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Original Contribution

Maternal Consumption of Seafood in Pregnancy and Child Neuropsychological Development: A Longitudinal Study Based on a Population With High Consumption Levels

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Seafood consumption during pregnancy is thought to be beneficial for child neuropsychological development, but to our knowledge no large cohort studies with high fatty fish consumption have analyzed the association by seafood subtype. We evaluated 1,892 and 1,589 mother-child pairs at the ages of 14 months and 5 years, respectively, in a population-based Spanish birth cohort established during 2004–2008. Bayley and McCarthy scales and the Childhood Asperger Syndrome Test were used to assess neuropsychological development. Results from multivariate linear regression models were adjusted for sociodemographic characteristics and further adjusted for umbilical cord blood mercury or long-chain polyunsaturated fatty acid concentrations. Overall, consumption of seafood above the recommended limit of 340 g/week was associated with 10-g/week increments in neuropsychological scores. By subtype, in addition to lean fish, consumption of large fatty fish showed a positive association; offspring of persons within the highest quantile (>238 g/week) had an adjusted increase of 2.29 points in McCarthy general cognitive score (95% confidence interval: 0.42, 4.16). Similar findings were observed for the Childhood Asperger Syndrome Test. Beta coefficients diminished 15%–30% after adjustment for mercury or long-chain polyunsaturated fatty acid concentrations. Consumption of large fatty fish during pregnancy presents moderate child neuropsychological benefits, including improvements in cognitive functioning and some protection from autism-spectrum traits.

autistic spectrum; fatty acids; mercury; neuropsychological development; population-based birth cohorts; pregnancy; seafood intake

Abbreviations: DDE, 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene; DHA, docosahexanoic acid; FFQ, food frequency questionnaire; LC-PUFAs, long-chain polyunsaturated fatty acids; MSCA, McCarthy Scales of Children's Abilities.

Maternal consumption of seafood during pregnancy has been associated with improvements in neuropsychological development among children in several studies (1, 2). These beneficial associations are thought to be at least partly attributable to higher intakes of key nutrients, including long-chain polyunsaturated fatty acids (LC-PUFAs) such as ω-3 docosahexanoic acid (DHA), which is essential for optimal prenatal neurodevelopment (3), particularly during early stages of brain formation (3, 4). DHA is not widely distributed in the Western diet, and seafood, particularly fatty species of fish, is the major source (1, 3).

Nonetheless, elevated intakes of seafood during pregnancy are of concern, because seafood is an important source of neurotoxic contaminants such as methylmercury and organochlorine compounds, which have been associated with decrements in child neuropsychological scores (1, 2). To help balance these risks and benefits, guidelines issued by the United States, the United Kingdom, and the European Union

Table 1. Sociodemographic and Environmental Characteristics of Mothers and Offspring According to Median Maternal Seafood Consumption in the First Trimester of Pregnancy, Spanish Childhood and Environment (INMA) Project, 2004–2008

	No. of Subjects	Median Seafood Intake, g/week				
		Total	Large Fatty Fish	Smaller Fatty Fish	Lean Fish	Shellfish
Maternal Characteristics						
Age, years						
<31	946	422[a]	0[a]	14[a]	260[a]	45[a]
≥31	1,049	482[a]	50[a]	31[a]	296[a]	52[a]
Education						
Primary school or less	424	401[a]	0[a]	20	228[a]	44[a]
Secondary school	829	460[a]	42[a]	25	287[a]	52[a]
University or more	738	473[a]	49[a]	29	304[a]	49[a]
Social class						
Highly skilled	815	483[a]	50[a]	35[a]	308[a]	53[a]
Nonmanual	730	439[a]	38[a]	0[a]	268[a]	47[a]
Manual	423	434[a]	0[a]	28[a]	352[a]	46[a]
Prepregnancy body mass index[b]						
Tertile 1	647	439	31[a]	26	274[a]	47
Tertile 2	675	465	47[a]	23	296[a]	50
Tertile 3	673	459	46[a]	27	274[a]	51
Parity						
Nulliparous	1,135	457	44	20[a]	282	51[a]
Parous	858	453	41	31[a]	284	47[a]
Born in Spain						
Yes	1,858	463[a]	45[a]	28[a]	288[a]	50[a]
No, in Latin America	88	322[a]	0[a]	0[a]	171[a]	33[a]
No, in other place	46	421[a]	0[a]	0[a]	263[a]	30[a]
Smoked throughout entire pregnancy						
No	1,630	462[a]	45[a]	29[a]	288[a]	49[a]
Yes	333	423[a]	13[a]	18[a]	248[a]	46[a]
Alcohol use throughout entire pregnancy						
No	1,040	436[a]	37[a]	0[a]	275[a]	45[a]
Yes	929	475[a]	47[a]	36[a]	290[a]	52[a]

Table continues

advise pregnant women with regard to their seafood intakes (1, 5, 6). The US Food and Drug Administration's 2014 draft recommendations (6) emphasize selecting subtypes of seafood that are lower in these contaminants, with consistent advice to avoid the consumption of large predatory fish such as shark, swordfish, king mackerel, and tilefish and to limit consumption of albacore tuna, despite the fact that large fatty fish such as tuna contain some of the highest levels of DHA (7).

These guidelines have been debated, since some studies have found no evidence of adverse associations with maternal seafood consumption exceeding 340 g/week, the current recommended limit in the United States. However, the recently issued scientific opinion report of the European Food Safety Authority contained a less restrictive recommendation, in which beneficial health associations are limited to 1–4 servings of fish per week (150–600 g), despite the uncertainties regarding serving sizes in European epidemiologic studies (5, 8, 9). However, the studies supporting the guideline statements did not examine associations with different subtypes of seafood (2). Thus, at present there is insufficient knowledge on the association between seafood consumption in pregnancy and child neuropsychological outcomes.

