[36–38]. These compounds did not confound associations with maternal fish consumption and were omitted from the final models. Multiple imputation was used to assess the impact of incorporating subjects with missing test score data, using variables such as maternal education, parity, child sex and birth weight as predictors. Associations were meaningfully the same as in the complete case analysis (not shown).

Results

Maternal fish consumption

The mean (SD) weekly intake of fish during pregnancy was 1·69 (1·5) servings. About half of the women (49·2 %) reported eating fish ≤1 time/week during pregnancy, with few (3·3 %) non-consumers (Table 1). Among women with higher intakes, 32·9 % reported eating fish >1–2 times/week, 12·8 % reported fish consumption >2–3 times/week and 5·1 % consumed fish >3 times/week. Fish represented 57·7 % of women's overall seafood intakes. Women who consumed more fish also had higher intakes of other seafood ($P<0·05$, ANOVA) and reported higher fish intakes among their children at age 4 years ($P<0·05$, ANOVA).

Fish consumption in pregnancy was not related to the subsequent duration of breast-feeding or to numerous maternal characteristics including higher education, smoking during pregnancy and pre-pregnancy overweight (Table 1). More frequent fish consumption was associated with higher parity overall and among women who breast-fed for ≥6 months ($P<0·05$, χ^2 test), but not among women who breast-fed for shorter periods ($P>0·10$, χ^2 test). Parous women also reported higher intakes of other types of seafood than nulliparous women (not shown). Unlike fish, however, intakes of squid and shellfish were related to maternal education, with more frequent consumption reported by women with primary *v.* higher levels of education (46·6 % *v.* 34·0 % with intake >1 time/week; $P<0·05$, χ^2 test). Intakes of these other types of seafood were not related to other socio-demographic variables examined or with breast-feeding duration (not shown).

Maternal fish consumption, breast-feeding and neurodevelopment

In descriptive analyses, standardized global cognitive and subscale scores were highest among children whose mothers reported fish intakes of >2–3 times/week (global and perceptual-performance scores *v.* other intake categories; $P<0·05$, ANOVA; Table 2). However, the small group whose mothers reported fish intakes >3 times/week had mean scores similar to those with intakes of ≤1 time/week ($P>0·10$ for all scores, ANOVA). Moreover, fish consumption was associated with higher scores only among children breast-fed for <6 months. In these children, maternal intakes of >2–3 times/week *v.* ≤1 time/week were associated with increases of 5·9 to 8·6 points compared with intakes of ≤1 time/week ($P<0·05$ for all but the motor skills subscale, ANOVA), although children breast-fed for ≥6 months had higher mean scores than those breast-fed for shorter periods ($P<0.05$ for all but the motor skills score, two-sided *t* test; not shown). However, maternal fish consumption was not strongly or consistently associated with test performance among these children (Table 2).

Multivariate associations resembled the descriptive analysis (Table 3). Given the significant interactions between breast-feeding duration and maternal fish intakes of >2–3 times/week (interaction term $P<0·10$ for all but the motor skills subscale), results are presented stratified by breast-feeding duration. Among children breast-fed for <6 months, maternal fish intakes

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Table 1 Characteristics of the sample by maternal fish intake in pregnancy: full-term children (*n* 392) from a prospective birth cohort study, Menorca, Spain, 1997–2001

