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# Association of maternal fish consumption and ω-3 supplement use during pregnancy with child autism-related outcomes: results from a cohort consortium analysis

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*Abbreviations:* ASD, autism spectrum disorder; ECHO, Environmental influences on Child Health Outcomes; SRS, Social Responsiveness Scale.

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A B S T R A C T

**Background:** Prenatal fish intake is a key source of omega-3 (ω-3) polyunsaturated fatty acids needed for brain development, yet intake is generally low, and studies addressing associations with autism spectrum disorder (ASD) and related traits are lacking.
**Objective:** This study aimed to examine associations of prenatal fish intake and ω-3 supplement use with both autism diagnosis and broader autism-related traits.
**Methods:** Participants were drawn from 32 cohorts in the Environmental influences on Child Health Outcomes Cohort Consortium. Children were born between 1999 and 2019 and part of ongoing follow-up with data available for analysis by August 2022. Exposures included self-reported maternal fish intake and ω-3/fish oil supplement use during pregnancy. Outcome measures included parent report of clinician-diagnosed ASD and parent-reported autism-related traits measured by the Social Responsiveness Scale (SRS)-second edition ($n$ = 3939 and v3609 for fish intake analyses, respectively; $n$ = 4537 and $n$ = 3925 for supplement intake analyses, respectively).
**Results:** In adjusted regression models, relative to no fish intake, fish intake during pregnancy was associated with reduced odds of autism diagnosis (odds ratio: 0.84; 95% confidence interval [CI]: 0.77, 0.92), and a modest reduction in raw total SRS scores (β: −1.69; 95% CI: −3.3, −0.08). Estimates were similar across categories of fish consumption from "any" or "less than once per week" to "more than twice per week." For ω-3 supplement use, relative to no use, no significant associations with autism diagnosis were identified, whereas a modest relation with SRS score was suggested (β: 1.98; 95% CI: 0.33, 3.64).
**Conclusions:** These results extend previous work by suggesting that prenatal fish intake, but not ω-3 supplement use, may be associated with lower likelihood of both autism diagnosis and related traits. Given the low-fish intake in the United States general population and the rising autism prevalence, these findings suggest the need for better public health messaging regarding guidelines on fish intake for pregnant individuals.

*Keywords*: fish, ω-3 supplement, pregnancy, autism, quantitative traits

## Introduction

Autism spectrum disorder (ASD or, hereafter, autism) is a neurodevelopmental condition with an etiology that is complex and not well-understood. Evidence supports both genetic and environmental contributions to autism, including prenatal nutrition [1]. Maternal fish intake during pregnancy is a key source of essential nutrients, such as omega (ω)-3 (n–3) PUFAs, critical for fetal brain development [2]. In particular, fish is the primary source of the ω-3 PUFA DHA [3], the most abundant fatty acid in the brain, and may represent a modifiable factor in the risk for adverse neurodevelopmental outcomes. However, evidence suggests that the fish and ω-3 PUFA intake in the United States is low [4,5]. In results from nationally representative data [6], 95%–100% of pregnant and childbearing-age females consumed less than the recommended amounts of fish and DHA. However, in addition to neurodevelopmentally beneficial ω-3 PUFAs, certain contaminants, including the known neurotoxicant methylmercury, are also present in some fish species, suggesting potential risks as well. Although studies have supported the benefits of fish intake even after accounting for methylmercury exposure [7–12] and have not found associations between methylmercury and autism [13,14], concerns regarding coexposures may contribute to low intake [15] and reiterate the need for clarity in associations.

A large number of studies have examined associations between maternal prenatal fish intake and child neurodevelopmental outcomes [10,16–19], with many suggesting that prenatal fish intake is generally associated with higher developmental and cognitive scores among offspring [12]. However, not all studies have shown benefits, and few have addressed associations with autism. Despite some supportive findings based on small samples and differing outcome assessments, a systematic review performed in support of the 2020–2025 Dietary Guidelines for Americans concluded that there is insufficient evidence to determine whether seafood consumption during pregnancy is associated with risk of autism-like traits, behaviors, or diagnosis in children [12]. In addition, even fewer studies have shown associations of DHA or ω-3 supplements with autism outcomes [12,20].