In the present study, we examined maternal seafood consumption during pregnancy and child neuropsychological development in a Spanish multicenter birth cohort, where average consumption exceeds current US recommended levels and allows the study of numerous seafood subtypes. We aimed to assess associations of consumption of large and small fatty fish, lean fish, and shellfish, as well as total seafood, with a

Table 1. Continued

	No. of Subjects	Median Seafood Intake, g/week				
		Total	Large Fatty Fish	Smaller Fatty Fish	Lean Fish	Shellfish
Child Characteristics						
Sex						
Male	1,016	452	41	31[a]	280	48
Female	979	454	44	20[a]	284	50
Birth weight, g						
<3,000	458	439	46	0[a]	279	48
3,000–3,500	939	459	41	35[a]	284	51
>3,500	585	451	44	15[a]	283	47
Gestational age, weeks						
≤40	1,123	465[a]	46[a]	24	291[a]	47
>40	872	444[a]	38[a]	26	270[a]	51
Duration of breastfeeding (any), weeks						
≤24	1,078	439[a]	40	0[a]	278[a]	48
>24	872	475[a]	45	36[a]	286[a]	50
Umbilical cord blood mercury level, μg/L						
<8.5	746	396[a]	0[a]	24	248[a]	44[a]
≥8.5	795	509[a]	60[a]	30	325[a]	54[a]
Cord blood ω-6 AA:ω-3 EPA/ω-3 DHA ratio[c]						
≤Median	389	511[a]	49[a]	46[a]	324[a]	54[a]
>Median	379	423[a]	0[a]	22[a]	259[a]	43[a]

Abbreviations: AA, arachidonic acid; DHA, docosahexanoic acid; EPA, eicosapentaenoic acid; INMA, Infancia y Medio Ambiente.

[a] $P < 0.10$ for difference between groups (Wilcoxon rank-sum test), by seafood subtype.

[b] Weight (kg)/height (m)^2.

[c] Ratio of ω-6 AA to ω-3 EPA and ω-3 DHA in umbilical cord blood.

range of neuropsychological outcomes, including cognitive and motor functioning and autism-spectrum traits, at 2 ages (14 months and 5 years). We also investigated the roles of mercury and LC-PUFAs in umbilical cord blood, maternal biomarkers of other environmental pollutants and nutrition, and child seafood consumption in these associations.

METHODS

Subjects

The Spanish Childhood and Environment (Infancia y Medio Ambiente) Project, a multicenter birth cohort study, was established between 2004 and 2008 in 4 regions of Spain: Asturias, Gipuzkoa (the Basque Country), Sabadell (Catalonia), and Valencia (10). Participant recruitment and follow-up procedures have been reported in detail elsewhere (10). A total of 2,644 eligible women were recruited during prenatal visits in the first trimester of pregnancy. Women agreed to participate and met the inclusion (≥16 years of age, singleton pregnancy, intention to deliver at the reference hospital) and exclusion (communication handicap, fetuses with malformations, assisted conception) criteria. Women were followed up during pregnancy, and their children were enrolled at birth and followed until age 5 years. After exclusion of women who withdrew, were lost to follow-up, or had an elective or spontaneous abortion, a total of 2,506 pregnant women were monitored through delivery. Final analyses included 1,892 children at 14 months of age and 1,589 children at 5 years of age. The analysis excluded 93 preterm infants (<37 weeks gestation), because preterm births are known to differ from term births with respect to neuropsychological development (11), and 18 children with pathologies, including plagiocephaly. A total of 522 children were lost to follow-up at age 14 months, and 341 were lost to follow-up at age 5 years. The remaining exclusions were attributable to missing data on some covariates. All participants provided written informed consent, and the study protocol was approved by hospital and institutional ethics committees in each region. Further information is given in the Web Appendix (available at http://aje.oxfordjournals.org/).

Exposure and covariate information

Questionnaires, completed twice during pregnancy and at child ages of 14 months and 5 years, were administered by trained interviewers to obtain extensive information on maternal and child characteristics (Web Appendix, Web Tables 1 and 2).