		Maternal weekly fish intake frequency†								
		≤1 time (*n* 193, 49.2 %)		>1–2 times (*n* 129, 32.9 %)		>2–3 times (*n* 50, 12.8 %)		>3 times (*n* 20, 5.1 %)		
	n	Mean or %	SD	Mean or %	SD	Mean or %	SD	Mean or %	SD	*P*‡
Maternal characteristics										
Age (years)	392	28·42	4·59	29·74	4·35	28·78	4·25	30·45	5·18	0·03
Frequency/week	392									
Fish		0·76	0·34	1·90	0·20	2·75	0·25	5·78	3·86	–
Squid/shellfish		1·03	0·75	1·17	0·79	1·30	0·89	2·23	3·10	0·00
All seafood		1·80	0·83	3·08	0·80	4·05	1·00	8·30	6·42	0·00
Education (%)	378									
Any higher		13·1		14·8		21·3		27·8		0·38
Secondary		26·7		30·3		23·4		11·1		
Primary or less		60·2		54·9		55·3		31·1		
No. of children (%)	392									
None		54·9		38·8		56·0		45·0		0·05
One		35·2		47·3		34·0		30·0		
Two or more		9·8		14·0		10·0		25·0		
Smoked during pregnancy (%)	392									
Never		62·7		65·1		70·0		50·0		0·13
1st trimester		15·0		19·4		8·0		10·0		
2nd/3rd trimester		22·3		15·5		22·0		40·0		
Weight status (%)	378									
Normal weight		80·0		80·9		83·7		83·3		0·94
Overweight/obese§		20·0		19·1		16·3		16·7		
Child characteristics										
Age (years)	392	4·36	0·16	4·37	0·15	4·37	0·14	4·39	0·14	0·91
Frequency/week, age 4 years										
Fish	392	1·68	0·91	2·08	1·07	2·32	1·28	2·88	1·36	0·00
Squid/shellfish		0·99	0·75	1·00	0·72	1·16	0·69	1·05	0·76	0·49
All seafood		2·66	1·29	3·09	1·44	3·48	1·59	3·93	1·52	0·00
Weeks' gestation	391	39·6	1·16	39·4	1·31	39·3	1·26	39·7	1·22	0·38
Birth weight (g)	392	3236	471	3226	419	3176	359	3328	501	0·62
Child sex (%)	392									
Female		53·4		45·7		48·0		50·0		0·60
Male		46·6		54·3		52·0		50·0		
Breast-feeding duration (%)	392									
Breast-fed for <6 months		60·6		65·9		56·0		70·0		0·52
Breast-fed for ≥6 months		39·4		34·1		44·0		30·0		

†*n* 13 (3·3 %) women never ate fish.
‡*P* value from ANOVA or χ^2 test.
§Overweight/obese includes all women with BMI ≥ 25·0 kg/m^2.

of >2–3 times/week remained associated with significantly higher mean scores after multivariate adjustment (coefficient $P<0·05$ for all scales). However, the small group with maternal fish intakes >3 times/week had similar scores to those reporting intakes of ≤1 time/week. Maternal fish intakes were weakly associated with lower rather than higher scores among children breast-fed for ≥6 months.

Other seafood intake variables and neurodevelopment

In contrast to fish, maternal intakes of other types of seafood during pregnancy were associated with lower general cognitive, perceptual-performance, verbal and numeric scores at age 4 years (Table 4). Associations were similar regardless of breast-feeding duration (interactions not significant for all subscales; data not shown). As was true for fish intakes, crude associations were similar to multivariate results (e.g. for general cognitive scores, coefficient (SE) for intakes of >0·5 to 1 time/week and >1 time/week respectively were −1·2 (1·9) and −6·3 (1·8) before adjustment *v.* −1·0 (1·7) and −5·4 (1·6) in multivariate models). As a consequence of the contrasting directions of association for other seafood *v.* fish, maternal intakes of all types of seafood combined were not associated with developmental test scores (see Fig. 1 for general cognitive scores).

Child intakes of fish and other types of seafood at age 4 years were not strongly associated with test performance. Mean scores increased only slightly with increasing child fish intakes ($P>0·10$ for all scales, ANOVA). For example, mean (SD) general cognitive scores were 98·0 (16·0), 99·3 (14·4), 100·7 (13·2) and 100·4 (15·1), respectively, over increasing intake categories of ≤1 time/week,

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Table 2 Mean test scores† at age 4 years by maternal fish intake frequency during pregnancy: full-term children (*n* 392) from a prospective birth cohort study, Menorca, Spain, 1997–2001

