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Seafood Intake and Neurodevelopment: A Systematic Review

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Abstract Exposure to fish intake is of particular interest for neurodevelopment. Seafood contains nutrients that are essential for brain development and function. Seafood is also a potential source of well-established neurotoxic pollutants. We conducted a systematic search of the literature to review human studies on seafood intake and neurodevelopment. We identified 16 studies, most of them prospective cohort studies with prenatal and postnatal seafood intake exposure assessed through food frequency questionnaires. Most studies found positive associations with neurodevelopment outcomes, without particularly stronger associations for specific developmental areas (general, cognitive, and behavioral). Some studies observed an inverted U-shape association in relation with higher seafood-intake frequency. A few reports assessed type of seafood but no clear pattern was disentangled. In conclusion, seafood intake during pregnancy and postnatal periods seems to be beneficial to a wide range of neurodevelopment outcomes, with some potential risk at higher levels. Although studies adjusted for a variety of sociodemographic factors, residual confounding is possible. Larger prospective studies are required to define which seafood species are more important for neurodevelopment while minimizing the potential neurotoxic effect of the related pollutants.

Keywords Fish intake · Pregnancy · Postnatal · Neurodevelopment · Seafood Chemicals · Review

Introduction

Essential nutrients are critical for brain development and function [1]. Humans have particularly long neurodevelopmental periods, and the human brain is in development until the early 20s. The early life period, however, is decisive because of the rapid and intense neurodevelopment processes that are fully activated during that time. The long-term consequences of disturbing neurodevelopment in early life by environmental and nutritional hazards can be enormous [2]. In the evaluation of the evidence on the protection of the developing human brain from environmental hazards, it is also important to consider potentially beneficial factors such as breastfeeding, physical activity and seafood intake [3].

An increasingly large number of epidemiologic studies have analyzed the association between seafood intake and neurodevelopment. Seafood contains high concentrations of long-chain n-3 polyunsaturated fatty acids (n-3 PUFA), which are essential nutrients for cell membrane formation, the development of neurons and their synaptic connexions [4]. Seafood contains other essential nutrients that are also required for normal brain function and development, such as selenium, vitamin D, and iodine [5]. It is also, however, frequently contaminated by environmental pollutants including well-established neurotoxicants such as persistent organic pollutants (POPs) and mercury. These toxicants may be found in seafood because of their accumulation along the food chain

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from plankton to large predator fish (i.e., tuna and swordfish). The potential neurotoxicity of these compounds is of concern when formulating dietary recommendations on seafood intake for pregnant women and children [2].

Several reviews and systematic reviews have evaluated the role of POPs or mercury exposure with neurotoxicity [2, 6–9]. No previous reviews, however, have systematically evaluated epidemiologic studies on seafood intake early in life and neurodevelopment.

We conducted a systematic review of the evidence on the association of seafood intake during pregnancy and childhood with neurodevelopment. Our goal was to review the evidence in a systematic manner, to describe the limitations in exposure and outcome assessment of current research, and to discuss future research needs for improving the understanding of the complex connection between seafood and neurodevelopment. Additionally, we evaluated whether the published data support the recommendation of no more than 340 g per week of seafood during pregnancy issued by the US Federal Government Agencies [10]. We excluded from this review studies evaluating fish-oil supplements, measuring n-3 fatty acids, or evaluating specific seafood contaminants such as mercury or POPs if they did not report the overall association between seafood intake and neurodevelopment.

Review Strategy

We identified original articles studying the association of fish or seafood intake during the prenatal period, childhood and adolescence with neurodevelopment. Articles were searched in PubMed and PsycINFO databases using the following keywords: fish, seafood (as exposures), pregnancy, prenatal, uterine period, prenatal exposure delayed effects, maternal exposure, maternal-fetal exchange, infant, toddler, child, teenager, adolescent (as time periods), attention deficit, hyperactivity, neuro, neurological, mental health, cognitive abilities, neurodevelopment, neurobehavior, and behavior (as outcomes). Initially, a search of each of these terms was performed separately, and afterwards, a second search step combining the terms together was carried out by taking each term from the exposure group and crossing the search with each term from the time period group and each term from the outcomes group. The search period was limited to the last 20 years (from January 1993 until July 2013). Only human studies were included (Fig. 1). No language restrictions were implemented.

Identified abstracts were reviewed and articles were excluded using the following criteria: (1) not an original article, (2) non-human research, (3) not focused on seafood intake as one of the main exposures, (4) seafood exposure was measured in adulthood only, (5) no neurodevelopmental endpoint, (6) duplicated between databases. Among 20 articles identified and fully reviewed, 3 were further excluded because they did not meet the criteria for inclusion [11–13]. We also excluded a randomized control trial of a fish flour bread spread because of the different nature of the exposure compared to observational studies of seafood intake [14••]. The two authors reviewed the articles independently, and differences in opinion regarding inclusion or exclusion of the articles were settled by consensus between them. A manual review was performed by scrutinizing the reference list of each one of the retrieved studies. No additional articles were identified through manual search.

For each study included we collected the following data: authors, journal, year of publication, study design, study population, study period, sample size, outcome assessment, age at outcome assessment, seafood assessment, and measure of association and confidence intervals in the most adjusted model and covariates controlled for in the analyses (Tables 1 and 2). Most studies reported estimated measures of relative risk (odds ratios, relative risk). For studies that reported associations with both continuous and dichotomous measures of the study outcome, we selected the results for the dichotomous measures only [15]. Some studies reported findings only for continuous measures of the outcome, and we report those results (mainly β coefficients). For the subset of studies that adjusted the association between seafood intake and neurodevelopment outcomes for mercury and PCBs, we report the findings both before and after adjustment for those established neurotoxicants in a separate table (Table 3).

Results

Study Characteristics

A total of 16 articles were found (Tables 1 and 2). Eight studies evaluated seafood exposure prenatally, five studies evaluated seafood exposure postnatally, and three studies evaluated seafood exposure both pre- and postnatally. After birth, seafood intake was evaluated during childhood [1, 14••, 15–17, 18•] and adolescence [19–21]. Most of the studies were prospective cohorts [1, 10, 15–17, 18•, 20–26, 27•], probably the best-suited methodology to evaluate whether maternal intake of fish can influence the development of the offspring. Other study designs were cross-sectional [19] and case control [28] .

The studies were from different geographical regions, although predominantly from developed countries. Most studies have been carried out in Europe [1, 10, 15, 16, 18•, 19–21, 23, 25, 28], followed by others in the US [22, 27•], Japan [26], and New Zealand [17]. Almost all of them were conducted in general population groups [1, 10, 15–17, 18•, 22–26, 27•]. Most studies used a Food Frequency Questionnaire (FFQ) [1, 10, 15–17, 18•, 22–26, 27•, 28] to assess dietary seafood

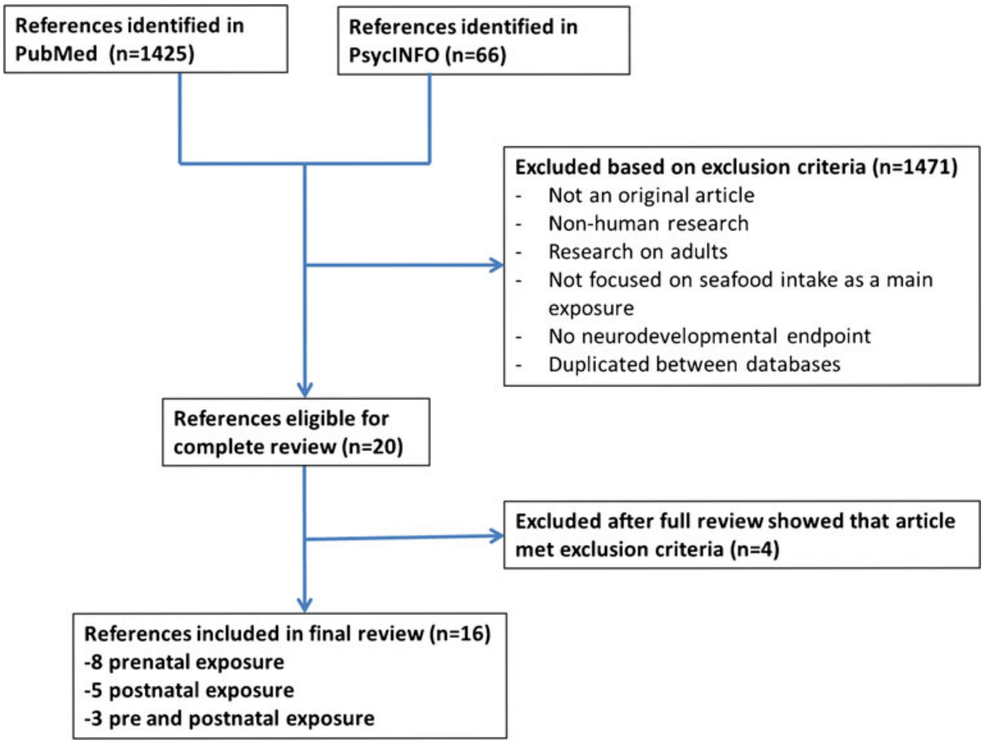

Fig. 1 Flow chart of study selection

intake, especially for studies examining prenatal exposure. Other dietary questionnaires were also used in postnatal exposure studies [15, 16, 19–21], ranging from simple questions to dietary diaries (Table 2).