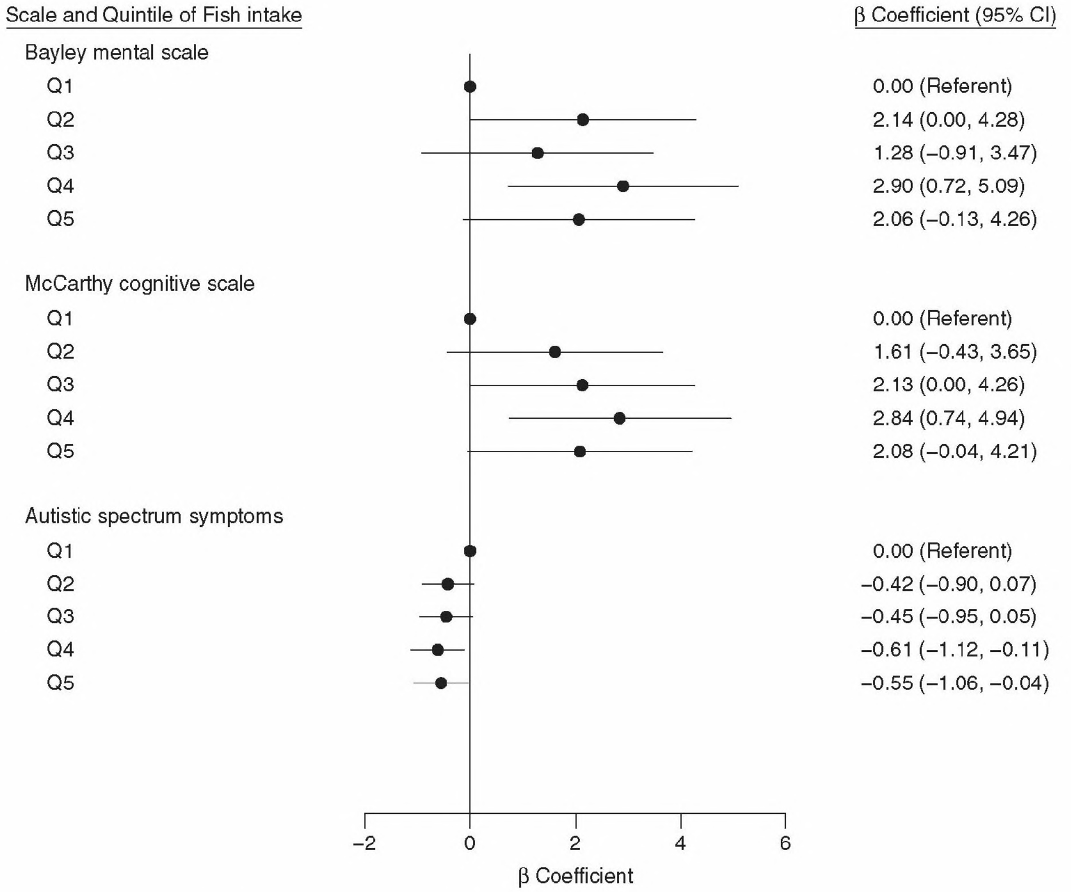

Figure 1. Associations between total maternal seafood consumption in the first trimester of pregnancy (quintiles) and general scores on the Bayley Scales of Infant Development, the McCarthy Scales of Children's Abilities, and the Childhood Asperger Syndrome Test in the Spanish Childhood and Environment (Infancia y Medio Ambiente) Project, 2004–2008. Regression models adjusted for sex of the child, cohort, quality of the test, child's birth weight, gestational age, duration of breastfeeding, child's age during testing, maternal age, energy intake (kcal/day) during pregnancy, educational level, social class, prepregnancy body mass index, parity, and country of origin/birth. Median total seafood intake in each quintile (Q): Q1, 195 g/week; Q2, 338 g/week; Q3, 461 g/week; Q4, 600 g/week; Q5, 854 g/week. Q1 (vertical line) was the reference category. Bars, 95% confidence intervals (CIs).

We used a semiquantitative food frequency questionnaire (FFQ) of 101 food items to assess the usual daily intake of foods and nutrients at 10–13 weeks of pregnancy and again at 28–32 weeks. The FFQ was a modified version of a previous FFQ based on the Harvard questionnaire (12), adapted and validated among the pregnant women of the Valencia cohort (13). Further information is provided in the Web Appendix.

Women reported their usual intake of foods from the last menstrual period to the first prenatal visit, using reference portions and 9 frequency categories ranging from never/less than once a month to more than 6 times per day. The questionnaire included 10 seafood items. The response to each seafood item was converted to average weekly intake in grams; then all seafood items were summed to compute total consumption and consumption of seafood subtypes (in g/week). Seafood was classified a priori as follows: 1) large fatty fish, based on 1 item from the questionnaire ("baked or steamed larger fatty fish such as tuna, swordfish, albacore"); 2) smaller fatty fish, based on 2 items from the questionnaire ("baked or steamed smaller fatty fish such as mackerel, sardines, anchovies, salmon" and "tinned sardines/mackerel"); 3) lean fish, based on 3 items from the questionnaire ("fried fish"; "baked or steamed lean fish such as hake, sole, or bream"; and "tinned tuna," which has similar levels of DHA and mercury as lean fish); 4) shellfish, based on 3 items from the questionnaire ("shrimp, prawns, lobster, or crab"; "clams, mussels, oysters"; and "squid, octopus, cuttlefish"); 5) smoked/salted fish, based on 1 item from the questionnaire ("salted or smoked fish: anchovies, cod, salmon"); and 6) overall seafood intake, calculated as the sum of consumption of all items. The fifth subtype group (smoked/salted fish) was excluded from individual analyses because of its low frequency of intake in this cohort.

Seafood consumption was adjusted for energy intake using the residual method (14) and analyzed primarily in quantile categories of weekly grams. The quantile categories were created prior to analysis. For some of the seafood subtypes, the number of quantiles created was constrained by low intake frequency. In order to check for potential systematic bias in reporting by