	Maternal weekly fish intake frequency								
	≤1 time		>1–2 times		>2–3 times		>3 times		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	*P*‡
All children	*n* 193		*n* 129		*n* 50		*n* 20		
General cognitive	98·6	14·3	99·3	15·5	103·4	14·5	96·2	10·4	0·04
Perceptual-performance	98·0	14·3	99·3	16·2	103·6	13·3	99·1	9·0	0·02
Memory	99·1	14·1	99·9	15·3	102·3	16·2	95·1	15·0	0·16
Verbal	99·5	14·2	99·5	15·8	103·2	14·5	95·1	12·3	0·08
Numeric	98·5	14·2	99·5	14·3	100·7	16·6	97·3	13·9	0·38
Motor skills	98·8	14·6	100·1	16·4	102·8	12·9	98·5	11·6	0·12
Breast-fed for <6 months§	*n* 117		*n* 85		*n* 28		*n* 14		
General cognitive	95·9	14·1	97·4	15·0	104·5	13·8	95·5	12·4	0·01
Perceptual-performance	95·7	13·7	97·3	15·6	104·3	14·1	97·6	9·4	0·01
Memory	96·9	14·2	98·3	14·7	105·6	16·1	97·2	17·5	0·01
Verbal	97·2	14·0	98·2	15·4	104·0	13·2	95·1	14·1	0·03
Numeric	96·3	14·4	97·5	13·1	102·4	17·5	96·8	15·0	0·06
Motor skills	97·7	14·1	100·0	15·7	103·9	12·4	97·4	12·7	0·06
Breast-fed for ≥6 months	*n* 76		*n* 44		*n* 22		*n* 6		
General cognitive	102·7	13·8	103·1	16·1	102·0	15·5	97·8	2·4	0·84
Perceptual-performance	101·6	14·7	103·1	16·8	102·7	12·4	102·5	7·5	0·87
Memory	102·6	13·4	103·1	16·1	98·2	15·7	90·3	4·4	0·24
Verbal	103·0	13·8	102·1	16·4	102·2	16·2	95·1	7·6	0·99
Numeric	101·9	13·3	103·3	15·9	98·7	15·6	98·4	12·4	0·29
Motor skills	100·3	15·4	100·2	17·7	101·3	13·6	101·1	9·2	0·78

†Scores standardized to a mean (SD) of 100 (15).
‡*P* values from ANOVA comparing scores for intakes of >2–3 times/week *v.* other intakes.
§*P* values from ANOVA comparing mean scores among children breast-fed for ≥6 months *v.* <6 months were significant for all except the motor skills subscale.

Table 3 Multivariate-adjusted associations between neurodevelopment and maternal fish intakes frequency during pregnancy: full-term children (*n* 392) from a prospective birth cohort study, Menorca, Spain, 1997–2001

	Maternal weekly fish intake frequency†					
	>1–2 times		>2–3 times		>3 times	
	Coefficient	95 % CI	Coefficient	95 % CI	Coefficient	95 % CI
Breast-fed for <6 months (*n* 234)						
General cognitive	+2·7	−1·2, 6·5	+11·0*	5·0, 17·1	−1·2	−9·8, 7·3
Perceptual-performance	+2·3	−1·5, 6·1	+10·0*	4·1, 16·0	+1·5	−7·0, 9·9
Memory	+2·0	−2·1, 6·1	+10·5*	4·1, 16·9	−3·3	−12·4, 5·8
Verbal	+2·2	−1·8, 6·3	+9·9*	3·5, 16·2	−1·8	−10·8, 7·2
Numeric	+2·1	−1·8, 6·0	+6·8*	0·7, 12·9	−3·3	−11·9, 5·4
Motor skills	+2·1	−1·8, 6·0	+6·7*	0·7, 12·8	−2·3	−10·9, 6·3
Breast-fed for ≥6 months (*n* 143)						
General cognitive	−0·7	−7·0, 5·7	−0·7	−8·3, 6·9	−5·3	−17·9, 7·3
Perceptual-performance	−0·2	−6·1, 6·6	+0·8	−6·8, 8·5	−0·2	−12·4, 12·9
Memory	−1·8	−8·2, 4·5	−4·6	−12·3, 3·3	−12·7*	−25·5, 0·0
Verbal	−1·1	−7·7, 5·4	−0·5	−8·3, 7·4	−8·2	−21·3, 4·9
Numeric	−0·5	−6·8, 5·9	−3·1	−10·7, 4·6	−2·8	−15·5, 9·9
Motor skills	−2·1	−8·5, 4·3	−0·8	−8·5, 7·0	−2·1	−14·8, 10·7