Given the gaps in our understanding of the relationships between key sources of PUFAs with autism and autism-related traits and the need to identify modifiable factors to reduce associated challenges in autism, we sought to examine these associations in a large United States sample. Based on the biological importance of PUFAs in brain development [2], and associations with broader neurodevelopment, we hypothesized that both prenatal fish intake and ω-3 supplement use would be inversely associated with autism and related traits.

## Methods

### Study population

The Environmental influences on Child Health Outcomes (ECHO) Program is a large collaborative United States consortium focused on early life environmental factors that impact child health [21,22]. Briefly, ECHO comprises 69 individual cohorts across the United States, whose participants follow a common protocol to assess the effects of exposures on child-focused outcomes, including neurodevelopment. In this study, we analyzed data available from ≤32 cohorts that enrolled children born before 2019, to allow time for symptom development and reporting of diagnosis, which typically occurs after age 3 [23]. We included singleton births and excluded participants who were missing exposure or outcome information (Supplemental Figure 1). We allowed the sample size to vary across exposure-outcome analyses to maximize the sample size for each analysis. Following exclusions, analyses of associations with autism diagnosis included 3939 individuals for fish intake and 4537 individuals for ω-3 supplement use. Analyses of autism traits included 3609 individuals for fish intake and 3925 individuals for ω-3 supplement use. A list of cohorts contributing to these analyses is provided in Supplemental Table 1; 3 cohorts were drawn from samples that are considered at higher risk of autism owing to family history [24] (cohorts following younger siblings of a child with autism) or preterm birth (which also increases the likelihood of autism) [25].

The study protocol was approved by each cohort's local or the single ECHO institutional review board. Written informed consent or parent/guardian permission was obtained along with child assent as appropriate, for ECHO-wide Cohort Data Collection Protocol participation and for participation in specific cohorts. This study followed the STROBE reporting guideline for cohort studies.

## Exposure information

Information on maternal fish and seafood intake was collected across cohorts through validated semiquantitative or quantitative food frequency questionnaires (FFQs), including the Block FFQ ($n = 6$ cohorts) [26], the Harvard/Willett FFQ ($n = 2$ cohorts) [27], the Dietary History Questionnaire ($n = 1$ cohort) [28], and dietary screeners (remaining cohorts) (see the Supplemental Data for a list of fish and seafood items and assessment methods by cohort), with most cohorts collecting this information midpregnancy. Fish and seafood intake was determined according to responses on these questionnaires and harmonized by summing an individual's overall intake of servings across these questions and then categorizing servings as follows: none or <once a month; >once per month but <weekly; weekly; and 2 or more servings per week. Information on ω-3 supplements was collected from maternal report on questionnaires, with most cohorts asking if DHA or fish oil supplements were used during pregnancy (yes/no) and a subset ($n = 20$ cohorts, 42% of the participants) further querying frequency of use. The majority of cohorts collected information prospectively. Only 1 autism case–control study, ReCHARGE [29], was included (Supplemental Table 1).

## Covariate information

All information on covariates was collected via self-report questionnaires. All covariates included in the current analyses were harmonized in common categories by the ECHO Data Analysis Center.

## Outcome information

### *Autism diagnosis*

We defined autism diagnosis based on parent/caregiver report of physician-diagnosed ASD. In addition, several cohorts (including an autism case–control study and familial autism cohorts) (Supplemental Table 1) used clinical assessments and gold-standard measures to confirm an autism diagnosis. We excluded individuals missing information on autism diagnosis from the analyses of this outcome.

### *Social Responsiveness Scale*

Autism-related traits were assessed using the Social Responsiveness Scale (SRS)-second edition, one of the most widely used quantitative measures of the autism-related phenotype [30,31]. The SRS is a 65-item informant-report tool yielding a continuous total score ranging from 0 to 195, with higher scores indicating greater expression of the autism phenotype and greater social-communication deficits. Scores can also be converted into normed T-scores (with a mean of 50 and SD 10) to facilitate clinical interpretation; scores >65 tend to be consistent with moderate ASD-related traits and those >75 with clinically impairing traits. The SRS has well-established psychometric properties, capturing traits in both the general population and clinical settings [32,33], with high-internal validity, reliability, and reproducibility [31,34,35], and strong agreement with gold-standard diagnostic measures of autism [34,35]. Age-appropriate forms (preschool, school age, and adult) allow for trait measurement across a wide age range. A short form, including 16 of the 65 items, has also been developed using item response theory and validated in several samples [36,37]. For this analysis, SRS forms were collected at ages 2.5–18 y via parent/caregiver reports, and total raw scores were used as suggested by the publisher for population-level analyses. Approximately 20% of the analytic sample used preschool forms; 80% used school age forms; and 8% used 16-item SRS forms, with scores equated to full 65-item scores using equipercentile equating. Previous work supports strong agreement between short and full 65-item scores [36,37] and the stability of SRS scores over these ages, particularly for the school-aged form [33,38].