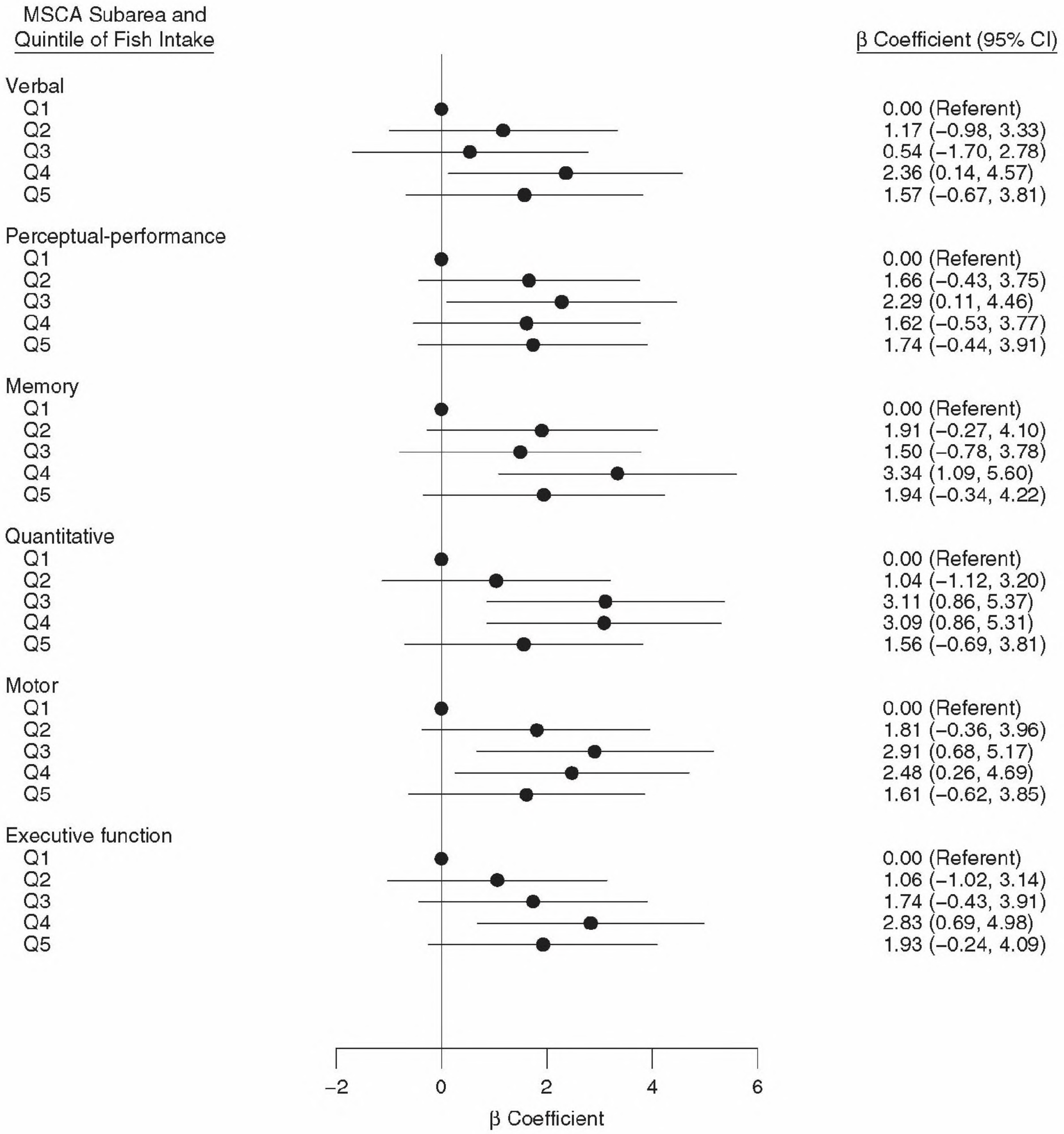

Figure 2. Associations between total maternal seafood consumption in the first trimester of pregnancy (quintiles) and subarea scores on the McCarthy Scales of Children's Abilities (MSCA) in the Spanish Childhood and Environment (Infancia y Medio Ambiente) Project, 2004–2008. Regression models adjusted for sex of the child, cohort, quality of the test, child's birth weight, gestational age, duration of breastfeeding, child's age during testing, maternal age, energy intake (kcal/day) during pregnancy, educational level, social class, prepregnancy body mass index, parity, and country of origin/birth. Median total seafood intake in each quintile (Q): Q1, 195 g/week; Q2, 338 g/week; Q3, 461 g/week; Q4, 600 g/week; Q5, 854 g/week. Q1 (vertical line) was the reference category. Bars, 95% confidence intervals (CIs).

educational level, we checked to see whether the sum of mean intakes by seafood subtype was similar to the mean total intake in each educational level category; we found no mean differences (data not shown). Similar methods were applied to estimate seafood consumption of mothers at 28–32 weeks of pregnancy and seafood consumption of children at age 5 years.

Dietary intakes of ω-3 fatty acids (DHA and eicosapentaenoic acid) were estimated from the FFQ, and use of supplements containing ω-3 fatty acids, iodine, and folic acid was recorded (13). Cord-blood mercury and concentrations of total fatty acids (including DHA), serum maternal organochlorine, and plasma 25-hydroxyvitamin D_3 and urinary iodine during pregnancy were measured as previously described (extended information is provided in the Web Appendix and Web Tables 1 and 2).

Neuropsychological assessments

Child neuropsychological development was assessed at ages 14 months and 5 years using the Bayley Scales of Infant

Table 2. Associations Between Maternal Seafood Consumption in the First Trimester of Pregnancy and Child's Score on the Bayley Mental Scale at Age 14 Months, Spanish Childhood and Environment (INMA) Project, 2004–2008

Seafood Intake[a]	No. of Subjects	Difference in Child's Neurobehavioral Score[b]			
		Minimally Adjusted[c]		Fully Adjusted[d]	
		β	95% CI	β	95% CI
All Seafood					
Continuous variable, 10 g/week[e]	1,892	0.02[f]	−0.00, 0.06	0.02[f]	−0.00, 0.05
Quintiles					
1[g]	383	0.00	Referent	0.00	Referent
2	392	2.13[f]	−0.03, 4.29	2.14[h]	0.00, 4.28
3	364	1.53	−0.67, 3.73	1.28	−0.91, 3.47
4	386	3.03[h]	0.84, 5.22	2.90[h]	0.72, 5.09
5	367	2.02[f]	−0.19, 4.22	2.06[f]	−0.13, 4.26
P for trend		0.08		0.08	
Large Fatty Fish					
Continuous variable, 10 g/week	1,892	0.00	−0.07, 0.08	0.00	−0.07, 0.08
Quartiles					
1	853	0.00	Referent	0.00	Referent
2	341	0.28	−1.66, 2.22	0.08	−1.84, 2.01
3	345	−0.16	−2.12, 1.79	−0.12	−2.06, 1.82
4	353	0.71	−1.24, 2.67	0.51	−1.43, 2.46
P for trend		0.510		0.623	
Small Fatty Fish					
Continuous variable, 10 g/week	1,892	0.06	−0.02, 0.14	0.06	−0.02, 0.15
Quartiles					
1	877	0.00	Referent	0.00	Referent
2	333	2.16[h]	0.14, 4.19	1.79[f]	−0.22, 3.80
3	338	−0.47	−2.40, 1.46	−0.37	−2.29, 1.55
4	344	2.63[h]	0.71, 4.55	2.45[h]	0.54, 4.36
P for trend		0.02		0.03	

Table continues

Development (15) and the McCarthy Scales of Children's Abilities (MSCA) (16), respectively. Autism-spectrum traits were assessed at age 5 years using the Childhood Asperger Syndrome Test (17), which was administered after the MSCA test session. Further information is given in the Web Appendix and in Web Table 3.

Statistical analysis

Associations between total seafood consumption and intake of different subtypes of seafood and neuropsychological scores were evaluated using separate multivariate linear regression analyses. Seafood consumption was evaluated as both an ordinal (quantiles) and a continuous (10 g/week) variable (after testing of linearity by means of generalized additive models). Tests for linear trend were performed by including the median value of consumption within each quantile category in the regression models. Minimally adjusted regression models included adjustment for the age and sex of the child, cohort, total energy intake (kcal/day), and quality of the test (good, regular, or low) as recorded by the psychologist after examination. Other important variables, evaluated as potential confounders and mediators, are described in Web Tables 1 and 2. Confounders were retained only if they modified the coefficient of the seafood consumption parameter in the basic model by more than 5% (18). The final models further adjusted for child's gestational age and weight at birth, duration of breastfeeding, maternal age, educational level, social class, parity, prepregnancy body mass index (weight (kg)/height (m)^2), and country of origin/birth.