*Coefficient (the mean difference in standardized test score compared with children whose mothers reported intakes in the referent category) was significant ($P < 0·05$).
†Data (referent category = ≤1 time/week) are from models adjusted for child age and sex, grade/trimester at test administration, psychologist administering test, child seafood intake at age 4 years, maternal intake of other seafood in pregnancy, parity, maternal education, birth weight and weeks of gestation. Coefficients represent differences in scores standardized to a mean (SD) of 100 (15).

>1–2 times/week, >2–3 times/week and >3 times/week. Similarly, for other types of seafood, mean (SD) scores were 101·0 (14·0), 99·0 (14·6) and 98·2 (15·2) for intakes of ≤0·5 time/week, >0·5–1 time/week and >1 time/week. Results for other subscales were similar (not shown).

Discussion

In this Mediterranean island population, children whose mothers reported fish intakes of >2–3 times/week in pregnancy had significantly higher scores on tests of cognitive and motor development at age 4 years compared

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Table 4 Multivariate-adjusted associations between neurodevelopment and frequency of maternal intakes of other types of seafood† in pregnancy: full-term children (*n* 392) from a prospective birth cohort study, Menorca, Spain, 1997–2001

	Maternal weekly intake frequency of other seafood‡			
	>0·5–1 time (*n* 107, 28·4 %)		>1 time (*n* 155, 41·1 %)	
	Coefficient	95 % CI	Coefficient	95 % CI
All children				
General cognitive	−1·0	−4·7, 2·6	−5·2*	−8·8, −1·7
Perceptual-performance	−2·4	−6·0, 1·3	−5·0*	−8·5, −1·5
Memory	+0·9	−3·0, 4·7	−3·5	−7·2, 0·2
Verbal	+0·3	−3·6, 4·1	−3·7*	−7·4, −0·0
Numeric	−1·3	−5·0, 2·4	−5·2*	−8·8, −1·6
Motor skills	−1·1	−4·7, 2·6	−2·2	−5·7, 1·4

*Coefficient (the mean difference in standardized test score compared with children whose mothers reported intakes in the referent category) was significant ($P<0·05$).
†Other types of seafood include shellfish and squid.
‡Data (referent category = ≤0·5 time/week; *n* 115, 30·5 %) from models adjusted for child age and school course at test administration, child sex, psychologist administering developmental tests, child fish intake at age 4 years, maternal fish intake in pregnancy, parity, maternal education, child birth weight and weeks of gestation. Coefficients represent difference in scores standardized to a mean (SD) of 100 (15).