The neurodevelopmental outcomes and the tools used for outcome assessment varied widely across studies. Outcomes can be classified as pertaining to cognitive, behavioral, or general developmental areas. Cognitive outcomes were ascertained by using VRM (Visual Recognition Memory) [22], WISC (Wechsler Intelligence Scale for Children) [10, 17, 25, 27•], PPVT (Peabody Picture Vocabulary Test), WRAVMA (Wide Range of Visual Motor Ability) [24], MSCA (McCarthy Scales of Children's Abilities) [1, 18•], AVT (Amsterdam Vocabulary Test) [19], Swedish military conscription intelligence test [21], Stanford-Binet intelligence scales [17], CPT (Continuous Performance Test) [27•], or school grades [19, 20]. Behavioral outcomes were measured by the SDQ (Strengths and Difficulties Questionnaire) [10, 25], CRS-T (Conner's Rating Scale-Teacher's version) [27•], and the YSR (Youth Self-Report) [19]. General development tests included: the stereoacuity test [16], MCDI (MacArthur Communicative Development Inventory) and DDST (Denver Developmental Screening Test) [15], ALSPAC scale (Avon Longitudinal Study of Parents and Children) [10], NBAS (Neonatal Behavioral Assessment Scale) [26], neurological exam [28], and maternal interview.

Common covariates were child age [15, 19, 22–24, 27•, 28], sex [1, 10, 15, 16, 19, 22–24, 26, 27•], and breastfeeding [1, 10, 15, 16, 18•, 22–25], as well as maternal age [10, 15, 16, 22, 24, 25, 27•, 28], sociodemographic characteristics [1, 10, 15–17, 18•, 19, 21–26, 27•], smoking [10, 15–17, 18•, 24–26, 27•], and alcohol use [10, 15, 24–26, 27•]. Of special interest, seven articles also reported having adjusted in some way for the possible effects of contaminants such as mercury [15, 18•, 22, 24, 26, 27•] or persistent organic pollutants [1, 26, 27•] (Table 3). In some but not all studies, adjusting for mercury and/or POPs further strengthened the positive association between seafood intake and neurodevelopmental outcomes.

Studies of Prenatal Seafood Intake

In the cohorts that studied prenatal maternal seafood intake, the ages of children at testing ranged from days to 10 years (Table 1). Prenatal exposure to seafood as part of the maternal diet was found to have a positive relation with general developmental outcomes including improved scores on the MCDI and DDST scales at 18 months [15], higher scores on the ALSPAC scale from 6 to 42 months of age [10], having achieved foveal stereoacuity (an indicator of visual cortex maturity at 3.5 years of age; the association was only significant for oily fish) [16] and acquirement of developmental milestones at 6 and 18 months [23]. A Japanese study found no significant differences in newborns [26].

Seafood intake was also positively associated with cognitive benefits in several studies including higher verbal IQ at 8 years [10], higher full-scale IQ in children at 9 years [25], better results for VRM at 5.5-8.4 months of age [22] (which was strengthened after adjustment for maternal hair mercury

Table 1 Main characteristics of articles studying the relationship between prenatal seafood consumption and neurodevelopment

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
Petridou 1998 [28]	Case–control matched for 1) age, sex and neighborhood or 2) healthy sibling of another neurology patient with similar age and sex.	Greater Athens area, Greece	1991-1992	337 (91/ 246)	3-8 yrs	Seafood intake during pregnancy	Semiquantitative FFQ (1 seafood item)	Diagnosis of cerebral palsy by child neurologist	OR for cerebral palsy by fish intake Positive relationship for cerebral palsy by meat/ fish ratio.	0.63 (0.37, 1.08) p=0.01	Child: age, sex and neighborhood. Mother: age at delivery and menarche, chronic disease, previous spontaneous abortion, persistent vomiting during pregnancy, multiple pregnancy, number of obstetric visits, iron supplement in pregnancy, exercise in pregnancy, painless delivery classes, timing of membrane rupture, general anaesthesia in delivery, mode and place of delivery, abnormal placenta, head circumference, congenital malformation.
Williams 2001 [16]	Prospective cohort (ALSPAC study)	Bristol area, United Kingdom	1991-1996	435	3.5 yrs	Seafood intake during pregnancy	FFQ (Number of seafood items NR)	Stereoacuity test by orthoptist	*OR for foveal stereoacuity with intake of:* Oily fish: Any fish: Shellfish:	1.57 (1.00, 2.45) NS (numbers NR) NS (numbers NR)	Child: Breastfed, sex, siblings, paid child care. Mother: education, employment, age and smoking, housing tenure, financial difficulties, diet: vegetarian, eats any fish, white fish, oily fish, shellfish, child eats oily fish.
Daniels 2004 [15]	Prospective cohort (ALSPAC Study)	Bristol area, United Kingdom	1991-1994	7421	15-18 mo	Seafood intake during pregnancy	FFQ (Number of seafood items NR)	MCDI at 15 months. DDST at 18 months.	*OR for low test scores by seafood servings**: MCDI Social Activity: Rarely/never 1 / 2 wks 1-3 /wk 4+ /wk	1.00 (ref) 0.8 (0.6, 1.1) 0.6 (0.5, 0.8) 0.7 (0.5, 0.9)	Child: sex and age at testing, birth order, breastfed. Mother: dental treatment, age, prenatal smoking and alcohol use, education.

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									MCDI Vocabulary comprehension:		
									Rarely/never	1.00 (ref)	
									1 / 2 wks	0.8 (0.6, 1.1)	
									1-3 /wk	0.8 (0.6, 1.0)	
									4+ /wk	0.9 (0.7, 1.2)	
									DDST Language:		
									Rarely/never	1.00 (ref)	
									1 / 2 wks	0.8 (0.6, 1.2)	
									1-3ser/wk:	0.7 (0.5-0.9)	
									4+ser/wk:	0.7 (0.5-0.9)	
									DDST Social:		
									Rarely/never	1.00 (ref)	
									1/2wks	1.2 (0.8, 1.8)	
									1-3/wk	1.0 (0.7-1.4)	
									4+/wk	1.1 (0.7-1.5)	
									Mean Developmental Assessment Scores by seafood servings: *MCDI Vocabulary Comprehension:*		
									Rarely/never	68.2(66.3,70.5)	
									1/ 2 wks	70.9 (69.0, 72.9)	
									1-3/wk	73.0 (71.2, 74.8)	
									4+/wk	71.9 (70.5-73.8)	
									β± SD (p) per ounce increase of fish per wk	0.11 ± 0.05 (0.03)	
									MCDI Social Activity:		
									Rarely/never	16.4 (16.0, 16.7)	
									1/ 2 wks	17.0 (16.6, 17.3)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									1-3/wk	17.1 (16.8, 17.4)	
									4+/wk	17.2 (16.9, 17.5)	
									β± SD (p) per ounce increase of fish per wk	0.03 ± 0.009 (0.002)	
									DDST Total:		
									Rarely/never	37.2 (36.9, 37.6)	
									1/ 2 wks	37.7 (37.3, 38.0)	
									1-3/wk	37.9 (37.6, 38.2)	
									4+/wk	37.8 (37.5, 38.1)	
									β± SD (p) per ounce increase of fish per wk	0.02 ± 0.01 (0.03)	
									DDST Language:		
									Rarely/never	7.1 (6.9, 7.3)	
									1/ 2 wks	7.4 (7.2, 7.5)	
									1-3/wk	7.4 (7.3, 7.5)	
									4+/wk	7.4 (7.3, 7.6)	
									β± SD (p) per ounce increase of fish per wk	0.01 ± 0.004 (0.004)	
									DDST Social:		
									Rarely/never	8.1 (7.9, 8.2)	
									1/ 2 wks	8.1 (8.0, 8.2)	
									1-3/wk	8.2 (8.1, 8.3)	
									4+/wk	8.2 (8.0, 8.3)	
									β± SD (p) per ounce increase of fish per wk	0.002 ± 0.004 (0.5)	
Oken 2005 [22]	Prospective cohort (Project Viva)	Massachusetts, USA	1999-2003	135	5.5-8.4 mo	Seafood intake during pregnancy	Semiquantitative FFQ (4 seafood items)	VRM at 6 mo	Change in VRM point score per weekly fish serving	+4.0 (1.3, 6.7)	Child: sex gestational age at birth, birth weight, breastfeeding duration, age at testing. Mother: age, race, education, marital status, hair mercury.
Hibbeln 2007 [10]	Prospective cohort (ALSPAC Study)	Bristol and surrounding area,	1991-2000	8916	0.5-8 yrs	Maternal seafood intake during pregnancy	FFQ (3seafood items)	ALSPAC Scale at 6, 18, 30 and 42 mo. SDQ at 81 mo. WISC-III	*OR for several outcomes comparing seafood*		Child: sex, gestational age at delivery, birth weight, breastfed.