Sensitivity analyses adjusted for concentrations of cord-blood mercury and LC-PUFAs and other biomarkers and food supplements (listed in Web Tables 1 and 2), through inclusion in regression models as continuous variables. Generalized additive models were used to assess the linearity assumption. As a result, the mercury variable was $\log_{10}$-transformed to achieve linearity. In secondary analyses, final-model calculations were repeated with maternal seafood consumption during the third trimester of pregnancy (Spearman's $r = 0.50$, first-trimester consumption) and child seafood consumption

Table 2. Continued

		Difference in Child's Neurobehavioral Score[b]			
Seafood Intake[a]	No. of Subjects	Minimally Adjusted[c]		Fully Adjusted[d]	
		β	95% CI	β	95% CI
		Lean Fish			
Continuous variable, 10 g/week	1,892	0.03[f]	−0.00, 0.07	0.03[f]	−0.00, 0.07
Quintiles					
1	387	0.00	Referent	0.00	Referent
2	386	0.93	−1.23, 3.10	0.44	−1.71, 2.58
3	380	2.35[h]	0.14, 4.56	2.07[f]	−0.12, 4.26
4	372	1.55	−0.66, 3.75	1.41	−0.78, 3.59
5	367	2.00[f]	−0.24, 4.24	1.77	−0.46, 3.99
P for trend		0.09		0.10	
		Shellfish			
Continuous variable, 10 g/week	1,892	0.04	−0.07, 0.16	0.05	−0.06, 0.16
Quintiles					
1	373	0.00	Referent	0.00	Referent
2	370	1.10	−1.13, 3.34	0.80	−1.41, 3.01
3	384	2.26[h]	0.07, 4.44	1.86[f]	−0.30, 4.03
4	394	1.65	−0.53, 3.83	1.45	−0.70, 3.61
5	371	1.71	−0.55, 3.97	1.52	−0.72, 3.75
P for trend		0.18		0.21	

Abbreviations: CI, confidence interval; INMA, Infancia y Medio Ambiente.

[a] Median intakes in specific quantiles (Q), in g/week: total seafood—Q1, 195; Q2, 338; Q3, 461; Q4, 600; Q5, 854; large fatty fish—Q1, none; Q2, 48; Q3, 92; Q4, 238; small fatty fish—Q1, none; Q2, 37; Q3, 69; Q4, 147; lean fish—Q1, 90; Q2, 192; Q3, 286; Q4, 382; Q5, 557; shellfish—Q1, none; Q2, 27; Q3, 49; Q4, 76; Q5, 139.

[b] Bayley Scales of Infant Development (15).

[c] Results were adjusted for sex of the child, child's age at testing, cohort, quality of the test, and maternal energy intake (kcal/day) during pregnancy.

[d] Results were additionally adjusted for child's birth weight, gestational age, duration of breastfeeding, maternal age, educational level, social class, prepregnancy body mass index, parity, and country of origin/birth.

[e] Per 10-g/week increase.

[f] $P < 0.10$.

[g] Results were similar when the reference group included all mothers with seafood consumption less than or equal to 340 g/week (Web Table 5).

[h] $P < 0.05$.

($r = 0.22$, first-trimester-consumption) included as independent variables; exclusion of tinned tuna from the lean fish subtype group; the reference group for total seafood consumption changed to ≤340 g/week; and stratification of the analyses by geographical location (Cantabric Sea (Asturias + Gipuzkoa) vs. Mediterranean Sea (Sabadell + Valencia)). All analyses were conducted with the STATA 12 (StataCorp LP, College Station, Texas) statistical software package.

RESULTS

Average reported total seafood consumption was 498 g/week (median, 454 g/week), which is considered by the European Food Safety Authority to be about 3 servings per week. Very few participants ($n = 15$; 0.8%) were nonconsumers. As shown in Table 1, overall seafood consumption during early pregnancy was generally related to maternal and child characteristics. Intakes were higher among mothers who were older, had been born in Spain, had higher socioeconomic and educational status, did not smoke during pregnancy, consumed alcohol during pregnancy, breastfed for longer periods, and had higher cord-blood mercury and LC-PUFA levels. For specific subtypes of seafood, consumers showed similar characteristics. The Spearman coefficients for correlations between intakes of different seafood subtypes were positive, albeit weak to moderate. Among them, the strongest correlation was between large fatty fish and lean fish ($r = 0.29$). Consumption of large fatty fish showed the strongest Spearman coefficients for correlation with cord-blood mercury levels ($r = 0.34$) and DHA levels ($r = 0.20$).

Associations of total seafood consumption with the main neuropsychological outcomes are shown in Figure 1. The strongest associations were observed in the outcome scores (MSCA and Childhood Asperger Syndrome Test) measured

Table 3. Associations Between Maternal Seafood Consumption in the First Trimester of Pregnancy and Child's Score on the McCarthy General Cognitive Scale at Age 5 Years, Spanish Childhood and Environment (INMA) Project, 2004–2008