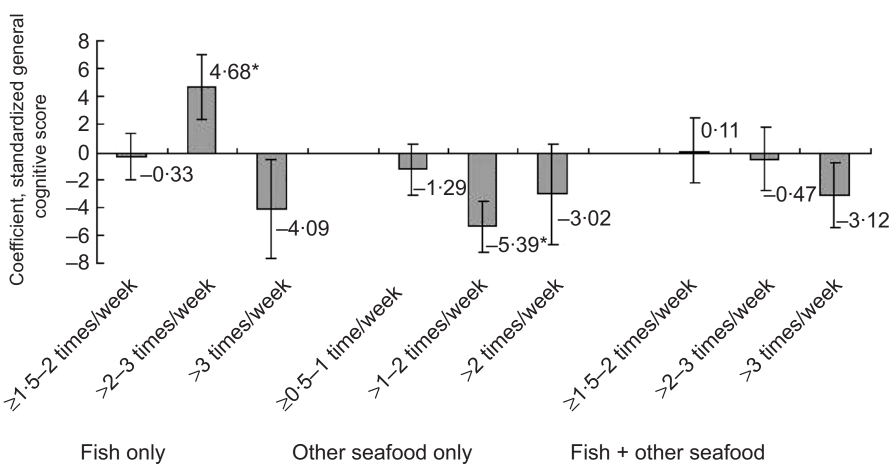

Fig. 1 Multivariate associations between maternal seafood intakes in pregnancy and child development at age 4 years. Data shown are coefficients (with their 95 % confidence intervals represented by vertical bars) from models adjusted for child age and school course at test administration, child sex, psychologist administering developmental tests, child fish intake at age 4 years, parity, maternal education, child birth weight and weeks of gestation. Results for fish only and other seafood only are from models including both variables. Coefficients represent difference in scores compared with subjects with lower intakes; scores have been standardized to a mean (SD) of 100 (15). *Coefficient was significant ($P<0·05$)

with those children whose mothers reported intakes of ≤1 time/week. Although data were too sparse to make strong conclusions, higher intakes, exceeding >3 times/week, did not appear to be associated with increased scores. Positive associations between moderately high maternal fish intakes and children's test scores were observed only among children breast-fed for <6 months. Among children breast-fed for longer periods, who had higher mean scores[39], there was no improvement in scores associated with maternal fish consumption. In contrast to fish intakes, higher maternal intakes of other types of seafood were associated with lower scores on several developmental tests. Consequently, overall seafood intakes in pregnancy were not associated with better performance in these neurodevelopmental tests.

Previous studies conducted in two populations from the USA and UK reported positive associations between maternal fish[15] or overall seafood[13,14,16] intakes in pregnancy and neurodevelopment in infancy or childhood, despite higher levels of Hg among women with higher levels of seafood intake. Although previous studies included non-consumers rather than low fish intakes as the referent, results were in many ways consistent with the present report. As in our analysis, these papers reported significant positive associations between higher maternal fish or seafood intakes and scores on intelligence, verbal, motor and memory tests after multivariate adjustment. Here, we also report positive associations with tests of quantitative ability. Like the current analysis, one earlier study reported that children's own fish consumption later in life

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was not strongly or consistently associated with test performance[15]. Similarly, a recent small (n 341) study reported evidence suggesting an interaction between breast-feeding duration and maternal seafood intake for cognitive outcomes ($P = 0{\cdot}08$ for verbal test)[16], although other studies did not report exploring this interaction. Unlike the present analysis, earlier studies did not report examining seafood subtypes separately to explore possible heterogeneous associations, in some cases[14,16] due to the small sample with moderately high (>2 servings/week) seafood intakes. Additionally, earlier studies reported fairly linear associations, rather than the possible absence of beneficial effects at very high levels of fish intake[13].

The interactions observed with breast-feeding duration are consistent with the main mechanism postulated to link maternal fish consumption and offspring neurodevelopment, which involve the n-3 fatty acid DHA for which breast milk is an important source[1]. Any adverse effects of lower maternal DHA supplies during pregnancy, associated with lower fish consumption, may be partially offset by breast milk supplies of DHA and other essential nutrients during the postnatal phase of the brain growth spurt. Mechanisms involving DHA may also explain our finding of beneficial effects specific to fish consumption, rather than for other types of seafood[13,14]. On average, levels of DHA in fatty fish are several times greater than those in shellfish, although there is also substantial variability in levels across different fish and shellfish species[10–12]. Varying levels of contaminants other than those measured in the present study (DDT, DDE and several PCB) may also have contributed to the heterogeneous associations for fish *v.* other seafood. As elevated levels of chemicals potentially relevant for neurodevelopment have been observed in both types of seafood, however, it is difficult to speculate on how such contaminants may have influenced the pattern of associations observed. For example, cord blood Hg was strongly related to consumption of fish but not other seafood in one recent Spanish study[40] and another Spanish study reported similar or higher levels of both Hg and dioxin-like PCB in commonly consumed fish than in shellfish (μg Hg/g: 0·48 in tuna and 0·19 in hake *v.* 0·12 in shrimp and 0·06 in squid; ng PCB/kg: 1·17 in tuna and 0·34 in hake *v.* 0·03 in shrimp and 0·61 in squid)[11].