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
		United Kingdom						abbreviated form at 8 yrs.	*>340g/wk vs. none*		Mother: age, parity, education, housing, crowding, stressful life events at 18 wk, partner at time of birth, smoking in pregnancy, alcohol use in pregnancy, ethnicity, other food groups. Family adversity index, facilities for child care at home.
									WISC-III		
									Lowest quartile verbal IQ:	*1.48 (1.16, 1.90)*	
									Lowest quartile Performance IQ:	*0.98 (0.76, 1.27)*	
									Lowest quartile Full Scale IQ:	*1.29 (0.99, 1.69)*	
									SDQ		
									Suboptimum prosocial behavior:	*1.44 (1.05-1.97)*	
									Suboptimum Hyperactivity:	*1.13 (0.84, 1.53)*	
									Suboptimum emotional behavior:	*1.09 (0.83, 1.44)*	
									Suboptimum conduct:	*1.21 (0.89, 1.62)*	
									Suboptimum peer behavior:	*1.25 (0.96, 1.62)*	
									SDQ total score:	*1.17 (0.86, 1.60)*	
									ALSPAC		
									Suboptimum Gross motor skills:		
									6 mo	*1.10 (0.90-1.34)*	
									18 mo	*1.02 (0.85, 1.22)*	
									30 mo	*0.97 (0.80, 1.22)*	
									42 mo	*0.96 (0.78, 1.18)*	
									Suboptimum Social development at:		
									6 mo	*1.15 (0.95, 1.40)*	
									18 mo	*1.01 (0.83, 1.24)*	
									30mo	*1.24 (1.01, 1.53)*	
									42 mo	*1.21 (0.98, 1.50)*	
									Suboptimum fine motor skills at:		

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									6 mo	(0.83, 1.23)	
									18 mo	1.25 (1.04, 1.51)	
									30 mo	1.04 (0.85, 1.27)	
									42 mo	1.35 (1.09, 1.66)	
									Suboptimum communication at:		
									6mo	1.30 (1.04, 1.63)	
									18 mo	1.26 (1.03, 1.53)	
Oken 2008 [24]	Prospective cohort (Project Viva)	Massachusetts, USA	1999-2003	341	3 yrs	Seafood intake 2nd trimester pregnancy	Semiquantitative FFQ (4 seafood items)	PPVT, WRAVMA	*Change in outcome by seafood servings per wk:*		Child: sex, birth weight, date of birth, age, duration of breastfeeding, primary language. Mother: race, age, education, parity, smoking, alcohol use, marital status, pre-pregnancy weight and height, erythrocyte mercury. Paternal education.
									All fish:		
									PPVT score:		
									>2/wk	2.2 (−2.6, 7.0)	
									≤2/wk	−1.8 (−5.4, 1.8)	
									Never	0 (Ref)	
									WRAVMA drawing score:		
									>2/wk	6.4 (2.1, 10.7)	
									≤2/wk	1.3 (−1.8, 4.5)	
									Never	0 (Ref)	
									WRAVMA pegboard Score:		
									>2/wk	3.5 (−0.8, 7.8)	
									≤2/wk	−0.5 (3.7, 2.7)	
									Never	0 (Ref)	
									WRAVMA matching score:		
									>2/wk	4.1 (−1.8, 10.0)	
									≤2/wk	2.3 (−2.1, 6.7)	
									Never	0 (Ref)	
									WRAVMA total score:		
									>2/wk	6.4 (2.0, 10.8)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									≤2/wk	1.5 (−1.8, 4.7)	
									Never	0 (Ref)	
									Canned Tuna:		
									PPVT total score:		
									≥2/wk	3.7 (−0.9, 8.3)	
									Never	0 (Ref)	
									WRAVMA total score:		
									≥2/wk	5.6 (1.4, 9.8)	
									Never	0 (Ref)	
									Fish other than canned tuna:		
									PPVT total score:		
									>2/wk	−1.4 (−8.9, 6.1)	
									Never	0 (Ref)	
									WRAVMA total score:		
									>2/wk	6.1 (−0.7, 12.8)	
									Never	0 (Ref)	
									All fish excluding shellfish:		
									PPVT Total Score:		
									Any	4.3 (−0.5, 9.0)	
									Never	0 (Ref)	
									WRAVMA Total Score:		
									Any	5.9 (1.6, 10.3)	
									Never	0 (Ref)	
Gale 2008 [25]	Prospective cohort	Southha-mpton, United Kingdom	1991-2001	217	9 yrs	Seafood intake during pregnancy	FFQ (4 seafood items)	SDQ, Weschler Abbreviated Scale of Intelligence	*Odds ratio for seafood intake vs. never:*		Child: birth weight, duration of breastfeeding. Maternal: social class, education, age, IQ, smoking in pregnancy, alcohol in pregnancy.
									Oily fish in early pregnancy and hyperactivity:		
									Never	1.0 (Ref)	
									<1ser/wk	0.30 (0.12, 0.76)	
									≥1ser/wk	0.41 (0.15, 1.12)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									Oily fish in late pregnancy and hyperactivity:		
									Never	1.0 (Ref)	
									<1ser/wk	0.40 (0.16, 0.98)	
									≥1ser/wk	0.72 (0.26, 1.55)	
									Oily fish in early pregnancy and conduct problems:		
									Never	1.0 (Ref)	
									<1 ser/wk	0.58 (0.22, 1.53)	
									≥1 ser/wk	0.36 (0.11, 1.21)	
									Oily fish in late pregnancy and conduct problems:		
									Never	1.0 (Ref)	
									<1 ser/wk	0.46 (0.18, 1.17)	
									≥1 ser/wk	0.31 (0.08, 1.10)	
									Oily fish in early pregnancy and peer problems:		
									Never	1.0 (Ref)	
									<1 ser/wk	0.79 (0.27, 2.32)	
									≥1 ser/wk	1.44 (0.47, 4.80)	
									Oily fish in late pregnancy and peer problems:		
									Never	1.0 (Ref)	
									<1 ser/wk	0.68 (0.25, 1.82)	
									≥1 ser/wk	0.82 (0.27, 2.57)	
									Oily fish in early pregnancy and emotional symptoms:		
									Never	1.0 (Ref)	
									<1 ser/wk	0.63 (0.19, 2.06)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									≥1 ser/wk	0.79 (0.20, 3.08)	
									Oily fish in late pregnancy and emotional symptoms:		
									Never	1.0 (Ref)	
									<1 ser/wk	2.32 (0.73, 7.34)	
									≥1 ser/wk	1.04 (0.23, 4.66)	
									Oily fish in early pregnancy and total difficulties:		
									Never	1.0 (Ref)	
									<1 ser/wk	1.23 (0.41, 3.66)	
									≥1 ser/wk	0.83 (0.22, 3.04)	
									Oily fish in late pregnancy and total difficulties:		
									Never	1.0 (Ref)	
									<1 ser/wk	1.25 (0.43, 3.60)	
									≥1 ser/wk	1.20 (0.32, 4.49)	
									All seafood in early pregnancy and IQ	NS (data NR)	
									Change in verbal IQ for seafood in late pregnancy:		
									<1ser/wk	7.66 (−0.1, 15.4)	
									1-2ser/wk	7.32 (0.26, 14.4)	
									3+ser/wk	8.07 (0.28, 15.9)	
									Change in performance IQ	NS (data NR)	
									All seafood early and late pregnancy	NS (data NR)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									Oily fish early and late pregnancy		
									Change in full-scale IQ:		
									All seafood in early pregnancy:		
									Never	(Ref)	
									<1 ser/wk	5.12 (−1.95, 12.2)	
									1-2 ser/wk	3.07 (−3.74, 9.88)	
									≥3 ser/wk	1.19 (−6.24, 8.61)	
									All seafood in late pregnancy:		
									Never	(Ref)	
									<1 ser/wk	7.76 (0.38, 15.1)	
									1-2 ser/wk	6.91 (0.19, 13.6)	
									≥3 ser/wk	5.86 (−1.55, 13.3)	
									Oily fish in early pregnancy:		
									Never	(Ref)	
									<1 ser/wk	2.52 (−1.89, 6.94)	
									≥1 ser/wk	−0.99 (−6.01, 4.02)	
									Oily fish in late pregnancy:		
									Never	(Ref)	
									<1 ser/wk	3.43 (−0.80, 7.65)	
									≥1 ser/wk	−0.29 (−5.34, 4.76)	
Oken 2008 [23]	Prospective cohort (Danish National Birth Cohort)	Denmark	1997-2005	25446	6 and 18 mo	Seafood intake during pregnancy	Semiquantitative food-frequency questionnaire (Number	Developmental milestones according to	OR for meeting developmental milestones in		Child: age, sex, growth, duration of breastfeeding.