Seafood Intake[a]	No. of Subjects	Difference in Child's Neurobehavioral Score[b]			
		Minimally Adjusted[c]		Fully Adjusted[d]	
		β	95% CI	β	95% CI
All Seafood					
Continuous variable, 10 g/week[e]	1,589	0.03[f]	0.00, 0.05	0.02[g]	0.00, 0.05
Quintiles					
1[h]	320	0.00	Referent	0.00	Referent
2	340	1.91[g]	−0.23, 4.04	1.61	−0.43, 3.65
3	299	3.46[f]	1.24, 5.67	2.13[f]	0.00, 4.26
4	323	3.60[f]	1.41, 5.79	2.84[f]	0.74, 4.94
5	308	2.93[f]	0.72, 5.14	2.08[g]	−0.04, 4.21
P for trend		0.007		0.049	
Large Fatty Fish					
Continuous variable, 10 g/week	1,589	0.10[f]	0.02, 0.17	0.06[g]	−0.00, 0.13
Quartiles					
1	704	0.00	Referent	0.00	Referent
2	285	2.99[f]	1.05, 4.93	2.26[f]	0.40, 4.11
3	296	2.36[f]	0.43, 4.30	1.93[f]	0.09, 3.79
4	304	3.46[f]	1.51, 5.40	2.29[f]	0.42, 4.16
P for trend		0.001		0.02	
Small Fatty Fish					
Continuous variable, 10 g/week	1,589	−0.03	−0.11, 0.05	−0.03	−0.10, 0.05
Quartiles					
1	736	0.00	Referent	0.00	Referent
2	280	1.41	−0.61, 3.44	0.60	−1.33, 2.53
3	288	0.94	−0.98, 2.87	1.25	−0.59, 3.10
4	285	1.27	−0.67, 3.21	0.91	−0.93, 2.76
P for trend		0.18		0.25	

Table continues

at age 5 years. In Figure 2, McCarthy subarea scales are presented; positive associations were observed among all scales, with the largest coefficients generally being found in seafood quantile 4 (median, 600 g/week or about 4 servings/week).

Minimally and fully adjusted associations between maternal seafood subtype consumption and Bayley mental scale at 14 months of age are shown in Table 2. Positive associations were observed for lean fish and small fatty fish, the latter with a trend (*P* for trend = 0.03). Associations with the Bayley psychomotor scale were somewhat weaker (Web Table 4). A positive trend in MSCA general cognitive score was found with large fatty fish intake (*P* for trend = 0.020), and a weak trend was found with lean fish (*P* for trend = 0.110) (Table 3). Generally, when using categorical variables for seafood consumption in the regression models, quantiles 3 and 4 tended to have the largest coefficients and to show a slight decrease in the last quantile (Tables 2 and 3).

As shown in Table 4, maternal seafood consumption, in total and by subtype, was generally associated with a reduction in the number of traits on the Childhood Asperger Syndrome Test. Lean fish intake showed an association with the outcome from quantile 2. A trend was observed for large fatty fish intake (*P* for trend = 0.013). In all models presented in Tables 2–4, shellfish intake had the weakest associations.

Similar results were observed after excluding tinned tuna from the lean fish subtype and when treating tinned tuna as an independent variable (data not shown) and when the reference group for total seafood consumption included all mothers with intakes less than or equal to 340 g/week (Web Table 5). The association of large fatty fish consumption with MSCA general score was similar after adjustment for lean fish intake (quartile 4 vs. quartile 1: β = 2.00, 95% confidence interval: 0.07, 5.60; *P* for trend = 0.047). Associations were somewhat weaker when seafood consumption was assessed in the third trimester of pregnancy (Web Table 6). Association patterns were similar when the data were stratified by geographical location (Cantabric Sea vs. Mediterranean Sea) (Web Table 7). Inclusion of the 93 preterm children or exclusion

Table 3. Continued

Seafood Intake[a]	No. of Subjects	Difference in Child's Neurobehavioral Score[b]			
		Minimally Adjusted[c]		Fully Adjusted[d]	
		β	95% CI	β	95% CI
		Lean Fish			
Continuous variable, 10 g/week	1,589	0.04[f]	0.00, 0.08	0.03	−0.01, 0.06
Quintiles					
1	328	0.00	Referent	0.00	Referent
2	325	2.65[f]	0.49, 4.80	1.76[g]	−0.29, 3.81
3	322	2.79[f]	0.60, 4.99	2.01[g]	−0.08, 4.11
4	307	3.42[f]	1.20, 5.62	2.47[f]	0.36, 458
5	307	3.01[f]	0.78, 5.25	1.89[g]	−0.25, 4.03
P for trend		0.017		0.11	
		Shellfish			
Continuous variable, 10 g/week	1,589	−0.03	−0.15, 0.09	−0.02	−0.13, 0.09
Quintiles					
1	307	0.00	Referent	0.00	Referent
2	307	0.09	−2.16, 2.35	−0.12	−2.26, 2.02
3	331	1.16	−1.02, 3.35	0.81	−1.27, 2.90
4	332	1.10	−1.09, 3.28	0.79	−2.29, 2.88
5	312	−0.83	−3.10, 1.44	−0.94	−3.10, 1.22
P for trend		0.51		0.44	

Abbreviations: CI, confidence interval; INMA, Infancia y Medio Ambiente.

[a] Median seafood intake in each quantile (g/week) is shown in the Table 2 footnotes.

[b] McCarthy Scales of Children's Abilities (16).

[c] Regression models adjusted for sex of the child, age during testing, cohort, quality of the test, and maternal energy intake (kcal/day) during pregnancy.

[d] Regression models additionally adjusted for child's birth weight, gestational age, duration of breastfeeding, maternal age, educational level, social class, prepregnancy body mass index, parity, and country of origin/birth.

[e] Per 10-g/week increase.

[f] $P < 0.05$.

[g] $P < 0.10$.

[h] Results were similar when the reference group included all mothers with seafood consumption less than or equal to 340 g/week (Web Table 5). Further inclusion of all seafood subtypes in the final model showed similar association patterns (data not shown).

of consumers of large fatty fish ($n = 886$) did not change the results (data not shown).

The associations with the MSCA scales (Table 3) were attenuated by 15%–30% after further adjustment for cord-blood mercury and LC-PUFA levels in separate models (Web Table 8). Separate models adjusting for organochlorines (polychlorinated biphenyls and 2,2-bis(*p*-chlorophenyl)-1,1-dichloroethylene (DDE)), iodine, and 25-hydroxyvitamin D_3 levels, estimated LC-PUFA intakes, and use of supplements containing LC-PUFAs, folic acid, or iodine during pregnancy did not affect the results (data not shown).