## Statistical analyses

We first examined prenatal fish intake and ω-3 supplement use by demographic characteristics of study participants. Next, we used logistic regression to estimate crude and adjusted odds ratios (ORs) for autism associated with categories of fish intake and ω-3 supplement use (yes/no), separately. We parameterized fish intake as binary (any/none) and in the above-described 4 categories. We also examined supplement use as a binary variable, following the same modeling strategy used for fish intake. Adjusted analyses included maternal age, prepregnancy BMI, race and ethnicity, education, smoking status, and child's sex assigned at birth, and year of birth as covariates. Adjustment for cohort was included as a random effect. Adjustment for additional covariates was tested in sensitivity analyses as described further. We imputed data on missing covariates using multiple imputation with chained equations.

Analyses of SRS scores followed the exposure parameterization and covariate adjustment strategy outlined for autism diagnosis but used linear regression for our primary analyses. As a secondary approach, we used quantile regression to examine effect sizes across quantiles of SRS. Quantile regression is a flexible modeling approach that handles nonnormally distributed outcomes while allowing for examination of effects across different quantiles of the outcome measure [39,40]. In addition, we ran secondary models using SRS T-scores (rather than raw scores used in primary models) to facilitate clinically relevant interpretations.

We also fitted a series of secondary models and conducted sensitivity analyses to test the robustness of our results. First, in models addressing associations with autism, we tested differences by cohorts with differing baseline level risk of autism (preterm birth and family-based cohorts) and examined potential differences in associations by child's sex (given the much higher prevalence of autism in males), in stratified models. Next, for supplement use, we examined potential differences by frequency of supplement use (none, 1–3 times/wk, 4–6 times/wk, or daily or more) in the subset of participants with this information ($n = 1884$). To test the robustness of our primary findings, we adjusted primary models for additional covariates by individually adding household income to the primary adjusted model, which may relate to both fish and supplement intake and access to autism diagnostic resources, with coadjustment for the other exposure (e.g., fish for supplement use and vice versa). We also tested adjustment for prenatal vitamin use, which has been linked to autism in a previous work. Adjustment for preterm birth, which could lie on the pathway between these exposures and outcomes, was also explored as a simple test of potential mediation. Finally, we conducted analyses leaving out individual cohorts one at a time for associations with our primary outcome, autism diagnosis, to confirm if any 1 cohort (or specific assessment methods or sample characteristics) was driving the results. All statistical analyses were conducted in SAS, version 9.4.

## Results

The basic characteristics of our study population are summarized in Table 1. Approximately 20% of all participants reported no fish intake, and most (65%–85% depending on the analytic sample) reported no ω-3 supplement use. Child participants were born between 1999 and 2019. Owing to the inclusion of several cohorts following younger siblings of a child with autism and a case–control study, the autism