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
							ofseafood items NR)	maternal interview.	by quintile of seafood intake		<u>Mother</u>: size, pregnancy characteristics, postpartum depression; Parental education and social status.
									At 6 mo:		
									Q1	1.0 (Ref)	
									Q2	0.99 (0.92, 1.05)	
									Q3	1.05 (0.99, 1.13)	
									Q4	1.09 (1.02, 1.17)	
									Q5	1.25 (1.17, 1.34)	
									At 18 mo:		
									Q1	1.0 (Ref)	
									Q2	0.99 (0.93, 1.07)	
									Q3	1.09 (1.01, 1.17)	
									Q4	1.14 (1.06, 1.22)	
									Q5	1.29 (1.2, 1.38)	
Mendez 2008 [1]	Prospective cohort (INMA- Menorca)	Menorca, Spain	1997-2000	392	4 yrs	Fish during pregnancyOther seafood (shellfish and squid).	Semiquantitative FFQ Number of seafood items NR)	MSCA	Change in MSCA scores by seafood servings per wk: *<u>Breast-fed for <6mo</u>*		<u>Child</u>: sex, birthweight, gestational age, breastfeeding duration, current grade. <u>Mother</u>: education, parity; evaluating psychologist.
									General Cognitive:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	2.7 (−1.2, 6.5)	
									2-3 fish/wk	11.0 (5.0, 17.1)	
									>3 fish/wk	−1.2 (−9.8, 7.3)	
									Perceptual-Performance:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	2.3 (−1.5, 6.1)	
									2-3 fish/wk	10.0 (4.1, 16.0)	
									>3 fish/wk	1.5 (−7.0, 9.9)	
									Memory:		
									≤1 fish/wk	O (Ref)	
									1-2 fish/wk	2.0 (−2.1, 6.1)	
									2-3 fish/wk	10.5 (4.1, 16.9)	
									>3 fish/wk	−3.3 (−12.4, 5.8)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									Verbal:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	2.2 (−1.8, 6.3)	
									2-3 fish/wk	9.9 (3.5, 16.2)	
									>3 fish/wk	−1.8 (−10.8, 7,2)	
									Numeric:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	2.1 (−1.8, 6.0)	
									2-3 fish/wk	6.8 (0.7, 12.8)	
									>3 fish/wk	−2.3 (−10.9, 6.3)	
									Motor Skills:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	2.1 (−1.8, 6.0)	
									2-3 fish/wk	6.7 (0.7, 12.8)	
									>3 fish/wk	−2.3 (−10.9, 6.3)	
									Breast-fed for ≥6mo		
									General Cognitive:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	−0.7 (−7.0, 5.7)	
									2-3 fish/wk	−0.7 (−8.3, 6.9)	
									>3 fish/wk	−5.3 (−17.9, 7.3)	
									Perceptual-Performance:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	−0.2 (−6.1, 6.6)	
									2-3 fish/wk	0.8 (−6.8, 8.5)	
									>3 fish/wk	−0.2 (−12.4, 12.9)	
									Memory:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	−1.8 (−8.2, 4.5)	
									2-3 fish/wk	−4.6 (−12.3, 3.3)	
									>3 fish/wk	−12.7 (−25.5, 0.0)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									Verbal:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	−1.1 (−7.7, 5.4)	
									2-3 fish/wk	−0.5 (−8.3, 7.4)	
									>3 fish/wk	−8.2 (−21.3, 4.9)	
									Numeric:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	−0.5 (−6.8, 5.9)	
									2-3 fish/wk	−3.1 (−10.7, 4.6)	
									>3 fish/wk	−2.8 (−15.5, 9.9)	
									Motor Skills:		
									≤1 fish/wk	0 (Ref)	
									1-2 fish/wk	−2.1 (−8.5, 4.3)	
									2-3 fish/wk	−0.8 (−8.5, 7.0)	
									>3 fish/wk	−2.1 (−14.8, 10.7)	
									Other seafood:		
									General Cognitive:		
									≤0.5 ser/wk	0 (Ref)	
									>0.5-1 ser/wk	−1.0 (−4.7, 2.6)	
									>1ser/wk	−5.2 (−8.8, -1.7)	
									Perceptual-performance:		
									≤0.5 ser/wk	0 (Ref)	
									>0.5-1 ser/wk	−2.4 (−6.0, 1.3)	
									>1ser/wk	−5.0 (−8.5, -1.5)	
									Memory:		
									≤0.5 ser/wk	0 (Ref)	
									>0.5-1 ser/wk	0.9 (−3.0, 4.7)	
									>1ser/wk	−3.5 (−7.2, 0.2)	
									Verbal:		
									≤0.5 ser/wk	0 (Ref)	
									>0.5-1 ser/wk	0.3 (−3.6, 4.1)	
									>1ser/wk	−3.7 (−7.4, 0.0)	
									Numeric:		

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									≤0.5 ser/wk	0 (Ref)	
									>0.5-1 ser/wk	−1.3 (−5.0, 2.4)	
									>1ser/wk	−5.2 (−8.8, -1.6)	
									Motor Skills:		
									≤0.5 ser/wk	0 (Ref)	
									>0.5-1 ser/wk	−1.1 (−4.7, 2.6)	
									>1ser/wk	−2.2 (−5.7, 1.4)	
Suzuki 2010 [26]	Prospective cohort (TSCD)	Tohoku district, Japan	2001-2004	498	3 days	Seafood intake during pregnancy	FFQ postpartum (13 seafood items).	NBAS	Relation between seafood intake and NBAS motor cluster.	p>0.1	Child: sex, gestational age, birth weight, APGAR score at 1 minute, delivery type cord blood PCBs, cord blood TSH and T3. Mother: hair mercury, age, BMI, education, alcohol in pregnancy, smoking in pregnancy, parity, total energy intake.
									Adjusted results for other NBAS clusters	NR	
Sagiv 2012 [27•]	Prospective cohort (New Bedford cohort)	New Bedford,-Massa-chusetts, USA	1993-2006	515	7-10 yrs	Seafood intake during pregnancy	FFQ postpartum (5 seafood items).	CRS-T, CPT, WISC-III (processing speed and freedom from distractibility)	RR or β for different endpoints per servings of seafood:		Child: age, sex, race. Mother: age, education, marital status, IQ, depression, prenatal smoking, prenatal alcohol use, illicit drug use. Paternal education, household income, Home observation for the measurement of the environment score. Hair mercury.
									CRS-T:		
									Inattentive :		
									≤2/wk	1 (Ref)	
									>2/wk	0.6 (0.4, 0.9)	
									Impulsive/ hyperactive :		
									≤2/wk	1 (Ref)	
									>2/wk	0.4 (0.2-0.6)	
									Total:		
									≤2/wk	1 (Ref)	
									>2/wk	0.6(0.4, 0.9)	
									WISC-III:		
									Processing speed		
									≤2/wk	0 (Ref)	
									>2/wk	2.0 (−0.8, 4.8)	

Table 1 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome Assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									Freedom from distractibility		
									≤2/wk	0 (Ref)	
									>2/wk	1.5 (−1.1, 4.0)	
									CPT:		
									Mean reaction time		
									≤2/wk	0 (Ref)	
									>2/wk	10.1 (−3.9, 24.1)	
									Reaction time variability:		
									≤2/wk	0 (Ref)	
									>2/wk	−0.5 (−6.3, 5.4)	
									Errors of omission		
									≤2/wk	1 (Ref)	
									>2/wk	0.9 (0.7, 1.2)	
									Errors of commission		
									≤2/wk	1 (Ref)	
									>2/wk	1.1 (0.9, 1.3)	

The results with adjustment for most covariates are reported for each article. Results for dichotomous measures of association are selected if both are presented. For the study by Daniels 2004, only the results for low test scores were retrieved as the results for high test scores were consistent in the opposite direction.