Current child seafood consumption and MSCA general cognitive score showed similar but weaker patterns of association with maternal seafood consumption than those shown in Table 3. After adjustment for maternal seafood consumption, the coefficients from the models were reduced by 21% (Web Table 9). The associations with maternal seafood consumption were similar to those from previous models (Table 3) after adjustment for the child's seafood consumption (data not shown).

DISCUSSION

This study, conducted in a population characterized by high seafood consumption, found moderate positive associations between seafood consumption during pregnancy and child neuropsychological development, particularly at 5 years of age. Intake of small fatty fish explained part of the positive associations at 14 months of age, and lean and large fatty fish appeared to be predictors of child neuropsychological function at age 5 years. As a new finding, a consistent reduction in autism-spectrum traits was also observed with total, lean, and large fatty fish consumption. These associations generally remained positive above the level recommended by the current US guidelines (total fish consumption of 340 g/week during pregnancy) (5). Only part of these associations was reduced by adjustments for cord-blood mercury and LC-PUFA levels. Child seafood consumption showed similar results, with somewhat reduced associations after controlling for maternal consumption.

Table 4. Associations Between Maternal Seafood Consumption in the First Trimester of Pregnancy and Child's Score on the Childhood Asperger Syndrome Test at Age 5 Years, Spanish Childhood and Environment (INMA) Project, 2004–2008

Seafood Intake[a]	No. of Subjects	Difference in Child's Neurobehavioral Score[b]			
		Minimally Adjusted[c]		Fully Adjusted[d]	
		β	95% CI	β	95% CI
All Seafood					
Continuous variable, 10 g/week[e]	1,393	−0.01[f]	−0.01, −0.00	−0.01[f]	−0.01, −0.00
Quintiles					
1[g]	289	0.00	Referent	0.00	Referent
2	294	−0.47[h]	−0.96, 0.03	−0.42[h]	−0.90, 0.07
3	271	−0.69[f]	−1.20, −0.18	−0.45[h]	−0.95, 0.05
4	280	−0.75[f]	−1.26, −0.24	−0.61[f]	−1.12, −0.11
5	260	−0.72[f]	−1.23, −0.20	−0.55[f]	−1.06, −0.04
P for trend		0.006		0.037	
Large Fatty Fish					
Continuous variable, 10 g/week	1,393	−0.02[f]	−0.04, −0.01	−0.02[f]	−0.04, −0.00
Quartiles					
1	613	0.00	Referent	0.00	Referent
2	237	−0.42[h]	−0.88, 0.04	−0.32	−0.77, 0.13
3	269	−0.34	−0.79, 0.11	−0.28	−0.72, 0.16
4	274	−0.74[f]	−1.19, −0.29	−0.57[f]	−1.01, −0.13
P for trend		0.002		0.013	
Small Fatty Fish					
Continuous variable, 10 g/week	1,393	−0.00	−0.02, 0.02	−0.00	−0.02, 0.01
Quartiles					
1	668	0.00	Referent	0.00	Referent
2	235	−0.36	−0.83, 0.12	−0.19	−0.66, 0.27
3	240	−0.15	−0.61, 0.30	−0.14	−0.59, 0.31
4	250	−0.45[f]	−0.90, 0.00	−0.37	−0.81, 0.07
P for trend		0.056		0.11	

Table continues

Average seafood consumption in this population (498 g/week; about 3 servings per week or 71 g/day) was similar to levels reported in other Spanish studies (e.g., 72 g/day in the Basque Country) (19). These high consumption levels facilitated the analyses of associations for intakes substantially exceeding US recommended levels, as well as analyses of specific seafood subtypes, with the outcomes of interest. Thus, unlike previous studies, we were able to examine how maternal consumption of seafood subtypes specified in the US recommendations—most notably larger fatty fish species versus smaller fatty fish species—related to child neuropsychological development. The positive association observed for MSCA cognitive scores among women consuming moderate amounts of large fatty fish would suggest that some of the current guidelines may be slightly stringent (6). In fact, the present findings tend to support recent recommendations issued by the European Food Safety Authority, which are less restrictive in limiting seafood consumption and which conclude that there are no adverse health associations apparent when exceeding the amount recommended, which is 1–4 servings of fish per week (150–600 g) (9). Furthermore, given that the associations observed using seafood consumption in pregnancy were stronger than those using seafood intake in childhood as the exposure, uterine life seems to be an important window for neurodevelopment—particularly during the early pregnancy period, when there is intense activity in neuron formation, differentiation, and migration (4).

We identified some studies evaluating the association between prenatal seafood intake and neuropsychological development (2). Most studies found positive associations with a wide range of outcomes, such as neurological development, motor development, verbal intelligence quotient, perception, social behavior, and (less) inattention and hyperactivity (2, 8, 20, 21). In just a few of them, there was attenuation of a positive association in the highest seafood intake category (2, 21). Our findings support the idea of a generally beneficial association with brain development and potentially a light attenuation at the highest levels of consumption. The surprisingly protective association with autism-spectrum traits has not been previously reported, although prosocial behavioral

Table 4. Continued

Seafood Intake[a]	No. of Subjects	Difference in Child's Neurobehavioral Score[b]			
		Minimally Adjusted[c]		Fully Adjusted[d]	
		β	95% CI	β	95% CI
Lean Fish					
Continuous variable, 10 g/week	1,393	−0.01[f]	−0.02, −0.00	−0.01[h]	−0.02, 0.00
Quintiles					
1	298	0.00	Referent	0.00	Referent
2	291	−1.03[f]	−1.52, −0.54	−0.89[f]	−1.37, −0.41
3	282	−0.91[f]	−1.41, −0.40	−0.77[f]	−1.26, −0.28
4	261	−0.63[f]	−1.14, −0.12	−0.48[h]	−0.98, 0.02
5	261	−0.92[f]	−1.45, −0.41	−0.70[f]	−1.22, −0.19
P for trend		0.017		0.10	
Shellfish					
Continuous variable, 10 g/week	1,393	0.02	−0.01, 0.04	0.01	−0.01, 0.04
Quintiles					
1	278	0.00	Referent	0.00	Referent
2	268	−0.12	−0.64, 0.40	−0.15	−0.66, 0.36
3	288	−0.61[f]	−1.17, −0.11	−0.58[f]	−1.08, −0.09
4	289	−0.12	−0.63, 0.38	−0.12	−0.61, 0.38
5	270	−0.07	−0.60, 0.45	−0.05	−0.57, 0.46
P for trend		0.97		0.92	

Abbreviations: CI, confidence interval; INMA, Infancia y Medio Ambiente.