**TABLE 1**
Basic characteristics of the study population.

| Variable, *n* (%) | Fish consumption | | Supplement use | |
|---|---|---|---|---|
| | Autism sample ($n = 3939$) | SRS sample ($n = 3609$) | Autism sample ($n = 4537$) | SRS sample (n=3925) |
| Cohort type | | | | |
| ASD familial study | 123 (3.1) | 190 (5.3) | 35 (0.8) | 113 (2.9) |
| Preterm birth study | NA | NA | 258 (5.7) | 240 (6.11) |
| Other/general population study | 3816 (96.9) | 3419 (94.7) | 4244 (93.5) | 3572 (91.0) |
| Maternal age at child's birth (y) | | | | |
| <18–28 | 1506 (38.2) | 1111 (30.8) | 1805 (39.8) | 1302 (33.2) |
| 29–34 | 1529 (38.8) | 1515 (42.0) | 1733 (38.2) | 1599 (40.7) |
| 35–40 | 817 (20.7) | 871 (24.1) | 894 (19.7) | 894 (22.8) |
| 41+ | 87 (2.2) | 112 (3.1) | 99 (2.2) | 120 (3.1) |
| Missing | 0 (0) | 0 (0) | 6 (0.1) | 10 (0.3) |
| Maternal race and ethnicity | | | | |
| Non-Hispanic White | 1528 (38.8) | 1980 (54.9) | 2083 (45.9) | 2380 (60.6) |
| Non-Hispanic Black | 1125 (28.6) | 625 (17.3) | 1242 (27.4) | 694 (17.7) |
| Non-Hispanic Asian | 311 (7.9) | 260 (7.2) | 175 (3.9) | 141 (3.6) |
| Hispanic | 793 (20.1) | 600 (16.6) | 825 (18.2) | 532 (13.6) |
| Non-Hispanic other race | 176 (4.5) | 135 (3.7) | 205 (4.5) | 165 (4.2) |
| Missing | <10 (<0.2) | <10 (<0.3) | 7 (0.2) | 13 (0.3) |
| Annual household income ($) | | | | |
| <30,000 | 835 (21.2) | 478 (13.2) | 989 (21.8) | 539 (13.7) |
| 30,000–49,999 | 288 (7.3) | 198 (5.5) | 332 (7.3) | 190 (4.8) |
| 50,000–74,999 | 348 (8.8) | 243 (6.7) | 307 (6.8) | 191 (4.9) |
| 75,000–99,999 | 217 (5.5) | 155 (4.3) | 121 (2.7) | 63 (1.6) |
| ≥100,000 | 504 (12.8) | 396 (11.0) | 242 (5.3) | 128 (3.3) |
| Missing | 1747 (44.4) | 2139 (59.3) | 2546 (56.1) | 2814 (71.7) |
| Maternal education | | | | |
| <High school | 277 (7.0) | 150 (4.2) | 332 (7.3) | 202 (5.2) |
| High school degree or equivalent | 828 (21.0) | 564 (15.6) | 954 (21.0) | 626 (16.0) |
| Some college | 896 (22.8) | 811 (22.5) | 970 (21.4) | 825 (21.0) |
| Bachelor degree | 1097 (27.9) | 1124 (31.1) | 1250 (27.6) | 1195 (30.5) |
| Master, professional, or doctoral degree | 822 (20.9) | 899 (24.9) | 1009 (22.2) | 1014 (25.8) |
| Missing | 19 (0.5) | 61 (1.7) | 22 (0.5) | 63 (1.6) |
| Maternal prepregnancy BMI ($kg/m^2$) | | | | |
| <18.5 | 113 (2.9) | 95 (2.6) | 134 (3.0) | 101 (2.6) |
| 18.5–24.9 | 1466 (37.2) | 1529 (42.4) | 1684 (37.1) | 1677 (42.7) |
| 25–29.9 | 882 (22.4) | 841 (23.3) | 953 (21.0) | 871 (22.2) |
| 30 or more | 896 (22.8) | 777 (21.5) | 975 (21.5) | 790 (20.1) |
| Missing | 582 (14.8) | 367 (10.2) | 791 (17.4) | 486 (12.4) |
| Maternal smoking during pregnancy | | | | |
| Yes | 200 (5.1) | 164 (4.5) | 293 (6.5) | 230 (5.9) |
| No | 3612 (91.7) | 3237 (89.7) | 4174 (92.0) | 3618 (92.2) |
| Missing | 127 (3.2) | 208 (5.8) | 70 (1.5) | 77 (2.0) |
| Child's sex assigned at birth | | | | |
| Male | 2056 (52.2) | 1884 (52.2) | 2359 (52.0) | 2049 (52.2) |
| Female | 1883 (47.8) | 1725 (47.8) | 2178 (48.0) | 1876 (47.8) |
| Gestational age | | | | |
| <37 wk (preterm) | 313 (8.0) | 262 (7.3) | 639 (14.1) | 532 (13.6) |
| ≥37 wk (term) | 3623 (92.0) | 3345 (92.7) | 3896 (85.9) | 3392 (86.4) |
| Missing | <5 (<0.1) | <5 (<0.1) | <5 (<0.1) | <5 (<0.1) |
| Child year of birth | | | | |
| 1999–2004 | 636 (16.2) | 558 (15.5) | 646 (14.2) | 563 (14.3) |
| 2005–2009 | 567 (14.4) | 398 (11.0) | 564 (12.4) | 394 (10.0) |
| 2010–2014 | 1751 (44.5) | 1654 (45.8) | 2303 (50.8) | 2167 (55.2) |
| 2015+ | 985 (25.0) | 999 (27.7) | 1024 (22.6) | 801 (20.4) |
| Autism diagnosis | | | | |
| Yes | 345 (8.8) | 166 (4.6) | 356 (7.9) | 171 (4.36) |
| No | 3594 (91.2) | 2318 (64.2) | 4181 (92.1) | 2612 (66.6) |
| Missing (not in autism analyses)[1] | NA | 1125 (31.2) | NA | 1142 (29.1) |
| SRS score available | | | | |
| Yes | 2484 (63.1) | 3609 (100.0) | 2783 (61.3) | 3225 (100.0) |
| Missing (not in SRS analyses) | 1455 (36.9) | NA | 1754 (38.7) | NA |
| Fish intake during pregnancy | | | | |
| Never | 664 (16.9) | 713 (19.8) | 991 (21.8) | 894 (22.8) |
| <1 a week | 1373 (34.9) | 1290 (35.7) | 1626 (35.8) | 1419 (36.2) |
| ≤1–2 per week | 1167 (29.6) | 1054 (29.2) | 1078 (23.8) | 936 (23.9) |
| More than 2 per week | 735 (18.7) | 552 (15.3) | 624 (13.8) | 516 (13.2) |

