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The Association Between Maternal Prenatal Fish Intake and Child Autism-Related Traits in the EARLI and HOME Studies

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Abstract

We examined the association between prenatal fish intake and child autism-related traits according to Social Responsiveness Scale (SRS) and cognitive development scores in two US prospective pregnancy cohorts. In adjusted linear regression analyses, higher maternal fish intake in the second

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half of pregnancy was associated with increased child autism traits (higher raw SRS scores; ß = 5.60, 95%CI 1.76, 12.97). Differences by fish type were suggested; shellfish and large fish species were associated with increases, and salmon with decreases, in child SRS scores. Clear patterns with cognitive scores in the two cohorts were not observed. Future work should further evaluate potential critical windows of prenatal fish intake, and the role of different fish types in association with child autism-related outcomes.

Keywords

Autism; Maternal fish intake; Prenatal diet; Social responsiveness scale; Quantitative traits

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition defined by social communication deficits and restricted repetitive behaviors, which present along a heterogeneous spectrum (APA 2013). Maternal diet is known to influence fetal neurodevelopment, as evidenced by established associations between prenatal nutrient deprivation and offspring schizophrenia, and between folate and neural tube defects, yet research devoted to the role of maternal diet in ASD has only recently emerged. Maternal fish intake is a key source of nutrients such as polyunsaturated fatty acids (PUFAs) known to be critical for fetal brain development (Haggarty 2004; Liu et al. 2015). In particular, fish is the primary source of docosahexaenoic acid (DHA), the most abundant fatty acid in the brain. DHA and other PUFAs have been shown to be involved in neurogenesis, neuronal differentiation, and neurotransmission processes with some evidence for disruption in ASD (Wegiel et al. 2010). However, only a handful of studies, with limitations and conflicting findings, have considered the potential role of prenatal PUFAs in ASD (Julvez et al. 2016; Lyall et al. 2013).

A wealth of literature has focused on the association between maternal fish intake and child neurodevelopmental outcomes (Daniels et al. 2004; Gale et al. 2008; Hibbeln et al. 2007; Julvez et al. 2016; Llop et al. 2017; Lyall et al. 2013; Mendez et al. 2009; Oken and Bellinger 2008; Oken et al. 2005, 2008a, b; Valent et al. 2013). Though some conflicting findings exist (Grandjean et al. 1997), overall, findings support that higher prenatal fish intake is associated with improved neurodevelopmental outcomes, including higher developmental and cognitive scores, and modest increases in intelligence quotient (IQ) scores (Daniels et al. 2004; Gale et al. 2008; Hibbeln et al. 2007; Julvez et al. 2016). Discrepancies in results from prior work examining associations with neurodevelopmental outcomes may stem from differences in the timing of exposures and outcomes, the mode of exposure (supplement vs dietary intake), and/or consideration of mercury levels also present in some fish (Oken and Bellinger 2008). Overall, most studies with data on both prenatal mercury and fish intake have reported either no associations of neurodevelopmental outcomes with mercury levels, or stronger positive associations with fish intake when adjusting for methyl mercury levels (Davidson et al. 2006; Golding et al. 2018; McKean et al. 2015; Myers et al. 2003; Oken and Bellinger 2008). These findings generally support the influence of beneficial fats in fish over and above the potential harmful effects of mercury,

though there is also evidence that the type of fish consumed should be considered (Oken and Bellinger 2008), as larger fish may bioaccumulate more mercury and other toxicants.

Few studies have examined fish intake during pregnancy in association with ASD or ASD-traits specifically. A handful of investigations have considered the potential role of methyl mercury in fish in association with ASD, though did not directly examine fish intake; these generally have not supported associations between methyl mercury in fish and ASD (Golding et al. 2018; McKean et al. 2015). In the Nurses' Health Study II, though significant inverse associations were found between overall dietary PUFA intake and child ASD, no association between maternal fish consumption and child ASD was found (Lyall et al. 2013). However, fish intake was relatively low in this US population. The Generation R study of the Netherlands also found no association between maternal fish intake and a subset of items from the Social Responsiveness Scale (SRS), a measure capturing ASD-related traits (Steenweg-de Graaff et al. 2016). In contrast, a Spanish cohort study reported decreases in child ASD symptoms according to scores on the Childhood Asperger Syndrome Test (as well as improved cognitive scores on the McCarthy scales) with higher maternal fatty fish (typically defined as larger fish such as tuna, shark, and mackerel) consumption (Julvez et al. 2016). In addition, a small case–control study in China suggested an association between periconception intake of grass carp and ASD (Gao et al. 2016). Two studies, including the Nurses' cohort and a large Norwegian study, have both reported no association between fish oil supplementation during pregnancy and ASD diagnosis (Lyall et al. 2013; Suren et al. 2013). Thus, there is conflicting and limited literature examining prenatal fish intake in association with ASD-related outcomes, and information on potential effects of timing of fish intake during pregnancy is lacking.

Given these gaps, we sought to examine the association between frequency and type of maternal fish intake during pregnancy and child ASD traits and cognitive development scores. Given evidence that uptake of PUFAs in the developing brain is most rapid in the third trimester (Haggarty 2010), and that critical windows have been suggested for other dietary factors in association with ASD, (Lyall et al. 2014; Schmidt et al. 2012) we also sought to examine associations during different time periods in pregnancy. Our analyses focused on continuous ASD-related scores that capture traits along a continuum, thereby enabling assessment of associations not just with features consistent with a clinical diagnosis of ASD, but also with sub-clinical characteristics. Furthermore, by examining both ASD-specific traits and cognitive scores in the same children, comparison across developmental outcomes may shed light on the specificity of associations.