AM Arithmetic Mean, *ALSPAC* Avon Longitudinal Study of Pregnancy and Childhood, *CPT* Continuous Performance Test, *CRS-T* Conner's Rating Scale-Teachers, *DDST* ALSPAC adaptation of Denver Developmental Screening Test, *FFQ* Food Frequency Questionnaire, *GCS* Global Cognitive Score, *INMA* Child and Environment Project, *IQ* Intelligence Quotient, *MCDI* ALSPAC adaptation of MacArthur Communicative Development Inventory, *mo* months, *MSCA* McCarthy Scales of Children's Abilities, *NBAS* Neonatal Behavioral Assessment Scale, *NR* Not reported, *NS* non-significant, *PPVT* Peabody Picture Vocabulary Test, *Ref* Reference, *ser* servings, *SDQ* Strengths and Difficulties Questionnaire, *UK* United Kingdom, *USA* United States of America, *VRM* Visual Recognition Memory, *WISC-III* Weschler Intelligence Scale for Children-III, *wk* week, *WRAVMA* Wide Range Assessment of Visual Motor Ability, *YSR* Youth Self-Report, *yrs* years

Table 2 Main characteristics of articles studying the relationship between postnatal fish consumption and neurodevelopment

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
Williams 2001 [16]	Prospective cohort (ALSPAC study)	Bristol and surrounding area, UK	1991-1995	435	3.5 yrs	Seafood intake by child.	Questionnaires on infant feeding at 4 wk and 6 mo, dietary diary over 24 hours at 4 mo.	Stereoacuity test by orthoptist	Association of foveal stereoacuity with intake of oily fish by the child.	NS (data NR)	Child: Breastfed, sex, siblings, paid child care Mother: education, employment, age and smoking, housing tenure, financial difficulties, diet: vegetarian, eats any fish, white fish, oily fish, shellfish, child eats oily fish.
Daniels 2004 [15]	Prospective cohort (ALSPAC Study)	Bristol and surrounding area, UK	1991-1994	7421	15-18 mo	Seafood intake by the child.	Questionnaire on infant feeding at 6 and 15 mo.	MCDI at 15 months. DDST at 18 months.	*OR for low test scores by child seafood intake :* *MCDI*		Child: sex and age at testing, birth order, breastfed. Mother: dental treatment, age, prenatal smoking and alcohol use, education.
									Vocabulary Comprehension at: *6 mo:*		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.9 (0.8, 1.1)	
									12 mo:		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.7 (0.5, 0.8)	
									Social Activity at: *6 mo:*		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.8 (0.7, 1.0)	
									12 mo:		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.7 (0.6, 0.9)	
									DDST:		
									Total score at:		
									6 mo		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.9 (0.7, 1.1)	

Table 2 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									12mo		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.8 (0.6, 0.9)	
									Social at:		
									6 mo		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.9 (0.7, 1.2)	
									12 mo:		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.6 (0.4, 0.7)	
									Language at:		
									6 mo		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.8 (0.7, 1.0)	
									12 mo		
									Rarely/never	1 (Ref)	
									1+ ser/wk	0.9(0.7, 1.1)	
Aberg 2008 [21]	Prospective cohort	Västra Götaland Region, Sweden	2000-2003	3972 males	18 yrs	Fish intake at 15 yrs	Questionnaire for fish intake	Swedish military service conscription examination intelligence test.	Stanine score increase for outcomes by seafood servings: Verbal score:		Body mass index (BMI), living in rural area, living in apartment, foreign descent, having a dishwasher, elementary school, parental education
									<1/wk	5.09 (4.48, 5.71) (Ref)	
									1/wk	0.46 (0.29, 0.64)	
									>1/wk	0.20 (0.05, 0.34)	
									Visuospatial score:		
									<1/wk	4.85 (4.20, 5.50) (Ref)	
									1/wk	0.33 (0.18, 0.48)	
									>1/wk	0.51 (0.32, 0.69)	

Table 2 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
									Combined intelligence score:		
									<1/wk	4.91 (4.26, 5.55)(Ref)	
									1/wk	0.36 (0.21, 0.51)	
									>1/wk	0.58 (0.39, 0.77)	
Mendez 2008 [1]	Prospective cohort (INMA- Menorca)	Menorca, Spain	1997-2000	392	4 yrs	Child sea-food intake at 4 yrs.	Semiquan-titative FFQ	MSCA	Child Cognition by seafood intake: *Mean General Cognitive Score for fish:*	p>0.10	Child: sex, birthweight, gestational age, breastfeeding duration, current grade, evaluating psychologist; Mother: education, parity.
									≤1 ser/wk	98.0 SD: 16.0	
									>1-2 ser/wk	99.3 SD: 14.4	
									>2-3 ser/wk	100.7 SD: 13.2	
									>3 ser/wk	100.4 SD: 15.1	
									Mean General Cognitive Score for other seafood:		
									≤0.5 ser/wk	101.0 SD: 14.0	
									>0.5-1 ser/wk	99.0 SD: 14.6	
									>1 ser/wk	98.0 SD: 15.2	
Theodore 2009 [17]	Prospective cohort study based on an initial case–control study. (ABC Study)	Auckland and Waitemata Healthcare areas, New Zealand	1995-2003	3.5 yrs: 531 7 yrs: 589	3.5 and 7 yrs	Child sea-food intake	Semiquan-titative FFQ at 3.5 and 7 yrs (Number of seafood items NR)	Stanford-Binet Intelligence Scales (3.5yrs), and WISC –III (7yrs)	Mean difference in intelligence score at ages:		3.5yrs: gestation, parity, gender, maternal school-leaving age, parental occupation, marital status, maternal BMI, examiner. 7yrs: Gender, gestation, maternal smoking during pregnancy, maternal age, maternal marital status, birth order at 7yrs, parental occupation, parental education, child BMI at 7yrs, Maternal BMI, examiner.
									7 yrs:	p=0.004	
									<1/wk	0.00(Ref)	
									≥1/wk	3.64 (0.74, 6.54)	
									3.5 yrs:	p=0.37	
									<1/wk	0.00(Ref)	
									≥1/wk	1.17 (−3.70, 1.36)	

Table 2 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
Kim 2009 [20]	Prospective register-based follow-up of a questionnaire survey	Västra, Götaland Region, Sweden	2000-2001	9448	School age	Seafood intake by child	Questionnaire on dietary habits	School grades from Swedish pupil register	Change in grade estimate by seafood servings :		Parent's education, physical activity, gender, type of housing, residence area, dishwasher ownership
									<1/wk	119.0 (112.3-125.7) (Ref)	
									1/wk	14.5 (11.8, 17.1)	
									>1/wk	19.9 (16.5, 23.3)	
Freire 2010 [18•]	Prospective cohort (INMA - Granada)	Province of Granada, Spain	2000-2006	72 males	48-57 mo	Child fish intake	Semiquantitative FFQ (4 seafood ítems)	MSCA	Mean difference for GCS by seafood intake:		Child: duration of breastfeeding, passive smoking, weight and length at birth and 4 yrs, age at introduction to different food groups, place of residence Mother: socio-demographic characteristics, reproductive history, parity, smoking in pregnancy
									All fish:	p =0.02	
									GCS AM:		
									<3ser/wk:	104.9 (99.7, 110.1)	
									≥3ser/wk:	97.0 (92.6, 101.4)	
									Oily fish:	p=0.72	
									GCS AM:		
									Rarely/never	100.5 (94.2, 106.9)	
									1-3 ser/mo	97.8 (90.5, 105.2)	
									≥1 ser/wk	101.1 (96.0, 106.3)	
									Canned fish:	p=0.19	
									GCS AM:		
									Rarely/never	97.9 (92.6, 103.3)	
									1-3 ser/mo	98.3 (91.2, 105.5)	
									≥1 ser/wk	104.9 (99.0, 110.9)	
									White fish:	p=0.71	
									GCS AM:		
									Rarely/never		

Table 2 (continued)

Reference, year	Study design	Population	Study period	N (Cases/ Non-cases)	Age at Outcome assessment	Type of exposure	Seafood assessment	Outcome Measurement	Associations Studied	Effect Estimates (95% Confidence Interval)	Covariates
										96.9 (89.2, 104.6)	
									1-3 ser/mo	98.9 (90.0, 107.8)	
									1 ser/wk	102.4 (95.8, 108.9)	
									≥2 ser/wk	99.3 (93.9, 104.7)	
									Fried fish:	p=0.12	
									GCS AM:		
									Rarely/never	105.6 (96.3, 115.0)	
									1-3 ser/mo	103.5 (90.7, 116.2)	
									1 ser/wk	101.3 (96.5, 106.2)	
									≥2 ser/wk	93.6 (86.6, 100.6)	
De Groot 2012 [19]	Cross-Sectional	Secondary schools in South Holland	NR	700	12-18 yrs	Seafood intake by child	Self-report question-naire	YSR attention subscale, AVT, end of term grades for Dutch, English, Mathematics.	Contrast analyses AVT	Quadratic p=0.01	Parental education, sex, age, educational track.
									Contrast analyses:		
									Academic performance	Quadratic p=0.01	
									YSR attention subscale	p=0.42 Coefficients NR	

The results with adjustment for most covariates are reported for each article. Associations for dichotomous measures of exposure are selected if both dichotomous and continuous measures are presented. For the study by Daniels 2004, only the results for low test scores were retrieved as the results for high test scores were consistent in the opposite direction.

ABC Auckland Birthweight Collaborative study, *AM* Arithmetic Mean, *ALSPAC* Avon Longitudinal Study of Pregnancy and Childhood, *AVT* Amsterdam Vocabulary Test, *DDST* ALSPAC adaptation of Denver Developmental Screening Test, *FFQ* Food Frequency Questionnaire, *GCS* Global Cognitive Score, *INMA* Child and Environment Project, *MCDI* ALSPAC adaptation of MacArthur Communicative Development Inventory, *mo* months, *MSCA* McCarthy Scales of Children's Abilities, *NR* Not reported, *NS* non-significant, *ser* servings, *UK* United Kingdom, *WISC-III* Weschler Intelligence Scale for Children-III, *wk* week, *YSR* Youth Self-Report, *yrs* years.