[a] Median seafood intake in each quantile (g/week) is shown in the Table 2 footnotes.

[b] Childhood Asperger Syndrome Test (17).

[c] Regression models adjusted for sex of the child, age during testing, cohort, quality of the test, and maternal energy intake (kcal/day) during pregnancy.

[d] Regression models additionally adjusted for child's birth weight, gestational age, duration of breastfeeding, maternal age, educational level, social class, prepregnancy body mass index, parity, and country of origin/birth.

[e] Per 10-g/week increase.

[f] $P < 0.05$.

[g] Results were similar when the reference group included all mothers with seafood consumption less than or equal to 340 g/week (Web Table 5).

[h] $P < 0.10$.

improvements were observed in a previous study (8) and children with autistic spectrum traits tend to show lower prosocial behaviors (22). One potential pathway could be through LC-PUFAs, particularly DHA intake from seafood (23). Several controlled trials and observational studies of LC-PUFAs have reported improvements in cognition, attention-deficit/hyperactivity disorder, and antisocial symptoms (24). Our findings showing moderate attenuation after adjustment for LC-PUFA (including DHA) levels in umbilical cord blood are supportive of that hypothesis, given that other potential intermediate factors, such as vitamin D and iodine levels in pregnancy, did not explain any of the observed associations.

While a few previous studies on seafood consumption during pregnancy and child neuropsychological development have examined seafood subtypes (2, 5), none (to our knowledge) have separately examined associations with large versus small species of fatty fish. Somewhat inconsistently with our findings, Gale et al. (21) reported that while consumption of fatty fish of any kind less than once per week was associated with small increases in intelligence quotient at age 9 years, no associations were observed at higher levels of intake.

Current guidelines for seafood consumption during pregnancy have been developed largely on the basis of evidence linking mercury and other contaminants frequently found in marine foods with poorer neuropsychological development (1). Large fatty fish are of particular concern, as these long-lived, predatory species may accumulate high levels of both mercury and lipophilic contaminants such as organochlorines (25, 26). In the few previous studies where such measurements were available, positive associations between seafood consumption and child neuropsychological development were strengthened or not influenced by adjustments for cord-blood mercury, polychlorinated biphenyls, and/or DDE (2, 25). In this study, there was attenuation of the association estimate after adjustment for cord-blood mercury levels. In this regard, the precision of measurement of the independent variables (both the toxicant exposure and the beneficial dietary factors and other confounders) in our study was important. If a toxicant is measured with greater precision than the dietary factor through an FFQ, the association for the latter will generally be biased toward the null (27). In the present study, cord-blood mercury was probably an indicator of seafood consumption.

The complexity of separating the positive and adverse associations of seafood consumption and methylmercury (or mercury), respectively, with child neuropsychological development has been discussed elsewhere (28). Several factors may be masking any adverse association with methylmercury intake. For example, pregnant women with higher socioeconomic status tend to consume more seafood and be exposed to higher levels of methylmercury, but their children tend to perform better on cognitive tests (27). Additionally, variability in levels of both methylmercury and DHA are dependent on seafood subtype, with larger predators containing higher levels of methylmercury, but some, such as tuna, also containing higher concentrations of DHA (7). These factors and potential genetic vulnerabilities to methylmercury toxicity (27) make objective evaluation of the toxic risk of this exposure difficult, particularly since such exposure is closely linked to total seafood intake, which confers benefits for neuropsychological development.

A 2-point increase in a child's cognitive score is not remarkable for an individual but is important for the population. If a specific population, particularly a community with poor seafood consumption, benefited from greater consumption of seafood, the Gaussian distribution of scores would likely shift to the right. As an end result, the chance of finding "borderline" children would be diminished. If these beneficial associations are permanent, they could be related to positive social and economic changes (18, 29). Although we experienced a moderate loss to follow-up of 40%, this allows some generalizability of our findings.

Although this study contained more information on seafood subtypes than earlier studies, we observed moderate correlations between them, limiting the interpretation of fully independent associations by subtype. Moreover, while FFQs are valid tools for assessing dietary intakes, the use of self-reported data is a major limitation in this field of research, due to an increased level of statistical "noise" related to the subjectivity in recall of food habits and the potential influence of sociocultural background. Additionally, healthy nutritional habits that include more seafood consumption are also related to higher maternal intelligence quotient and educational level and to less smoking during pregnancy (2); hence, we cannot rule out the possibility of some residual confounding. However, we carefully considered a wide range of potential confounders, including the ones mentioned above (Web Tables 1 and 2), and conducted sensitivity analyses to address this potential limitation. Negative confounding by mercury exposure was not found here, probably due to the lack of an observed negative association for mercury, as reported previously in this cohort (30). The difficulty of disentangling both associations demonstrates the statistical limitations of epidemiologic studies. Finally, we found moderate association trends in some of the seafood subtypes, but there was also a weak tendency toward saturation in the highest quantiles of exposure. Probably the pattern of association is not completely linear, with stronger positive associations in the moderately high seafood consumption categories.

Overall, the present results suggest no adverse associations of high seafood consumption in pregnancy with offspring neurodevelopment. Moderate consumption of small and large fatty fish and lean fish during pregnancy is associated with moderate improvements in child neuropsychological development, including cognitive functions and autism-spectrum traits. A slight dilution of the association at the highest intake levels may be indicative of a weak counterbalancing association due to the potential harm of related contaminants. The moderate mediation role of LC-PUFAs observed here suggests that they may have a mechanistic function. The role of mercury was difficult to discern, since it appeared to be a stronger biomarker of seafood consumption rather than having any expected neurotoxic association. Finally, the present findings should be taken with caution, and future research should focus on older children in order to further explore whether the association patterns observed here continue into later life, with particular attention being given to large fatty fish species.

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