Methods

Study Participants

Participants in this study were drawn from two prospective pregnancy cohorts: the Early Autism Risk Longitudinal Investigation (EARLI) (Newschaffer et al. 2012) and the Health Outcomes and Measures of the Environment (HOME) (Braun et al. 2017) Study. EARLI is an enriched-risk ASD cohort that enrolled women who already had a child with confirmed ASD and followed them through a subsequent pregnancy until he/she reached 3 years of age. Eligibility criteria included being less than 29 weeks pregnant, speaking English or Spanish,

being 18 or older, and living within two hours of the site where the study was being conducted. Mothers were recruited at 4 sites: Drexel/CHOP; Johns Hopkins University; UC Davis; and Northern CA Kaiser Permanente. A total of 237 women were enrolled, and children were followed from 2009 to 2012. The HOME Study enrolled 401 pregnant women drawn from nine prenatal care clinics in the greater Cincinnati, OH metropolitan area from March 2003 to January 2006, and followed children through 12 years of age (Braun et al. 2017). Inclusion criteria for women enrolling into HOME were: less than 19 weeks gestation, older than 18, English speaking, did not have diabetes, cancer, HIV infection or bipolar disorder, living in a home that was built before 1978, not taking medications for seizure or thyroid disorders, and planning to deliver their child at one of the three hospitals in the region (Braun et al. 2017).

Both studies conducted extensive phenotyping of children over the follow-up periods; EARLI saw families at 12, 24, and 36 months, while HOME completed study visits annually from 1 to 5 years, 8 years, and 12 years. Mothers/caregivers in both studies gave written informed consent to study procedures, which were reviewed and approved by local IRBs. To be included in analyses, information on prenatal diet (and, specifically, reporting of fish intake for at least one time period) and child ASD-related outcomes was required (outcomes were collected at 36 months in EARLI and at 4 years for most participants (68%) in HOME; if measures at 4 years were not available, those at 5 years (21%) or 8 years (11%) were used). In addition, twins (n = 4 pairs from EARLI; n = 9 from HOME) were excluded given the potential for differing diet-neurodevelopment associations. Following these exclusions, 156 participants from EARLI and 270 from HOME (426 subjects in total) were included in the present analyses.

Prenatal Diet Information

In EARLI, information on maternal fish intake was collected through validated Food Frequency Questionnaires (FFQs). EARLI used a modified version of the National Cancer Institute's Dietary History Questionnaire (DHQ). The HOME Study included a series of questions on fish intake and diet in maternal interviews. Dietary information in both studies was collected at approximately the 20th and 36th week of pregnancy, covering weeks 1–20 and 21–36, respectively. Approximately 17% of participants had dietary information available only at one time point. In both studies, questions asked about frequency of intake of fish overall, as well as intake of particular types of fish. We defined fish intake in each time point (first and second half of pregnancy separately) as follows: women responding no to the overall fish intake question were the referent category (no intake), women reporting fish intake less than once per week but at least monthly were defined as low intake, and women reporting fish intake one to six times per week were defined as medium intake, and women reporting fish intake daily or more were defined as high intake. Finer categorizations of fish intake were not possible due to differences in the way response categories were provided across the two studies (e.g., 1–2 times per week and 3–4 times per week in EARLI vs 1–3 times and 4–6 times/week in HOME; see Appendix) and low proportions in both studies reporting higher intake (e.g., no individuals in EARLI reported intake of once or more per day; only 2 individuals in HOME reported intake almost every day). For total pregnancy fish intake, we created indicators for consistently low intake, including those in

the low and no fish categories for both time points (or those with low/no intake in one period and missing in the other), consistently high intake according to medium or high intake in both the first and second half of pregnancy (or medium intake in one time point and missing in the other), or "inconsistent intake" according to reporting low intake at one time point and medium/high intake in the other.

Both studies asked participants about frequency of consumption of different types of fish as well. These included salmon, fatty fish (including tuna, shark, mackerel, and swordfish), and shellfish (see Appendix provided in Supplemental Data for further information). In both studies, we defined categories of these fish types according to any reporting of intake of that fish over the defined period (e.g., first or second half of pregnancy; most women reporting intake were reporting monthly or several times per month), as compared to those not reporting intake of that fish type. In sensitivity analyses, we examined the impact of redefining the reference group as those reporting no fish intake during the time period of interest. We lacked sufficient numbers to examine frequency of intake of specific types of fish as defined in our primary analysis (given low reporting of weekly or greater intake for any one type of fish).

ASD-Related Outcomes

We measured ASD-related traits using the Social Responsiveness Scale (SRS) in both studies (Constantino and Gruber 2005, 2012). The SRS is a 65-item informant report measure (here, completed by mothers/parents) that yields a single quantitative score, with higher scores indicating greater ASD traits and poorer social communication (Constantino and Gruber 2005, 2012). Our analyses used total raw SRS scores, as is suggested for use in non-clinical, population-based settings (Constantino and Gruber 2012) and given slightly different T-score norms for different SRS forms used in EARLI and HOME. (EARLI used the preschool version of the SRS; HOME, the school-aged form). Secondary analyses examined associations stratified by cohort, and using T-scores to facilitate clinical interpretation. Cognitive abilities were assessed using two different clinical assessment measures in the two cohorts; the Mullen Scales of Early Learning (MSEL) in EARLI (Bishop et al. 2011), and the Bayley Scales of Infant Development, Second Edition in HOME (Braun et al. 2017). Bayley scores at 36 months were used here to facilitate comparability to EARLI 36-month measures. The MSEL early learning composite (ELC) score captures scores from fine motor skills, receptive and expressive language, and visual reception, while the Bayley scores assess mental (mental development index, MDI) and psychomotor development (psychomotor development index) (Bayley 2006). Higher scores on both scales are indicative of better performance. For the purposes of this analysis we focused solely on cognitive outcomes from these measures, using the ELC and the MDI for EARLI and HOME, respectively. Means and standard deviations of each of these scores by cohort are provided in Table 1.