Table 3 Association between seafood intake and neurodevelopmental endpoints before and after adjustment for mercury and/or persistent organic pollutants

Study	Time of Exposure	Association studied	Effect size before adjustment	Effect size after adjustment for mercury or POPs	Model includes
Daniels, 2004 [15]	Prenatal	OR by seafood intake: MCDI Social Activity:		NR. (association remained similar)	Cord blood mercury concentrations
		Rarely/never	1.00 (Ref)		
		1 / 2 wks	0.8 (0.6, 1.1)		
		1-3 /wk	0.6 (0.5, 0.8)		
		4+ /wk	0.7 (0.5, 0.9)		
		MCDI Vocabulary comprehension:			
		Rarely/never	1.00 (Ref)		
		1 / 2 wks	0.8 (0.6, 1.1)		
		1-3 /wk	0.8 (0.6, 1.0)		
		4+ /wk	0.9 (0.7, 1.2)		
		DDST Language:			
		Rarely/never	1.00 (Ref)		
		1 / 2 wks	0.8 (0.6, 1.2)		
		1-3ser/wk:	0.7 (0.5-0.9)		
		4+ser/wk:	0.7 (0.5-0.9)		
		DDST Social:			
		Rarely/never	1.00 (Ref)		
		1/2wks	1.2 (0.8, 1.8)		
		1-3/wk	1.0 (0.7-1.4)		
		4+/wk	1.1 (0.7-1.5)		
		Mean Developmental Assessment Scores by seafood servings: MCDI			
		Vocabulary Comprehension:			
		Rarely/never	68.2 (66.3,70.5)		
		1/ 2 wks	70.9 (69.0, 72.9)		
		1-3/wk	73.0 (71.2, 74.8)		
		4+/wk	71.9 (70.5-73.8)		
		β± SD (p) per ounce increase of fish per wk *MCDI*	0.11 ± 0.05 (0.03)		
		Social Activity:			
		Rarely/never	16.4 (16.0, 16.7)		
		1/ 2 wks	17.0 (16.6, 17.3)		
		1-3/wk	17.1 (16.8, 17.4)		
		4+/wk	17.2 (16.9, 17.5)		
		β± SD (p) per ounce increase of fish per wk	0.03 ± 0.009 (0.002)		
		DDST Total:			
		Rarely/never	37.2 (36.9, 37.6)		
		1/ 2 wks	37.7 (37.3, 38.0)		
		1-3/wk	37.9 (37.6, 38.2)		
		4+/wk	37.8 (37.5, 38.1)		
		β± SD (p) per ounce increase of fish per wk	0.02 ± 0.01 (0.03)		

Table 3 (continued)

Study	Time of Exposure	Association studied	Effect size before adjustment	Effect size after adjustment for mercury or POPs	Model includes
		DDST Language:			
		Rarely/never	7.1 (6.9, 7.3)		
		1/ 2 wks	7.4 (7.2, 7.5)		
		1-3/wk	7.4 (7.3, 7.5)		
		4+/wk	7.4 (7.3, 7.6)		
		β± SD (p) per ounce increase of fish per wk	0.01 ± 0.004 (0.004)		
		DDST Social:			
		Rarely/never	8.1 (7.9, 8.2)		
		1/ 2 wks	8.1 (8.0, 8.2)		
		1-3/wk	8.2 (8.1, 8.3)		
		4+/wk	8.2 (8.0, 8.3)		
		β± SD (p) per ounce increase of fish per wk	0.002 ± 0.004 (0.5)		
Oken, 2005 [22]	Prenatal	Change in VRM Score per weekly seafood serving	2.8 (0.2, 5.4)*	4.0 (1.3, 6.7)	Maternal hair mercury concentrations
Oken, 2008 [24]	Prenatal	*Change in outcome by seafood servings per wk:*			Maternal erythrocyte mercury concentrations
		PPVT score:			
		>2/wk	1.2 (−3.5, 6.0)*	2.2 (−2.6, 7.0)	
		≤2/wk	−2.1 (−5.7, 1.4)*	−1.8 (−5.4, 1.8)	
		Never	0 (Ref)	0 (Ref)	
		WRAVMA drawing score:			
		>2/wk	6.0 (1.8, 10.2)*	6.4 (2.1, 10.7)	
		≤2/wk	1.2 (−2.0, 4.4)*	1.3 (−1.8, 4.5)	
		Never	0 (Ref)	0 (Ref)	
		WRAVMA pegboard Score:			
		>2/wk	2.9 (−1.4, 7.1)*	3.5 (−0.8, 7.8)	
		≤2/wk	−0.7 (−3.9, 2.4)*	−0.5 (3.7, 2.7)	
		Never	0 (Ref)	0 (Ref)	
		WRAVMA matching score:			
		>2/wk	2.8 (−3.1, 8.6)*	4.1 (−1.8, 10.0)	
		≤2/wk	1.8 (−2.6, 6.3)*	2.3 (−2.1, 6.7)	
		Never	0 (Ref)	0 (Ref)	
		WRAVMA total score:			
		>2/wk	5.3 (0.9, 9.6)*	6.4 (2.0, 10.8)	
		≤2/wk	1.1 (−2.2, 4.4)*	1.5 (−1.8, 4.7)	
		Never	0 (Ref)	0 (Ref)	
Mendez, 2008 [1]	Pre and Post-natal	Change in MSCA scores by seafood servings *Breast-fed for <6mo*		NR (association remained similar)	Cord blood DDT, DDE, and PCB concentrations were examined but excluded from the final model
		General Cognitive:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	2.7 (−1.2, 6.5)		
		2-3 fish/wk	11.0 (5.0, 17.1)		
		>3 fish/wk	−1.2 (−9.8, 7.3)		
		Perceptual-Performance:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	2.3 (−1.5, 6.1)		

Table 3 (continued)

Study	Time of Exposure	Association studied	Effect size before adjustment	Effect size after adjustment for mercury or POPs	Model includes
		2-3 fish/wk	10.0 (4.1, 16.0)		
		>3 fish/wk	1.5 (−7.0, 9.9)		
		Memory:			
		≤1 fish/wk	O (Ref)		
		1-2 fish/wk	2.0 (−2.1, 6.1)		
		2-3 fish/wk	10.5 (4.1, 16.9)		
		>3 fish/wk	−3.3 (−12.4, 5.8)		
		Verbal:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	2.2 (−1.8, 6.3)		
		2-3 fish/wk	9.9 (3.5, 16.2)		
		>3 fish/wk	−1.8 (−10.8, 7,2)		
		Numeric:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	2.1 (−1.8, 6.0)		
		2-3 fish/wk	6.8 (0.7, 12.8)		
		>3 fish/wk	−2.3 (−10.9, 6.3)		
		Motor Skills:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	2.1 (−1.8, 6.0)		
		2-3 fish/wk	6.7 (0.7, 12.8)		
		>3 fish/wk	−2.3 (−10.9, 6.3)		
		Breast-fed for ≥6mo			
		General Cognitive:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	−0.7 (−7.0, 5.7)		
		2-3 fish/wk	−0.7 (−8.3, 6.9)		
		>3 fish/wk	−5.3 (−17.9, 7.3)		
		Perceptual-Performance:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	−0.2 (−6.1, 6.6)		
		2-3 fish/wk	0.8 (−6.8, 8.5)		
		>3 fish/wk	−0.2 (−12.4, 12.9)		
		Memory:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	−1.8 (−8.2, 4.5)		
		2-3 fish/wk	−4.6 (−12.3, 3.3)		
		>3 fish/wk	−12.7 (−25.5, 0.0)		
		Verbal:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	−1.1 (−7.7, 5.4)		
		2-3 fish/wk	−0.5 (−8.3, 7.4)		
		>3 fish/wk	−8.2 (−21.3, 4.9)		
		Numeric:			
		≤1 fish/wk	0 (Ref)		

Table 3 (continued)