(*continued on next page*)

**TABLE 1** (*continued*)

| Variable, *n* (%) | Fish consumption | | Supplement use | |
|---|---|---|---|---|
| | Autism sample ($n = 3939$) | SRS sample ($n = 3609$) | Autism sample ($n = 4537$) | SRS sample (n=3925) |
| Missing (not in fish intake analyses) | NA | NA | 218 (4.8) | 160 (4.1) |
| Fish oil/ω-3 supplement use during pregnancy | | | | |
| Yes | 390 (9.9) | 333 (9.2) | 643 (14.2) | 555 (14.1) |
| No | 2588 (65.7) | 2400 (66.5) | 3894 (85.8) | 3370 (85.9) |
| Missing (not in supplement use analyses) | 961 (24.4) | 876 (24.3) | NA | NA |

ASD, autism spectrum disorder; SRS, Social Responsiveness Scale.

[1] See also Supplemental Figure 1 for study flow chart and final sample sizes used in each analysis; sample size floats across exposure/outcome analyses owing to data availability. Multiple imputation was used in analyses of associations between exposures and outcomes.

prevalence was higher in our analytic samples (4%–9%) than that in the general population (~1.5%–2%) [41]. The mean SRS raw score was ~33 (SD = 22) and mean T-score 50 (SD = 9). Participants in our study population are broadly representative of those included in a recent summary of fish intake and supplement use in ECHO that did not exclude participants on the basis of ASD outcome information [42], although our sample had a somewhat higher proportion of White participants. Participants included in this study were also broadly representative of ECHO pregnant participants on education and income [22], although our study sample had a somewhat lower proportion of Hispanic participants than ECHO overall, and race varied somewhat across our analytic samples as presented in Table 1.

We observed an inverse association of fish intake with risk of autism diagnosis, comparing any fish intake to none. This association was similar with adjustment for potential confounders (adjusted OR: 0.84; 95% CI: 0.77, 0.92) (Table 2). In analyses of categorical, rather than binary (any), fish intake, we did not observe stronger associations with higher amounts of fish intake; instead, all categories of fish intake were associated with reductions in odds of ~20% compared with no fish intake (Table 2). The results were similar when stratified by cohort type (Supplemental Table 2), although point estimates were further below the null—and with wider CIs—in the cohorts enriched for autism risk. Results stratified by child sex suggested somewhat stronger (more inverse) associations in females and more attenuated associations in males (adjusted OR for any fish intake: 0.67; 95% CI: 0.52, 0.86 for females, and adjusted OR: 0.90; 95% CI: 0.73, 1.12 for males); however, CIs across strata overlapped and overall patterns were consistent with primary analyses.

We did not observe an association between ω-3 supplement use and autism diagnosis (adjusted OR: 1.14; 95% CI: 0.83, 1.57) (Table 2). No evidence was found for modification by cohort type, and although the results stratified by child sex suggested increased odds of autism in girls, but not in boys, with supplement use, estimates were not statistically significant and CIs overlapped across these strata (Supplemental Tables 2 and 3). In secondary analyses that examined the frequency of ω-3 supplement use (Supplemental Table 4), the estimate for daily supplement use was similar to the primary analysis relying on any use. Of note, most participants reporting any supplement use were regular users (nearly 90% reported 4 times/wk or more).