Statistical Analysis

We used descriptive statistics to examine the overall proportion of fish intake in each study, and to determine associations with covariates. We used crude and multivariable linear regression models to examine associations with frequency and type of fish intake (as defined

above) in each of the time periods examined in association with each of the outcomes under study. (As noted, for analyses of SRS scores, we used raw scores, though we also conducted secondary analyses considering associations with SRS T-scores). We selected variables considered as potential confounders on the basis of a priori associations with outcomes and potential or known associations with maternal diet (Croen et al. 2002; DeVilbiss et al. 2017; Lyall et al. 2014; Wu et al. 2017). Specifically, we adjusted for maternal age (as a continuous variable) and education (in categories as listed in Table 1) at time of delivery, pre-pregnancy BMI (as a continuous variable), maternal race/ethnicity (in categories of non-Hispanic White, non-Hispanic Black, Hispanic, and other), parity (as first, second, or laterborn), household income (in categories as listed in Table 1), prenatal vitamin use (as yes/no as shown in Table 1). We also adjusted for child sex given known relationships with ASD diagnosis and traits. Additionally, because we pooled data from two different studies whose ASD trait distributions may differ, we also adjusted for the study cohort. However, comparability of distributions of SRS scores in EARLI and HOME (Supplemental Fig. 1), supported pooling.

Secondary analyses examined associations with SRS scores stratified by cohort; analyses of cognitive scores were necessarily stratified by cohort given the different outcome measures used. We also tested additional adjustment for other potential confounders in secondary analyses, including an indicator for maternal pregnancy smoking status, reported breastfeeding at 6 months, multivitamin use, omega-3 and fish oil supplement use (only available for EARLI). Separately, we considered adjustment for child birth weight, which may be on the pathway between maternal fish intake and offspring neurodevelopmental outcomes. We explored potential modification by child sex in stratified models and using interaction terms, given the skewed sex ratio in ASD and evidence for sex differences in effects of other risk factors (Braun et al. 2014; Roberts et al. 2013). We also explored potential associations between DHA and fish oil supplement (defined as regular use of these supplements during pregnancy) and the ASD-related outcomes in the EARLI study. Sensitivity analyses examined results using no fish intake as the referent for fish type analyses (rather than no intake of that type of fish), as noted above.

Results

Sociodemographic characteristics of the study participants overall and by cohort are shown in Table 1. A higher percentage of participants were Hispanic in EARLI than in HOME (18% vs 2.6%). A higher percentage of participants were Black/African American in HOME than in EARLI (31.9% vs 7.1%). Furthermore, participants in EARLI had slightly higher household income, maternal education level, and (as expected by study design enrolling younger siblings), higher maternal age and parity than HOME. Other factors were similar across the cohorts.

Fish intake among study participants overall and by cohort is shown in Table 2. The majority of participants in both studies had no or low fish intake during pregnancy (69.7%). There were slightly more women reporting no intake in EARLI, and low intake in HOME, in both the first and second half of pregnancy. The most commonly reported types of fish were fatty

fish and shellfish (~ 60% for each), though salmon was also common (~ 40% overall; categories were not mutually exclusive).

Results of crude and adjusted analyses of fish intake in association with ASD-related outcomes are shown in Tables 3, 4, 5. In adjusted analyses, relative to no intake, higher fish intake (of at least once per week) in the second half of pregnancy was associated with increased SRS scores (e.g., greater ASD-related traits; ß = 5.60, 95% CI (− 1.76, 12.97); representing approximately a 1/5 standard deviation change in SRS raw score). We also observed a similar association for those with "inconsistent" intake across pregnancy (ß = 7.85, 95% CI 2.16, 13.54, representing approximately a 1/4 standard deviation change in SRS raw score). There was a somewhat stronger association for those who switched from lower to higher intake across pregnancy (ß = 9.44, 95% CI 1.03,17.86; representing approximately a 1/3 standard deviation change in SRS raw score), although the estimate was fairly similar for those switching from higher to lower intake (ß = 6.78, 95% CI − 0.29,13.84; representing approximately a 1/5 standard deviation change in SRS raw score). When examining associations with fish type (ie, eating certain type of fish vs. not eating that type), particularly in the second half of pregnancy, shellfish and fatty fish (including tuna, shark, mackerel, and swordfish) were both associated with higher SRS scores (ß = 4.50, 95%CI − 1.02, 10.02, ß = 1.58, 95%CI − 3.77, 6.93; representing approximately a 1/8 standard deviation change in SRS raw score), while salmon was associated with lower SRS scores (ß = −4.66, 95%CI − 10.3, 0.97; representing approximately a 1/7 standard deviation change in SRS raw score). Sensitivity analyses utilizing women who reported no fish intake as the referent group for fish type analyses yielded results materially unchanged from primary analyses.

No clear patterns between cognitive scores and fish type emerged in either cohort. Higher fish intake throughout pregnancy was associated with higher MSEL ELC scores in EARLI (ß = 6.55, 95% CI −1.94, 15.04; Table 4; representing approximately a third a standard deviation change in ELC score). In contrast, in HOME there was no association (Bayley MDI ß = − 0.78, 95% CI − 5.86, 4.31; Table 5). Children whose mothers switched from higher to lower intake across pregnancy had lower MDI scores in HOME (indicating poorer performance; ß = − 7.32 95% CI − 12.54, − 2.11), though this was not observed in EARLI (ELC ß = 4.77, 95% CI − 7.39, 16.94). Salmon intake in the first half of pregnancy was associated with lower MDI scores in HOME (ß = − 3.59, 95% CI − 6.80, − 0.039); but again, this finding was not seen in EARLI (ELC ß = 3.24, 95% CI − 4.42, 10.91).