Study	Time of Exposure	Association studied	Effect size before adjustment	Effect size after adjustment for mercury or POPs	Model includes
		1-2 fish/wk	−0.5 (−6.8, 5.9)		
		2-3 fish/wk	−3.1 (−10.7, 4.6)		
		>3 fish/wk	−2.8 (−15.5, 9.9)		
		Motor Skills:			
		≤1 fish/wk	0 (Ref)		
		1-2 fish/wk	−2.1 (−8.5, 4.3)		
		2-3 fish/wk	−0.8 (−8.5, 7.0)		
		>3 fish/wk	−2.1 (−14.8, 10.7)		
Freire, 2010 [18•]	Postnatal	Change in General Cognitive Score (MSCA) by seafood servings:	−7.9 (p =0.02)		Child hair mercury concentrations
		Oily fish: *GCS AM:*	p=0.72	β= 1.02 (−6.39, 8.42)	
		Rarely/never	100.5 (94.2, 106.9)		
		1-3 ser/mo	97.8 (90.5, 105.2)		
		≥1 ser/wk	101.1 (96.0, 106.3)		
		Canned fish: *GCS AM:*	p=0.19	β = 7.98 (0.28, 15.68)	
		Rarely/never	97.9 (92.6, 103.3)		
		1-3 ser/mo	98.3 (91.2, 105.5)		
		≥1 ser/wk	104.9 (99.0, 110.9)		
		White fish: *GCS AM:*	p=0.71	β= −3.32 (−11.09, 4.46)	
		Rarely/never	96.9 (89.2, 104.6)		
		1-3 ser/mo	98.9 (90.0, 107.8)		
		1 ser/wk	102.4 (95.8, 108.9)		
		≥2 ser/wk	99.3 (93.9, 104.7)		
		Fried fish: *GCS AM:*	p=0.12	β = −4.70 (−12.34, 2.94)	
		Rarely/never	105.6 (96.3, 115.0)		
		1-3 ser/mo	103.5 (90.7, 116.2)		
		1 ser/wk	101.3 (96.5, 106.2)		
		≥2 ser/wk	93.6 (86.6, 100.6)		
Suzuki, 2010 [26]	Prenatal	Positive change in NBAS motor cluster by maternal seafood intake	p=0.10 (coefficients NR)	p<0.05** (coefficients NR)	Maternal hair mercury concentrations Cord blood PCB concentrations
Sagiv, 2012 [27•]	Prenatal	*RR for CRS- Teachers' version by seafood intake:*: Inattentive			Maternal hair mercury Adjustment by cord serum PCB level NR
		≤2 ser/wk	1 (Ref)	1 (Ref)	
		>2 ser/wk	0.6 (0.4, 0.8)*	0.6 (0.4, 0.9)	
		Impulsive/hyperactive			
		≤2 ser/wk	1 (Ref)	1 (Ref)	

Table 3 (continued)

Study	Time of Exposure	Association studied	Effect size before adjustment	Effect size after adjustment for mercury or POPs	Model includes
		>2 ser/wk	0.4 (0.2, 0.6)*	0.4 (0.2-0.6)	
		Total			
		≤2 ser/wk	1 (Ref)	1 (Ref)	
		>2 ser/wk	(0.4, 0.7)*	0.6 (0.4, 0.9)	
		Change for WISC-III by seafood intake:			
		Processing speed			
		≤2 ser/wk	0 (Ref)	0 (Ref)	
		>2 ser/wk	1.3 (−1.2, 3.8)*	2.0 (−0.8, 4.8)	
		Freedom from distractibility			
		≤2 ser/wk	0 (Ref)	0 (Ref)	
		>2 ser/wk	0.3 (−1.9, 2.6)*	1.5 (−1.1, 4.0)	
		CPT:			
		β for Mean reaction time			
		≤2 ser/wk	0 (Ref)	0 (Ref)	
		>2 ser/wk	7.7 (−3.8, 19.3)*	10.1 (−3.9, 24.1)	
		β for reaction time variability			
		≤2 ser/wk	0 (Ref)	0 (Ref)	
		>2 ser/wk	(−3.6, 6.7)*	−0.5 (−6.3, 5.4)	
		RR for Errors of Omission			
		≤2 ser/wk	1 (Ref)	1(Ref)	
		>2 ser/wk	(0.7, 1.2)*	(0.7, 1.2)	
		RR for Errors of Comission			
		≤2 ser/wk	1 (Ref)	1(Ref)	
		>2 ser/wk	1.1 (1.0, 1.3)	1.1 (0.9, 1.3)	

*After adjustment for participant characteristics ** Adjustment for toxicants but not participant characteristics

AM Arithmetic Mean, *DDE* Dichlorodiphenyldichloroethylene, *DDST* ALSPAC adaptation of Denver Developmental Screening Test, *DDT* Dichlorodiphenyltrichlorethane, *MCDI* ALSPAC adaptation of MacArthur Children's Development Inventory, *MSCA* McCarthy Scales of Children's Abilities, *NBAS* Neonatal Behavioral Assessment Scale, *PCB* Polychlorinated Biphenyl, *POPs* Persitent Organic Pollutants, *VRM* Visual Recognition Memory, *ser* servings, *wk* week, *NR* not reported

(Table 3), and WRAVMA at 3 years of age [24]. No significant differences were found for vocabulary using the PPVT [24]. However, results for processing speed, freedom from distractibility [27•], and performance IQ [25] have not shown clear associations.

With regards to behavioral outcomes, prenatal intake of fish was found to be inversely related to inattention, hyperactivity/impulsivity, and total score when evaluated by Conner's Rating Scale–Teacher's Version [27•]. An inverse association was also noted for hyperactivity as measured by SDQ [25]. No significant differences were found for other behavioral problems, peer problems, or emotional difficulties [25].

Some studies have evaluated different types of seafood [1, 16, 18•, 24], showing that the type of seafood consumed during pregnancy can also be relevant. In a Spanish cohort, while fish was found to have positive effects, other kinds of seafood were associated with reduced cognitive scores [1] (Table 1). There may also be differences between fish types, such as was found in a study from the UK, in which the appearance of an effect of fish intake on behavior depended on the type of fish that had been consumed [25] (Table 1). In this case, only oily fish was inversely correlated with hyperactivity in childhood.

Few studies have evaluated the association of the same exposure with developmental outcomes on individuals with different characteristics. For example, a Spanish cohort study including 392 4-year-old children reported that prenatal fish intake of two or three servings per week was positively associated with higher IQ in children who had been breastfed for less than 6 months [1]. No association was found for children who had been breastfed for longer. However, no association or maybe even an inverse association was found for fish intake of three servings per week with no differences by breastfeeding. Maternal seafood intake may influence the neurodevelopment of their offspring not only through seafood consumption directly, but also through the relative composition of different food groups included in the diet. For instance, a Greek study [28] found that seafood intake was not associated with cerebral palsy, but an association was observed with the meat:fish dietary ratio during pregnancy.

Studies of Seafood Intake During Childhood

Seafood intake during childhood has been related to achieving better development [15], higher intelligence [17], and increased cognition scores [18•] in several studies. Other studies, however, reported no association between seafood intake during childhood and developmental outcomes. In a Spanish cohort, despite a positive tendency, no significant differences were found on the MSCA score according to child intake of seafood [1]. It may also be of importance to consider the type of fish that is eaten or the way it is prepared. In the INMA-Granada subcohort [18•] oily and canned fish were positively associated, while white or fried fish were negatively associated with cognition. The same study found that when children consumed three or more servings of fish per week, general cognitive scores decreased, implying that the quantity of fish intake may also have a specific role.

Studies of Seafood Intake during Adolescence

We found three articles that considered the relationship between seafood intake and neurodevelopment during adolescence [19–21] (Table 2). In these studies, dietary exposures were measured approximately 1-3 years before evaluation. Seafood consumption during adolescence was associated with higher intelligence scores, better visuospatial performance [21], and improved school grades [20]. However, in one of the studies [19], despite a positive association of moderate consumption, the benefits of seafood intake disappeared at higher levels of seafood intake.

Dose-Response Relationship

Despite concern surrounding the possible negative effects of fish intake due to contamination with toxicants, most of the identified studies [1, 6–13, 14••, 15–17, 18•, 19, 21] found a positive association between seafood intake and neurodevelopment outcomes. For example, in the ALSPAC study in the UK [10], a clear dose-response relationship was observed, higher amounts of seafood intake during pregnancy being associated with better developmental scores both before and after adjustment for covariates.

Although moderate seafood intake seemed beneficial across a majority of studies, some studies found that higher seafood intake could be correlated to lessening or reversal of the association between seafood and neurodevelopmental outcomes [1, 18•, 19, 25]. This has been described by De Groot as an upside-down U-shape relationship [19]. These findings may indicate that the relationship between seafood intake and cognition is not linear or that other negative influences strengthened by increasing the amount of seafood could counter its positive effects. Moreover, it is likely that the effects do not depend solely on the amount of seafood *per se* but on the type of seafood ingested [18•, 25], which also raises the question whether the dose-response relationship varies between seafood types.

Summary of Findings by Age of Outcome Examination

A summary of the association between seafood intake and neurodevelopmental outcomes by the age of examination is shown in Table 4.