Although the functions of DHA in the brain are not fully understood, numerous studies suggest this nutrient may be crucial during early brain development[4,7,9,41–44]. While mechanisms involving DHA provide a plausible explanation for differential effects of maternal fish intakes depending on breast-feeding duration, it is important to note that recent studies have cast doubt on the role of breast milk in cognitive development. After adjusting for maternal intelligence quotient (IQ) scores, associations between breast-feeding (any *v.* none) and child cognition were eliminated in one study[34], while positive associations with breast-feeding were observed only among mothers with post-secondary education in another analysis[45]. Further research is needed to determine whether prolonged breast-feeding remains associated with neurodevelopment independently of maternal intelligence. Unfortunately, as data on maternal IQ are not available, we were unable to examine effects of this adjustment. However, in contrast to studies on breast-feeding and child development, we found that adjusting for maternal education, which is strongly linked to maternal IQ, had a negligible effect on associations with maternal fish intakes.

Reasons for the negative associations observed with maternal intakes of other types of seafood besides fish are also uncertain. One possible explanation involves effects of MeHg, which biomarker data from contemporaneous Spanish studies suggest increases linearly with seafood consumption[46]. MeHg contamination could also explain the apparent threshold in beneficial effects at the highest levels of fish intake, although given the modest sample size, we are unable to adequately assess whether these associations are meaningful. Published data suggest that MeHg levels in fish from Spain are somewhat higher than those in the USA or UK, where previous studies were conducted (e.g. 0·32–0·48 *v.* 0·35–0·40 μg/g in tuna from Spain *v.* the USA and UK)[11,24,27,46,47]. Hair Hg levels in a random sub-sample of children from this cohort were somewhat higher than in US children[48]. However, adverse developmental effects of MeHg associated with seafood consumption have not been observed consistently[22,25]. Some evidence suggests PCB, which have been measured at fairly high concentrations in samples of seafood from Spain, may potentiate adverse developmental effects of MeHg[11,49–52]. It has also been suggested that adverse neurodevelopmental effects of PCB may be lower in breast-fed children[38]. However, adjusting for available data on PCB in cord blood (sum of congeners 25, 52 101, 118, 138, 153 and 180[36]) had no meaningful effect on relationships between maternal fish intakes and developmental scores (not shown). Alternatively, it is also possible that adverse effects of MeHg exposure may be exacerbated in the presence of low levels of Se, which have been reported in some Spanish populations[24,53]. Se is thought to reduce tissue accumulation of Hg[54] and is involved in activating selenoproteins believed to reduce Hg toxicity[55].

The present study has several important strengths, including the longitudinal design and relatively long follow-up; only one earlier study on this topic focused on children rather than infants or toddlers[13]. Data from animal studies suggest that adverse effects of early MeHg exposure may appear only later in life[23]. Additionally, in this cohort, developmental tests were administered by trained psychologists; some earlier studies relied at least in part on parental assessments[13,15]. Furthermore, in contrast to some earlier studies on this topic[56], maternal fish intakes in this population were not related to socioeconomic factors such as higher maternal education, reducing the likelihood that the associations observed may be due largely to residual confounding.

In summary, results of our study suggest that moderately high maternal fish intakes in pregnancy are associated with enhanced intellectual development in offspring, although it is uncertain whether intakes exceeding current recommendations are beneficial. These beneficial effects appear to be limited to children breast-fed for shorter periods than current recommendations. Moreover, maternal intakes of other types of seafood in pregnancy were associated with lower scores for several neurodevelopmental outcomes. Future studies in larger samples are needed to further explore relationships between neurodevelopment and maternal fish and other seafood consumption, in settings with varying patterns of intake and with differing levels of exposure to factors such as MeHg, other neurotoxins and Se. Biomarkers of exposure to these compounds, which were not available in the present study, may help to elucidate the pathways involved.

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