In secondary analyses, associations were similar using SRS-T scores instead of raw SRS scores (S-Table 1; for example, higher fish intake in the second half of pregnancy was non-significantly associated with approximately a 1/5 standard deviation increase in SRS T score; inconsistent intake was associated with approximately a 1/3 to ½ standard deviation increase in SRS T score). Analyses stratified by cohort (S-Table 2) also suggested similar patterns as the pooled analysis for most comparisons, though no significant associations were noted in the individual studies, and the estimate for high intake in early pregnancy and estimates for shellfish differed across the two studies. In sex-stratified analyses, there were some suggestions of stronger associations with maternal fish intake in the second half of pregnancy and the outcomes in male than in female children, though confidence intervals

were wide (for example, high vs. no fish intake for SRS, ß = 15.10, 95% CI 2.22, 27.98 in males; representing approximately a 1/2 standard deviation change in SRS raw score vs ß = 1.01, 95% CI − 7.27, 9.29 in females; representing approximately a 1/30 standard deviation change in SRS raw score S-Table 3).Analyses examining additional adjustment for other factors, including maternal smoking status, child birthweight, and breastfeeding (S-Table 4A) and omega-3 fatty acid supplementation and fish oil use (available only in EARLI; S-Table 4B) yielded results similar to those from the primary adjusted model. The number of women reporting use of omega-3 fatty acid and fish oil supplements in EARLI was low (n = 35). Analyses exploring potential associations with these supplements generally suggested lower SRS scores with either supplement, and no associations with ECL scores, though confidence intervals were wide.

Discussion

In this study using data from two prospective pregnancy cohorts, overall, we did not observe strong associations between prenatal fish intake and child ASD-related traits and cognitive scores. However, we observed several suggestive associations that should be further considered in future studies with larger sample size and greater variability in fish intake. Most notably here (and contrary to expectation), higher ASD-related traits as measured by the SRS were observed in children whose mothers had higher fish intake, an association that appeared to be stronger for the second half of pregnancy. We observed differences in associations related to type of fish consumed that may help to explain these findings, as discussed below. We were not able to examine combinations of fish types in these analyses. Our work adds to existing literature examining maternal fish intake by providing novel information on fish intake during pregnancy in relation to child ASD-related outcomes assessed on a quantitative scale.

As noted, our results suggested a positive association between SRS scores and fish intake in the second half of pregnancy. We also observed higher SRS scores in association with “inconsistent intake” across pregnancy, with some suggestion this was stronger for women switching intake from low to high across the first to second half of pregnancy. (Though the general similarity of estimates across categories of switching, eg, from low to high and high to low, suggests this may also be due to chance.) The observed positive associations with SRS scores ran counter to our hypothesis based on prior associations with broader neurodevelopment, and to the findings by Julvez and colleagues, who found higher fish intake was associated with lower ASD traits as measured by the Childhood Asperger Syndrome Test (Julvez et al. 2016). The discrepancy in results may be due to differences in average seafood consumption across the study populations (which was much higher in the work by Julvez and colleagues, 3 servings per week with very few non-consumers; as compared to an average of less than 1 serving per week in our study) (Julvez et al. 2016), or to differences in how fish intake was quantified (Julvez and colleagues examined fish in grams per week in quintiles, as compared to our broader groupings). However, differences could also be related to the types of fish ingested across populations.

In our study, we noted differences in associations by type of fish. In particular, higher intake of salmon was associated with lower SRS scores (indicative of lower levels of ASD traits),

while intake of other fish was associated with higher SRS scores. Since salmon is high in the polyunsaturated fatty acid DHA, known to play a key role in fetal brain development (Haggarty 2010), but lower in toxicants than larger fatty fish that can bioaccumulate lipophilic chemicals) ((FDA) 2019; Bosch et al. 2016; Khairy et al. 2019), these findings may be related to the beneficial effects of DHA or related PUFAs in salmon. Our findings suggesting reductions in SRS scores with supplement use (omega-3 or fish oil, which typically consists of either DHA alone or in combination with other fish-derived omega-3 s) are generally consistent with this explanation (though estimates in these secondary analyses were not calculated with much precision and should be interpreted with caution). Larger differences between crude and adjusted models for salmon that other fish types suggested greater impact of confounding on salmon, which may be more related to higher SES than certain other fish types. Though we adjusted for income and several SES-related factors, we cannot rule out the potential for residual confounding in these estimates by socio-economic factors.

In comparison to salmon, the observed higher SRS scores in association with intake of fatty fish and shell fish may relate to accumulated toxicants. Shellfish also tends to be lower in DHA than other types of fish (Bernstein et al. 2019). Though existing work examining methyl mercury exposure from fish intake has generally not supported an association with ASD,(Davidson et al. 2006; Golding et al. 2018; McKean et al. 2015; Myers et al. 2003) other toxicants are known to accumulate in large fatty fish.(Ibarluzea et al. 2011; Nemeth et al. 2016; Oken et al. 2008a, b). These may include polychlorinated biphenyls (PCBs), which have shown positive associations with ASD in some studies (Bernardo et al. 2019; Lyall et al. 2017), as well as perfluoroalkyl substances (PFAS). Few studies have examined associations with prenatal levels with ASD for the latter (Lyall et al. 2018); perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) in particular have been linked with negative impacts on neurodevelopment (Antonelli et al. 2017), though other studies have reported null or protective effects (Braun 2017).

As noted, fetal uptake of PUFAs is highest in the third trimester (Haggarty 2010). The potential suggestion of modest reductions in SRS scores with salmon intake in the second half of pregnancy may be consistent with a greater benefit of DHA-rich fish during the third trimester, as suggested in some prior work. Gale and colleagues suggested modest increases in verbal IQ for children whose mothers ate fish in late pregnancy (but not in early pregnancy) (Gale et al. 2008). However, another study reported weaker associations with third trimester fish consumption, perhaps due to differences in outcome assessment (quantiles of autistic traits according to the Childhood Asperger Syndrome Test were assessed) (Julvez et al. 2016). Other studies have suggested positive associations with postnatal consumption and developmental outcomes, (Avella-Garcia and Julvez 2014) including higher developmental scores on the McCarthy Scales (indicating improved cognitive outcomes) with maternal fish intake > 2–3 times per week during breastfeeding (Mendez et al. 2009), suggesting critical windows for PUFAs and fish may extend through postnatal neurodevelopment. More work is needed to examine fish intake by potential critical time windows in association with ASD-related outcomes, considering late pregnancy as well as early postnatal development, given these suggestive findings and known periods of rapid brain growth (Rice and Barone 2000).