In analyses with our quantitative trait measure of autism-related phenotype, we observed modest reductions of ~2 points in raw SRS scores with any fish intake (β for any fish intake: −1.69; 95% CI: −3.3, −0.08) (Table 3). Higher fish intake was not associated with reductions in SRS scores. Moreover, ω-3 supplement use was associated with a modest increase in SRS scores (β: 1.98; 95% CI: 0.33, 3.64) (Table 3), counter to our hypothesis. Overall, no strong differences were detected in these results across quantiles of the SRS (Supplemental Figure 2) in the quantile regression analyses. Results using SRS T-scores were similar to primary analyses of raw scores, albeit of smaller magnitude given the constrained distribution of the T score (Supplemental Table 5). Furthermore, in post hoc analyses testing SRS results stratified by sex and cohort type (parallel to those run for autism diagnosis), we did not see evidence of differences in associations across these strata.

In the sensitivity analyses, adjustment for other factors, including income, exposure coadjustment, prenatal vitamin use, or preterm birth, did not materially alter the findings (Supplemental Table 6). In the analyses that left out individual cohorts, we did not observe evidence that any 1 cohort drove the results of the autism diagnosis analyses (Supplemental Figures 3 and 4). Thus, the general pattern of results across cohorts remained consistent with the primary analyses.

**TABLE 2**
Association of maternal fish intake and ω-3 supplement use during pregnancy with child autism diagnosis.

| | *n*[1] | Crude OR (95% CI) | Adjusted OR (95% CI)[2] |
|---|---|---|---|
| Fish intake | | | |
| No | 664 | 1.0 (referent) | 1.0 (referent) |
| Yes | 3275 | 0.83 (0.77, 0.90) | 0.84 (0.77, 0.92) |
| Fish intake categories | | | |
| Never | 664 | 1.0 (referent) | 1.0 (referent) |
| <1×/wk | 1373 | 0.82 (0.73, 0.91) | 0.81 (0.71, 0.92) |
| 1–2×/wk | 1167 | 0.86 (0.73, 1.02) | 0.89 (0.75, 1.06) |
| >2×/wk | 735 | 0.82 (0.72, 0.92) | 0.84 (0.73, 0.97) |
| ω-3/Fish oil supplement use | | | |
| No | 3894 | 1.0 (referent) | 1.0 (referent) |
| Yes | 643 | 1.09 (0.81, 1.48) | 1.14 (0.83, 1.57) |

Crude and adjusted odds ratios (ORs) and 95% CIs from logistic regression models.

[1] Sample sizes for fish and supplement use analyses differed, owing to different numbers of participants with data available on these exposures.

[2] Adjusted for maternal race and ethnicity, maternal age, maternal education, prepregnancy BMI, smoking status, child's sex, child year of birth, and cohort as a random effect.

**TABLE 3**
Associations of maternal fish intake and ω-3 supplement use during pregnancy with child Social Responsiveness Scale scores (raw score).

| | *n* | Crude β coefficient (95% CI) | Adjusted β coefficient (95% CI)[1] |
|---|---|---|---|
| Fish intake | | | |
| No | 713 | (Referent) | (Referent) |
| Yes | 2896 | −2.01 (−3.86, −0.17) | −1.69 (−3.3, −0.08) |
| Fish intake categories | | | |
| Never | 713 | (Referent) | (Referent) |
| <1×/wk | 1295 | −2.07 (−3.58, −0.55) | −1.95 (−3.47, −0.44) |
| 1–2×/wk | 1051 | −2.34 (−4.77, 0.10) | −1.67 (−3.72, 0.39) |
| >2×/wk | 550 | −1.26 (−3.52, 1.00) | −1.06 (−3.05, 0.93) |
| ω-3/Fish oil supplement use | | | |
| No | 3370 | (Referent) | (Referent) |
| Yes | 555 | −0.45 (−2.4, 1.5) | 1.98 (0.33, 3.64) |

Results from linear regression; comparison results using quantile regression are shown in Supplemental Figure 2.
[1] Adjusted for maternal race and ethnicity, maternal age, maternal education, prepregnancy BMI, smoking status, child's sex, child year of birth and cohort as a random effect.
CI, confidence interval.