Discussion

This review shows a relatively small number of studies evaluating the association of seafood intake pre- and postnatally and neurodevelopment during childhood and adolescence. Most of the studies available were population-based prospective cohorts conducted in developed countries. Most studies showed positive associations between pre- and postnatal fish

Table 4 Association between seafood intake and neurodevelopment endpoints by age of outcome assessment

Age	*Reported outcomes*
Infancy and toddlerhood	Marginally improved motor development [26] Better communicative and social development [10, 15] Higher infant cognition score [22] Higher developmental scores [23]
Childhood	Possible inverse association with cerebral palsy [28] Better visual cortex maturation and visual-motor development [16, 24] Better verbal IQ [10] Higher IQ [1, 17, 18•, 25] Less inattention [27•] Less hyperactivity/impulsivity [25, 27•] Improved social behavior [10] *Attenuation/disappearance of positive association in highest seafood intake group [*1, 18•, 25]
Adolescence	Better school grades [19, 20] Higher IQ [21] Better visuospatial performance [21] *Disappearance of positive association in the group with higher than recommended seafood* intake [19]

intake and neurodevelopment. The exposure measures were generally based on semiquantitative food frequency questionnaires reported by the mothers. The children's age at examination ranged from newborns to teenagers, and the outcome assessments included neurological, behavioral, and cognitive functioning. Most studies adjusted their models for sociodemographic characteristics. A few studies additionally controlled for the potential neurotoxic effect of pollutants related to seafood, such as methylmercury and POPs. An inverted U-shape trend was reported in some of the published work.

Semiquantitative food frequency questionnaires are well-established tools to assess seafood intake. They are widely used in standardized forms and have cross-cultural applicability [1]. Most of the studies reviewed here used them to assess seafood intake; however, there was no homogeneity in relation to the categorization of the exposure. The tendency was to adapt the frequency intake categories to the sample levels without following any global agreement based on international recommendations (i.e., UK's Food Standards Agency). However, a few studies used cutoff points of two servings per week or 340 g per week (Tables 1 and 2). An important number of studies only measured all seafood intake without going further in their analyses to evaluate different types separately, such as oily fish, white fish, and shellfish. It is unclear if this was due to the limited sample size or lack of data on type of fish intake frequency. The use of self-reported data is a major limitation in this field of research due to an increased level of noise related to the person's subjectivity in remembering food habits and the potential influence of individual's socio-cultural background. Additionally, healthy nutritional habits that include more fish intake are also related to higher maternal IQ and education level, and lower smoking habits during pregnancy [24, 25]. We cannot rule out some residual confounding explaining the association with neurodevelopment. The assessment of some biomarkers of fish intake, such as serum docosahexaenoic acid (DHA) levels, strengthened only a couple of the reported seafood intake findings [14••, 16].

Fish intake was inversely associated with a variety of outcomes, including improved neurological functions and lower disorder prevalence such as superior foveal stereoacuity and cerebral palsy; better performances in cognitive functions related to verbal, memory, and visual-performance abilities; and improved behavioral outcomes related to hyperactivity, social competence, and school grades (Tables 1, 2, and 4). Even though the exact mechanisms explaining these benefits are not clear, these findings may indicate that the essential nutrients such as omega-3 fatty acids derived from fish globally enhance neurodevelopment in both early and later stages. For instance, DHA may play an important role through several biological pathways during neuron differentiation and migration, axonal and synaptic growth, and synaptic connections until the early 20s. Deficit of dietary DHA is also known to alter neuronal myelination and cause mental retardation, and improvement is observed when DHA is restored [4, 29]. Additionally, animal studies have linked insufficiency of omega-3 fatty acids to alterations in neurotransmitters [30]. This could be related to behavioral and emotional changes.

Currently there is no agreement on which is the best-suited test to assess neurodevelopmental outcomes. Each study chose different tests and scales to assess similar functions. Heterogeneity of study outcomes will need to be considered in future projects trying to pool the data from different cohorts. We would suggest a harmonization of the tests in future studies. In relation to general cognitive assessments, it is important to follow tools that are internationally validated, but chosen depending on the age of the child such as the Bayley Scales during early life, followed by the MSCA scales or Wechsler Preschool and Primary Scale of Intelligence (WPPSI), WISC, and then Wechsler Adult Intelligence Scale (WAIS). Regarding less extended computer-based tests, we suggest following common paradigms in the neuropsychology [31] and using some of these tests: the CPT, Attention Network Task (ANT) or Stroop, Raven Colored Progressive Matrices, Trail Making Test (TMT), and N-BACK, for example. It is important not to use tests that may be culturally biased; one way is avoiding the assessment of verbal skills and school grades. Behavioral rating scales are more indirect measurements [32]; however, from these scales we can get important information about complementary behavioral areas during childhood, such as personality traits and social competence. Probably, the most widely used behavioral scales in epidemiological studies are the Child Behavior Check List (CBCL), SDQ, and Conner's Rating Scale.

A few studies observed an inverted U-shape pattern in the association between seafood intake and neurodevelopment (Tables 1 and 2), while most studies tended to show positive associations across all seafood categories. Those inverted U-shape studies attributed their findings to the higher pollutant exposure in the heavy seafood eaters (i.e., more than two servings per week), particularly if the type of fish is large and oily. However, oily fish also contains the highest DHA concentrations, which may counterbalance the neurotoxic effects. The few studies that were able to separate the exposure by type of seafood described conflicting results in relation to oily seafood type; in some cases oily fish was beneficial and in others it was less positive (Tables 1 and 2). Some studies argued that the sample size of the highest seafood intake category was too small to provide any conclusive finding [1].

Methylmercury and POPs are well-established neurotoxicants in populations where local seafood intake is the major dietary component[2,116]. The role of potential confounding by persistent pollutants such methylmercury and

POPs in populations with low-moderate seafood intake, however, is less clear. In our review, the coefficients tended to increase after statistically controlling for these pollutants. Nevertheless, the coefficient change seems relatively small in relation to the overall beneficial association from seafood intake. Similar to the inverted U-shape trend among heavy seafood eaters, the strengthening of the association after adjustment for seafood pollutants could point to some potential counter-balanced effect from seafood toxicants. The high correlation between seafood intake and seafood pollutants, however, can make it very difficult to distinguish between the beneficial and detrimental effects of seafood intake, especially at low-moderate levels.

The general findings from the reviewed studies point toward a beneficial effect of consuming a moderate amount of seafood during pregnancy and early life. Overall, the observational studies included in this review support that a moderate amount of fish intake is beneficial to neurodevelopment. The findings from these observational studies are supported by a clinical trial that found higher scores in writing and reading tests after an intervention with a fish flour bread spread over a 6-month period [14••]. The majority of studies included in this review were carried out in developed regions, and exposure to toxicants may be more important in some developing areas. On the other hand, it would also be wise to consider that in today's globalized market, the seafood that is consumed in one part of the world could easily come from a very different location.

As a precautionary approach, it is preferable during these life periods to avoid heavy intakes of large oily fish rich in methylmercury and POPs such as swordfish and tuna. This is important because of the observation in several studies of the attenuation or reversal of beneficial effects in the groups with the highest seafood consumption. The evidence gathered by this review suggests that the dose-response relationship is not linear for improved neurodevelopmental outcomes. This may be because of the increasing amounts of neurotoxicants ingested as more seafood is eaten; it may be that more toxic effects occur in diets with heavy seafood content. As to the type of seafood that should be recommended, this is not clear yet.

Information to the public should be managed with care. We recommend acknowledging the risk of exposure that large amounts of seafood per week can represent (especially of species with high mercury content), while also noting the benefits of moderate intake. If both aspects are not presented, individuals could limit their intake of seafood excessively, which not only reduces the ingestion of toxicants but also that of essential nutrients found in fish that appear to improve neurodevelopment. In a US study, the offspring of mothers who had followed US guidelines advising diets with less than 340 g per week of fish were more likely to have suboptimum neurodevelopmental outcomes than the offspring of mothers who had consumed more than the recommended amount [10]. In this direction, governments and non-governmental institutions should collaborate in taking steps towards achieving equitable access to un-contaminated fish as part of a balanced diet, prioritizing pregnant women and children within socially, economically or environmentally vulnerable groups.

Larger cohort studies need to further address uncertainties and focus on wider ranges of frequency intakes and types of seafood. Using standard cutoffs based on international recommendations to classify the exposure and based on agreement on the neuropsychological tools used for assessments will help to increase comparability across studies, facilitating future efforts to merge the data for gaining power. Additionally, the measurements of fish intake biomarkers, such as blood DHA concentration, may help to disentangle the potential biological pathways and improve the validity of semiquantitative food frequency questionnaires. The use of neuroimaging in studies could also be contemplated in order to improve the understanding of the biological mechanisms through which fish intake is beneficial. Moreover, interventional studies are strongly required to rule out possible residual confounding and strengthen causality hypotheses.

Conclusion

Several studies conducted in the last 20 years support a beneficial role of seafood intake during neurodevelopment, both pre- and postnatally. Seafood intake benefits could cover an important range of behaviors, including neurological and cognitive functions, hyperactivity, social competence and school performance. Important questions remain, especially regarding the type of seafood, the shape of the dose response, and potential harmful exposures at the high end of seafood exposure. Larger cohort studies with more harmonized outcome assessments and detailed seafood intake information are needed to discriminate whether the positive associations are global or related to fish type and intake frequency. Interventional studies are strongly recommended. Finally and most importantly, these findings support the idea that steps should be taken to reduce contamination of water environments to continue having seafood as part of a healthy diet.

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Compliance with Ethics Guidelines

Conflict of Interest Claudia B. Avella-Garcia and Jordi Julvez declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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