When examining associations with cognitive development scores, we found evidence for higher MSEL ECL scores (suggesting modest increases in cognitive ability) with higher maternal fish intake throughout pregnancy in the EARLI study. However, this finding was not supported in the HOME study based on Bayley MDI scores. Suggestion of modest improvements in cognitive scores is consistent with the bulk of the prior literature examining maternal prenatal fish intake and offspring neurodevelopmental outcomes (Daniels et al. 2004; Julvez et al. 2016; Mendez et al. 2009; Oken et al. 2008a, b), though reports of no associations are also common (Oken et al. 2005). Potential reasons for differences across the two cohorts in our study may stem from differences in the outcome measures. While both assess cognitive development broadly, the MSEL ELC incorporates fine motor development and the Bayley MDI does not. Further, EARLI is a high familial risk cohort while HOME is drawn from the general population; thus, differences in the familial risk for ASD may influence observed associations (Folstein and Rutter 1977; Newschaffer et al. 2012). While proportions of intake of different types of fish were similar across the two studies, we cannot rule out potential differences according to intake of types of fish not assessed, or due to grouping into broader categories. It may also be that modest differences in frequency of intake influenced differences with cognitive scores (EARLI had a somewhat higher proportion with relatively greater intake than HOME).

In secondary analyses, we also observed some evidence for potentially stronger effects in males, though our small sample sizes led to imprecise estimates. It is possible that males are more sensitive to toxicants from fish than are females. Furthermore, animal models have shown differential absorption of PUFAs by sex (Ghasemifard et al. 2015; Nemeth et al. 2016), as well as different associations between PUFAs and developmental outcomes by sex (Dervola et al. 2012). PUFA intake in children has been shown to have sex-differentiated impacts on cognitive performance, with positive associations being greater in females (Lassek and Gaulin 2011). Future work should further consider potential effect measure modification by sex.

Fish intake in our study population was relatively low, with the majority of women consuming fish less than once per week. Current US dietary guidelines for pregnant women recommend 2–3 servings of seafood per week ((FDA) 2019). It is possible that concerns of contamination of fish, including not just methyl mercury but also microplastics and other environmental contaminants found in our water-systems, may influence fish intake ((EPA) 2001). Fish choice may also be influenced by the price of different types of fish. In both cohorts, consumption of fatty fish (a category containing fish which the FDA specifically recommends avoiding) was much higher than consumption of salmon (which the FDA recommends as one of the “best choices”) ((FDA) 2019). These discrepancies between recommendations and observed intake in our prenatal US cohorts suggest there may be a need for increased clarity in dietary guidelines for fish intake and types during pregnancy.

A key strength of this study is the use of prospectively collected dietary information during pregnancy. We were also able to examine associations with both ASD traits and cognitive development scores in two study populations. However, a number of limitations should be considered as well. While fish intake was prospectively collected, it was based on self-report, and we cannot rule out potential misreporting. We did not have the ability to adjust

for maternal blood mercury levels in our dataset, although prior work has suggested benefits of fish over and above mercury levels (Oken and Bellinger 2008). As noted, fish intake in our study populations was relatively low, limiting our ability to examine associations across finer (and higher intake) categories, or to address dose–response effects. In addition, results may not generalize across populations with high frequency of fish intake (and differing types). Further, we did not have the ability to examine differences by other fish types or by fish sources (fresh vs. ocean water) in both studies. We cannot rule out potential residual confounding by socio-economic factors that may be tied to fish intake, though these may be less related to our quantitative trait outcomes than to diagnosis. We also had small sample sizes in some categories and cannot rule out the potential for chance findings.

Findings here suggest future work should examine the second half of pregnancy as a potential susceptible window for fish intake in association with ASD-related traits. Future studies should also consider whether ASD-related traits may be more sensitive than broader cognitive development to the relative contribution of beneficial fats vs. potential contaminants in different fish types. Parsing these associations between fish intake, types of fish, and potential critical windows in association with ASD-related phenotypes may help to support clarity and completeness in the communication of dietary recommendations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Appendix

EARLI and HOME fish questions and harmonization process.

	EARLI		HOME	
	Question	**Response values**	**Question**	**Response values**
Overall fish intake	During the first 20 weeks of your current pregnancy, how many servings of seafood, including fish and shellfish (including canned tuna or tuna in foil pouches) did you eat per week or per day?	< 1 times per week 1–2 times per week 3–4 times per week	From {conception} until today how often did you eat fish or shellfish, on average?	Not at all < 1 times per month 1–3 times per month

	EARLI		HOME	
	Question	**Response values**	**Question**	**Response values**
		5–6 times per week		1–3 times per week
		1 per day		4–6 times per week
		2 or more per day		Almost every day
Intake of fish types	How often did you eat shellfish such as shrimp oysters, clams, crab, crayfish, or lobsters?[a]	< 1 times per week	*Participants were asked to report intake of the following fish:*	*Responses were provided as number of times participant ate that type of fish during the time period*
		1–2 times per week		
		3–4 times per week	Carp	
	How often did you eat fish sticks or fried fish? (NOT including shrimp or other shellfish)	5–6 times per week	Bass	
		1 per day	Catfish	
		2 or more per day	Drumfish	
	How often did you eat fish that was NOT FRIED? (not including shrimp or other shellfish and not including canned tuna or tuna in foil pouches)		Bullhead	
			Swordfish	
			Shark	
			Tuna of any type	
			Mackerel	
	When you ate fish that was NOT fried, how often was that fish salmon?	Almost never or never	Tilefish	
		About ¼ of the time	Shellfish, such as lobster, crab, shrimp, clams, or oysters	
		About ½ of the time		
	When you ate fish that was NOT fried, how often was that fish tuna steaks or other fresh tuna?	About ¾ of the time	Salmon	
		Almost always or always	Lake trout	
		Don’t Know		
	When you ate fish that was NOT fried, how often was the fish swordfish, shark, tilefish, or king mackerel?			