## Discussion

In this large study of the association between autism-related outcomes and prenatal fish intake and ω-3 supplement use in the United States ECHO program, we observed a reduction in the likelihood of an autism diagnosis and autism-related traits associated with maternal fish intake during pregnancy. In contrast, supplement use was not associated with an autism diagnosis and was associated with a modest increase in autism-related traits. Given that fish intake serves as a key source of nutrients critical for fetal neurodevelopment and maternal health and is consumed at lower than recommended levels in the United States population [12,23,42], these findings suggest the need for improved supports in translating guidelines for pregnant people in the United States into practice.

Few studies have examined prenatal fish intake in association with an autism diagnosis. The Nurses' Health Study II (317 ASD cases of >17,000 participants) did not find an association with reported autism and fish intake before and during pregnancy, although an inverse association with total dietary maternal polyunsaturated fat intake was observed [43]. Similarly, results from the United States Markers of Autism Risk in Babies-Learning Early Signs study reported an inverse association with ω-3 fatty acid concentrations based on reported dietary intake but did not examine fish intake specifically [44]. In a small case–control study (108 cases) conducted in China, an inverse association of maternal carp intake with autism was reported, but intake focused on the periconceptional period [45]. In the United Kingdom-based Avon Longitudinal Study of Parents and Children cohort, no association between white fish, oily fish, or shellfish and autism was found, although the sample included about half the number of cases as in our analysis, and some suggestive findings for autism-related traits were reported [46]. Our results extend these previous findings in a larger sample (including ~350 children with an autism diagnosis) and by assessing total fish intake during pregnancy. Previous work has not examined potential differences in these associations by sex. Our results of secondary analyses stratified by sex suggesting somewhat stronger associations with ASD in females may align with some evidence for stronger links between prenatal PUFA intake and ASD with co-occurring intellectual disability [47], and documentation of higher diagnosis of ASD with co-occurring intellectual disability in females [48] as well; however, these differences by sex and co-occurring diagnoses require further study.

Compared with studies that have assessed autism diagnosis, a larger number of studies have examined associations between prenatal fish intake and broader traits related to autism. No association between maternal fish intake and SRS scores (according to a subset of 18 items) was found in the Generation R cohort [49]. In a previous work that included 426 children drawn from 2 United States prospective pregnancy cohorts (one of which also participates in ECHO), no significant associations were found between overall fish intake during pregnancy and child SRS scores [50]. However, a greater intake of shellfish and large fish was associated with higher SRS scores, whereas a greater intake of salmon was associated with lower autism-related traits. In addition, stronger associations were observed for fish intake in the second half of pregnancy (a period that represents a high uptake of PUFAs in the developing brain). Additionally, a study within the Spanish Childhood and Environment Project (Infancia y Medio Ambiente) [51], including ~2000 mother–child pairs, also reported modest reductions in autism-related traits, as measured by the Childhood Asperger Syndrome Test, with prenatal fish intake. The results accounted for child seafood intake, or methylmercury concentrations, and were attenuated but persisted. Our analyses of SRS scores are consistent with these previous studies, suggesting modest inverse associations between fish intake and autism-related traits. Our study also suggests that these associations are consistent with the direction of association with an autism diagnosis and thus contributes important findings on United States fish intake to the existing literature.

Few studies have addressed prenatal ω-3 supplement use and autism-related outcomes. In both the United States–based Nurses' Health Study II and a study in Norway, no associations were reported between prenatal ω-3 fish oil supplement use and offspring autism, although use was very low in the former study population [43,52]. A recent meta-analysis of observational studies of neurocognitive developmental outcomes suggested no benefit of prenatal DHA supplement use on these outcomes overall and insufficient evidence for autism [12]. These previous results, along with our main null findings for supplement use, are also consistent with a majority of randomized trials that examined associations of prenatal maternal supplementation with offspring cognitive outcomes [53–55]. However, we also observed a minor increase in SRS scores with supplement use. Potential explanations for discrepancies across the results for fish intake and supplement use could relate to the bioavailability of fatty acids, differences in mitigating effects of coexposures that may increase risks such as additives or contaminants in supplements compared with those

in fish, unmeasured confounding, or, perhaps, the role of other beneficial nutrients in fish, such as selenium, iodine, iron, or vitamin D, acting alone or in combination with PUFAs.

In our analyses, we did not observe evidence of a trend or stronger inverse associations with greater fish intake across our analysis. This finding of an overall benefit with any intake could be due to the relatively low overall fish intake in our study population relative to United States dietary guidelines for pregnancy [56,57], with reduced power in higher intake categories, as trends have been noted in other studies of autism-related and cognitive outcomes in populations with higher fish intake [51,58]. Alternatively, it is also possible that a "threshold" effect may exist, whereby minimum concentrations of PUFAs are needed during development. Only 4 studies to date have examined associations between autism and prenatal or neonatal concentrations of PUFAs, with inconsistent findings [45,47,49,59]. The mixed evidence with measured PUFA concentrations could relate to differences in study populations across United States and European studies or differences in the timing of PUFA measurements. Fish intake, and in particular PUFAs, may impact neurodevelopmental outcomes through multiple mechanisms, including direct effects on neurogenesis and differentiation [60] and influences on inflammatory processes. Future work should seek to further resolve biomarker associations and mechanistic pathways.

Our study has many strengths, including its large sample size, the assessment of both autism diagnosis and an autism-related quantitative trait measure, and the ability to adjust for key confounders and to explore potential differences across differing cohort types. However, several limitations should be noted. First, we were not able to examine associations by type of fish or to assess the role of potential co-occurring pollutants or toxicants in fish. Different fish not only contain differing concentrations of beneficial PUFAs but also carry differing levels of contamination [61,62]. Although existing evidence does not support independent associations of methylmercury with autism [13,51,58] and support for other chemical exposures, such as perfluoroalkyl substances and polychlorinated biphenyls, is inconsistent for associations with autism [63–66], future work should further assess adjustment for cocontaminants to better understand overall benefits of fish [67]. Second, owing to limited data on timing across all cohorts, we did not conduct analyses by trimester of pregnancy or intake during lactation/early postnatal life. Third, our analyses of supplement use did not address dose, which should be explored in future work. Fourth, we relied on self-reported data, and we cannot rule out the potential for measurement error in exposure data. Although existing biomarker-based studies of PUFAs have some commonalities in findings with studies based on fish intake, the ideal future study design would be to incorporate both. Fifth, although we adjusted for a range of covariates, we cannot rule out potential residual confounding, such as by other health-related behaviors such as physical activity or avoidance of other chemical/toxicant exposures that could be associated with both diet and neurodevelopment. Sixth, as noted earlier, fish intake in the United States is lower than that in many other countries, and our results may not generalize to other countries with differing intake patterns. We also cannot rule out the potential for selection bias by factors related to availability of exposure and outcome information required for inclusion in analyses in this study, although as noted, participants were broadly representative of ECHO pregnant individuals and results were fairly robust to sensitivity analyses. Finally, our autism diagnoses were based on parent report of a clinician diagnosis, rather than direct assessment in all participants; however, several cohorts did conduct gold-standard diagnostic assessments, and the results did not differ in our leave-1-out analyses that assessed the impact of individual cohorts on findings. Despite these limitations, our findings were robust to several sensitivity analyses and broadly consistent across outcome measures.

In summary, our study contributes to a growing body of evidence supporting a role of prenatal diet in offspring autism-related outcomes. In particular, the results from this national study suggest that maternal fish intake, but not ω-3 supplement use, during pregnancy is associated with reductions in the likelihood of autism and autism-related traits. Our findings are consistent with current dietary guidelines that support fish intake during pregnancy and support continued public health efforts to encourage fish intake, accounting for types of fish with the lowest risk of toxicants.

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## Author contributions

The authors' responsibilities were as follows – KL, EO: conceived the study question and drafted the original manuscript. MW, KG: conducted statistical analyses; all coauthors: were involved in original data collection and/or funding acquisition for individual cohort data collections or ECHO follow-up; and all authors: provided feedback on results and edited the manuscript and have read and approved the final version of this manuscript.

## Conflicts of interest

The authors report no conflicts of interests.

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## Data availability

Deidentified data from the ECHO program are available through NICHD's Data and Specimen Hub (DASH) (https://dash.nichd.nih.gov). DASH is a centralized resource that allows researchers to access data from various studies via a controlled-access mechanism. Researchers can now request access to these data by creating a DASH account and submitting a Data Request Form. The NICHD DASH Data Access Committee will review the request and provide a response in approximately 2 to 3 weeks. Once granted access, researchers will be able to use the data for 3 years. See the DASH Tutorial for more detailed information on the process (https://dash.nichd.nih.gov/resource/tutorial).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2024.06.013.

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