*Questions shown for first half of pregnancy FFQ; questions for second half of pregnancy asked about intake since the first questionnaire rather than since conception

[a]Supplemental questions asked about serving size (for all fish types), whether the shellfish was fried, and what proportion of the time the intake was shrimp

Harmonization scheme for overall frequency of fish intake for early and late pregnancy.

Combined Definition	EARLI value	HOME value
0 = None	None, Don’t Know, Missing	Not at all, Missing
1 = Very Low	< 1 per week	1–3/month, < 1/month

Combined Definition	EARLI value	HOME value
2 = Medium	1–2, 3–4, 5–6/week	1–3, 4–6/week
3 = High	1/day and 2+/day	Almost every day

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Table 1

Basic characteristics of the study population, by parent cohort

	EARLI (n = 156)	HOME (n = 270)	Total (n = 426)
	n (%)		
Child sex			
Male	83 (53.2%)	121 (44.8%)	204 (47.9%)
Female	73 (46.8%)	149 (55.2%)	222 (52.1%)
Maternal ethnicity[a]			
Hispanic/Latino	28 (18.0%)	7 (2.6%)	35 (8.2%)
Not Hispanic/Latino	128 (82.1%)	263 (97.4%)	391 (91.8%)
Maternal race[a]			
White	104 (66.7%)	172 (63.7%)	276 (64.8%)
Black/African American	11 (7.1%)	86 (31.9%)	97 (22.8%)
Asian and Pacific Islander	21 (13.5%)	3 (1.1%)	24 (5.6%)
Multiple/other race	15 (9.5%)	9 (3.3%)	24 (5.6%)
Missing	5 (3.2%)	0 (0%)	5 (1.2%)
Household income[a]			
$0–50,000	37 (23.7%)	127 (47.0%)	164 (38.5%)
$50,001–100,000	55 (35.3%)	99 (36.7%)	154 (36.2%)
$100,001 +	61 (39.1%)	44 (16.3%)	105 (24.6%)
Missing	3 (1.9%)	0 (0%)	3 (0.7%)
Maternal education level			
High school diploma or less	28 (11.5%)	64 (23.7%)	82 (19.3%)
Some college	46 (29.5%)	73 (27.0%)	119 (27.9%)
Bachelor’s degree	48 (30.8%)	80 (29.6%)	128 (30.1%)
Graduate degree	44 (28.2%)	53 (19.6%)	97 (22.8%)
Prenatal smoking[a]			
Active smoking	5 (3.2%)	33 (12.2%)	38 (8.9%)
Secondhand, but no active smoking	2 (1.3%)	42 (15.6%)	44 (10.3%)
No smoking exposure	120 (76.9%)	188 (69.6%)	308 (72.3%)

	EARLI (n = 156)	HOME (n = 270)	Total (n = 426)
	n (%)		
Missing	29 (18.6%)	7 (2.6%)	36 (8.5%)
Birthweight			
Low	6 (3.9%)	16 (5.9%)	22 (5.2%)
Normal	150 (96.1%)	254 (94.1%)	404 (94.8%)
Ever breastfed (asked at 6 months)			
Yes	100 (64.1%)	217 (80.4%)	317 (74.4%)
No	37 (23.7%)	52 (19.3%)	89 (20.9%)
Missing	19 (12.2%)	1 (0.4%)	20 (4.7%)
Prenatal vitamin use[a]			
Yes	147 (93.8%)	236 (87.4%)	386 (89.8%)
No	9 (5.6%)	34 (12.6%)	43 (10.1%)
	Mean (std)		
Maternal age (years)[a]	34.0 (4.5)	29.2 (5.8)	31.0 (5.8)
Parity[a,b]	1.8 (0.9)	0.9 (1.3)	1.2 (1.2)
Pre-pregnancy BMI [a,b]	28.1 (7.2)	26.7 (7.0)	27.2 (7.1)
Total SRS raw score	36.5 (28.5)	33.9 (20.6)	34.8 (23.5)
Total SRS T score*	48.0 (11.0)	51.9 (10.5)	50.6 (10.8)
Mullen ELC score	99.6 (21.0)	N/A	
Bayley MDI score	N/A	93.0 (13.9)	

[a]Indicates $p < 0.05$ (from Chi-squared test for categorical variables and t-test for continuous variables)

[b]1 participant was missing information on parity and 5 were missing information on BMI. 24 individuals in EARLI did not have SRS scores and 10 did not have Mullen Scores (non-overlapping)

Table 2

Fish intake during pregnancy among study participants, by parent cohort

	EARLI (n = 156)	HOME (n = 270)	Combined (n = 426)
Total/any fish intake			
Early pregnancy intake			
None	44 (29.3%)	40 (14.8%)	84 (20.0%)
Low (< 1 ×/week)	68 (45.3%)	170 (63.0%)	238 (56.7%)
Medium (1–6 ×/week)	37 (24.7%)	58 (21.5%)	95 (22.6%)
High (daily or more)	1 (0.7%)	2 (0.7%)	3 (0.7%)
Missing	6	0	6
Late pregnancy intake			
None	26 (28.9%)	47 (17.9%)	73 (20.7%)
Low (< 1 ×/week)	29 (43.3%)	169 (64.3%)	208 (58.9%)
Medium (1–6 ×/week)	25 (27.8%)	47 (17.9%)	72 (20.4%)
High (daily or more)	0 (0%)	0 (0%)	0 (0%)
Missing	66	7	73
Total pregnancy intake			
Low (consistently none or low)	109 (69.9%)	188 (69.6%)	297 (69.7%)
High (consistently medium or high)	29 (18.6%)	27 (10.0%)	56 (13.2%)
Inconsistent intake	18 (11.5%)	55 (20.4%)	73 (17.1%)
Total pregnancy intake (secondary categorization of consistency of intake across pregnancy)			
Low (consistently none or low)	109 (69.9%)	188 (69.6%)	297 (69.7%)
High (consistently medium or high)	29 (18.6%)	27 (10.0%)	56 (13.2%)
Inconsistent intake (low to high)	7 (4.5%)	22 (8.2%)	29 (6.8%)
Inconsistent intake (high to low)	11 (7.1%)	33 (12.2%)	44 (10.3%)
Intake by fish type			
Early pregnancy intake			
Salmon	38 (25.5%)	112 (41.5%)	150 (35.8%)
Fatty fish[a]	71 (47.3%)	166 (61.5%)	237 (56.4%)
Shellfish	84 (56.0%)	160 (59.3%)	244 (58.1%)
Fried fish	44 (29.5%)	N/A	N/A

	EARLI (n = 156)	HOME (n = 270)	Combined (n = 426)
Late pregnancy intake			
Salmon	30 (33.3%)	87 (40.3%)	117 (38.2%)
Fatty fish[a]	39 (42.9%)	134 (62.0%)	173 (56.4%)
Shellfish	51 (56.0%)	128 (59.3%)	179 (58.3%)
Fried fish	30 (33.0%)	N/A	N/A
Total pregnancy intake			
Salmon	49 (31.6%)	122 (45.2%)	171 (40.2%)
Fatty fish[a]	81 (51.9%)	186 (68.9%)	267 (62.7%)
Shellfish	94 (60.3%)	177 (65.6%)	271 (63.6%)
Fried fish	57 (37.5%)	N/A	N/A

[a]Fatty fish includes Swordfish, Mackerel, Tuna, Shark, Tilefish

Table 3

Crude and adjusted associations (β estimates and 95% confidence intervals) between maternal fish intake during pregnancy and child raw total SRS scores

	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[a]
Analyses by frequency of fish intake			
Early pregnancy intake			
No intake	76	*(Referent)*	*(Referent)*
Low intake	228	−1.97 (−7.82, 3.88)	−1.06 (−6.72, 4.59)
High Intake	93	0.49 (−6.34, 7.33)	0.49 (−6.03, 7.02)
Late pregnancy intake			
No intake	71	*(Referent)*	*(Referent)*
Low intake	202	−0.15 (−6.58, 6.27)	0.71 (−5.37, 6.79)
High Intake	70	5.01 (−2.85, 12.87)	5.60 (−1.76, 12.97)
Total pregnancy intake[b]			
Low intake	278	*(Referent)*	*(Referent)*
Inconsistent intake	72	8.34 (2.27, 14.40)	7.85 (2.16, 13.54)
High intake	52	1.04 (−5.89, 7.97)	0.68 (−5.97, 7.34)
Consistency of intake across pregnancy			
Low intake	278	*(Referent)*	*(Referent)*
Inconsistent: low then high	29	8.60 (−0.35, 17.57)	9.44 (1.03, 17.86)
Inconsistent: high then low	43	8.15 (0.63, 15.68)	6.78 (−0.29, 13.84)
High intake	52	1.04 (−5.89, 7.98)	0.70 (−5.96, 7.36)
Analyses by type of fish[c]			
Early pregnancy intake			
Salmon	147	−4.32 (−8.89, 0.26)	−1.92 (−6.52, 2.57)
Fatty fish	228	−0.28 (−4.77, 4.20)	0.23 (−3.73, 4.90)
Shellfish	228	−2.53 (−7.01, 1.95)	0.75 (−3.61, 5.11)
Fried fish (EARLI Only)	37	2.62 (−7.54, 12.78)	3.40 (−6.76, 13.56)
Late pregnancy intake			
Salmon	114	−7.43 (−13.12, −1.74)	−4.66 (−10.29, 0.97)
Fatty fish	170	0.92 (−4.60, 6.70)	1.58 (−3.77, 6.93)
Shellfish	173	0.05 (−5.61, 5.71)	4.50 (−1.02, 10.02)

	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[a]
Fried fish (EARLI only)	26	−1.01 (−15.94, 13.92)	0.52 (−13.63, 14.67)
Total pregnancy intake			
Salmon	166	−5.00 (−9.81, −0.52)	−2.59 (−7.12, 1.93)
Fatty fish	256	−0.83 (−5.62, 3.96)	−0.45 (−5.03, 4.12)
Shellfish	255	0.35 (−4.44, 5.13)	4.05 (−0.56, 8.67)
Fried fish (EARLI Only)	49	2.57 (−6.83, 11.96)	3.52 (−5.91, 12.95)

[a] Adjusted for cohort, maternal age, maternal pre-pregnancy BMI, child sex, maternal education level, maternal race/ethnicity, parity, income, prenatal vitamin use

[b] As defined in text; low total pregnancy intake corresponds to low or no intake at both time points; inconsistent intake refers to high intake in one timepoint and low in the other; high intake refers to consistently high intake across both pregnancy timepoints

[c] For fish type analyses, reference category for each estimate is individuals reporting no intake of that type of fish (any intake during the survey period compared to no intake)

Table 4

Crude and adjusted associations (β estimates and 95% confidence intervals) between maternal fish intake during pregnancy and child MSEL scores (EARLI participants only)[a]

	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[b]
Analyses by frequency of fish intake			
Early pregnancy intake			
No intake	41	*(Referent)*	*(Referent)*
Low intake	63	4.27 (−3.93, 12.48)	3.19 (−4.43, 10.80)
High intake	37	9.62 (0.35, 18.89)	8.03 (−0.71, 16.76)
Late pregnancy intake			
No intake	23	*(Referent)*	*(Referent)*
Low intake	37	0.99 (−9.91, 11.89)	5.54 (−5.79, 16.88)
High intake	21	7.14 (−5.25, 19.52)	9.02 (−3.62, 21.66)
Total pregnancy intake			
Low intake	103	*(Referent)*	*(Referent)*
Inconsistent intake	16	2.52 (−8.62, 13.69)	−1.00 (−11.52, 9.53)
High intake	27	7.14 (−1.84, 16.12)	6.55 (−1.94, 15.04)
Consistency of intake across pregnancy			
Low intake	103	*(Referent)*	*(Referent)*
Inconsistent: low then high	5	−5.17 (−24.19, 13.85)	−14.26 (−32.01, 3.50)
Inconsistent: high then low	11	6.03 (−7.15, 19.20)	4.77 (−7.39, 16.94)
High intake	27	7.14 (−1.84, 16.12)	6.36 (−2.06, 14.78)
Analyses by type of fish[c]			
Early pregnancy intake			
Salmon	37	8.46 (0.72, 16.19)	3.24 (−4.42, 10.91)
Fatty fish	68	3.64 (−3.30, 10.58)	2.07 (−4.46, 8.61)
Shellfish	78	0.17 (−6.83, 7.17)	−1.68 (−8.25, 4.90)
Fried fish	41	6.52 (−1.11, 14.14)	6.85 (−0.38, 14.09)
Late pregnancy intake			
Salmon	28	−0.55 (−10.32, 9.23)	−2.50 (−12.63, 7.62)
Fatty fish	35	−6.36 (−15.63, 2.34)	−5.60 (−15.04, 3.85)

	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[b]
Shellfish	45	1.68 (−7.64, 11.00)	0.73 (−8.50, 9.96)
Fried fish	27	3.99 (−5.84, 13.82)	3.73 (−6.12, 13.57)
Total pregnancy intake			
Salmon	47	3.92 (−4.41, 11.24)	−0.47 (−7.66, 6.71)
Fatty fish	76	0.79 (−6.12, 7.70)	−0.50 (−7.07, 6.07)
Shellfish	87	−1.89 (−8.92, 5.14)	−2.88 (−9.48, 3.72)
Fried fish	51	3.65 (−3.65, 10.95)	3.41 (−3.53, 10.36)

[a] Analyses of MSEL scores include EARLI participants only, n = 146

[b] Adjusted for maternal age, maternal pre-pregnancy BMI, child sex, maternal education level, maternal race/ethnicity, parity, income, prenatal vitamin use

[c] For fish type analyses, reference category for each estimate is individuals reporting no intake of that type of fish (any intake during the survey period compared to no intake)

Table 5

Crude and adjusted associations (β estimates and 95% confidence intervals) between maternal fish intake during pregnancy and child Bayley MDI scores (HOME participants only)[a]

	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[b]
Analyses by frequency of fish intake			
Early pregnancy intake			
No intake	139	*(Referent)*	*(Referent)*
Low intake	32	−1.20 (−6.55, 4.15)	−1.29 (−5.86, 3.27)
High intake	45	−5.20 (−11.51, 1.11)	−4.44 (−9.82, 0.93)
Late pregnancy intake			
No intake	137	*(Referent)*	*(Referent)*
Low intake	38	1.09 (−3.96, 6.13)	−0.72 (−5.06, 3.62)
High intake	39	−1.66 (−7.93, 4.62)	−2.26 (−7.68, 3.16)
Total pregnancy intake[c]			
Low intake	156	*(Referent)*	*(Referent)*
Inconsistent intake	36	−7.20 (−12.19, −2.21)	−6.61 (−10.79, 2.43)
High intake	24	−1.86 (−7.77, 4.06)	−0.78 (−5.86, 4.31)
Consistency of intake across pregnancy			
Low intake	156	*(Referent)*	*(Referent)*
Inconsistent: low then high	15	−5.99 (−13.31, 1.31)	−5.55 (−11.78, 0.68)
Inconsistent: high then low	21	−8.06 (−14.35, −1.78)	−7.32 (−12.54, −2.11)
High intake	24	−1.86 (−7.79, 4.07)	−0.75 (−5.84, 4.35)
Analyses by type of fish[d]			
Early pregnancy intake			
Salmon	85	−0.59 (−4.41, 3.23)	−3.59 (−6.80, −0.39)
Fatty fish	134	0.28 (−3.57, 4.13)	−1.41 (−4.70, 1.86)
Shellfish	136	6.02 (2.24, 8.90)	2.32 (−1.01, 5.66)
Late pregnancy intake			
Salmon	73	2.17 (−2.16, 6.50)	−1.74 (−5.48, 2.00)
Fatty fish	108	−1.20 (−5.60, 3.19)	−0.02 (−3.83, 3.79)

	n	Crude (β, 95% CI)	Adjusted (β, 95% CI)[b]
Shellfish	106	7.14 (2.90, 11.38)	0.63 (−3.31, 4.56)
Total pregnancy intake			
Salmon	94	−0.94 (−4.71, 2.82)	−3.76 (−6.91, −0.60)
Fatty fish	148	−0.74 (−4.76, 3.28)	−1.17 (−4.59, 2.24)
Shellfish	146	5.97 (2.06, 9.87)	1.47 (−2.02, 4.96)

[a] Analyses in HOME participants only (n = 270) due to use of different cognitive assessments in the EARLI and HOME studies

[b] Adjusted for cohort, maternal age, maternal pre-pregnancy BMI, child sex, maternal education level, maternal race/ethnicity, parity, income, prenatal vitamin use

[c] As defined in text; low total pregnancy intake corresponds to low or no intake at both time points; inconsistent intake refers to high intake in one timepoint and low in the other; high intake refers to consistently high intake across both pregnancy timepoints

[d] For fish type analyses, reference category for each estimate is individuals reporting no intake of that type of fish (any intake during the survey period compared to no intake)