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Childhood and Adolescent Fish Consumption and Adult Neuropsychological Performance: An Analysis from the Cape Cod Health Study

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Abstract

Objective—This exploratory analysis examines the relationship between childhood and adolescent fish consumption and adult neuropsychological performance.

Design—Data from a retrospective cohort study that assessed fish consumption from age 7 to 18 years via questionnaire were analyzed. A subset of the population underwent domain-specific neuropsychological assessment. Functions evaluated included omnibus intelligence, academic achievement, language, visuospatial skills, learning and memory, attention and executive function, fine motor coordination, mood, and motivation to perform.

Setting—Eight towns in the Cape Cod region of Massachusetts, USA, an area characterized by high fish consumption and an active seafood industry.

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Subjects—A cohort of 1245 subjects were recruited based on Massachusetts birth records from 1969 to 1983. Sixty-five participants from the original cohort underwent neuropsychological testing in adulthood (average age = 30 years).

Results—Participant report of consuming fish at least twice per month was associated with better performance on tests of visual learning, memory, and attentional abilities. However, self-report of consuming fish at rates higher than twice per month were not associated with improved abilities. No statistically significant associations were observed between type of fish consumed (e.g., species known to be high in methylmercury content) and test outcomes.

Conclusions—The results suggest that moderate fish consumption during childhood and adolescence may be associated with some cognitive benefits and that consumption of fish during this exposure window may potentially influence adult neuropsychological performance. Future prospective studies should take into account this time period of exposure.

Keywords

fish consumption; methylmercury; mercury; neuropsychological assessment

1. Introduction

1.1 Mercury

Dietary consumption of fish and seafood is the main non-occupational source of exposure to the toxicant methylmercury (MeHg) (Birch et al., 2014). Mercury is a ubiquitous heavy metal that enters the environment from several anthropogenic and natural sources. It is emitted into the atmosphere from coal burning power plants, mining and smelting operations, incineration of solid waste, volcanic activity, forest fires and other sources (UNEP, 2013). When elemental mercury from these sources is emitted into the atmosphere it undergoes photochemical oxidation resulting in inorganic mercury and enters the aquatic environment through rainwater. Inorganic mercury is then methylated in the aquatic environment by natural bacterial processes. MeHg, in turn, bioaccumulates in marine animals and moves up the food chain, thereby contaminating fish and seafood (Morel, 1998; Wang et al., 2004). The highest levels of contamination appear in long living, large, predatory marine species such as swordfish and shark (WHO, 1990).

MeHg exposure can affect multiple organ systems in humans but it is well established that the central nervous system is most sensitive. Because the prenatal period is a critical window of neurodevelopment numerous studies have focused on exposure to MeHg from the mother's fish consumption during pregnancy. Studies of three geographically distinct cohorts of children have been paramount to understanding the developmental effects of this toxicant. These population cohorts are located in the Faroe Islands, New Zealand, and the Seychelles (Rice et al., 2003; Grandjean et al., 1997; Debes et al., 2006; Crump et al., 1998; Myers et al., 1997; Myers et al., 1995a; Myers et al., 1995b; Davidson et al., 1995; Davidson et al., 1998).

In the Nordic fishing population of the Faroe Islands, the main source of exposure to MeHg occurs through the consumption of pilot whale meat. A prospective cohort study of this high

exposure population enrolled 1022 singleton births between 1986 and 1987 and analyzed mercury levels in cord blood and mother's hair at parturition. At age 7 years, 917 of these children underwent an extensive battery of neuropsychological tests. Poorer performance on neuropsychological tasks that assess the domains of language, attention, memory, visuospatial skills, and motor function were related to prenatal MeHg exposure as measured in cord blood (Grandjean et al., 1997). At age 14 years, 878 of these children underwent a second set of neuropsychological tests and poorer performance on tests assessing motor, attention, and verbal skills was again associated with higher prenatal MeHg exposure (Debes et al., 2006). These results suggested that prenatal exposure to MeHg has long-lasting impacts on multiple neuropsychological domains (Grandjean et al., 1997; Debes et al., 2006).

The New Zealand cohort of 237 children whose mother's hair mercury had been measured at birth underwent 26 psychologic and academic achievement tests between the ages of 6 and 7 years. This study reported associations for high prenatal MeHg exposure with decreased performance on tests of language, visuospatial ability, attentional ability, and fine motor skills (Kjellstrom et al., 1986; Kjellstrom et al., 1989; Crump et al., 1998).

The Seychelles Child Development Study (SCDS) followed 779 mother-infant pairs from a high-fish eating population from birth to 19 years and administered tests to evaluate multiple neurological domains. In contrast to the Faroes and New Zealand studies the SCDS found null associations for peripartum maternal hair mercury with neurodevelopment. Using an alternative postnatal exposure metric (taking samples of the children's hair at the time of neurological evaluation), the SCDS found a beneficial association between higher hair mercury and improved IQ in 9-year-old males. The primary explanation for this association has been confounding by the presence of nutrients highly beneficial for brain development also contained in fish (Myers et al., 2009)

1.2 Polyunsaturated Fatty Acids

Fish and seafood are the primary dietary source of long-chain n-3 polyunsaturated fatty acids (PUFAs), specifically, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) (Kris-Etherton et al., 2000; 2002; Molendi-Coste et al., 2011). PUFAs, the most abundant fatty acid in the mammalian central nervous system, are concentrated in the membrane lipids of brain grey matter and the visual elements of the retina (Innis, 2008). These fatty acids are critical nutrients for brain development and are often low in the Western diet (Ryan et al., 2010).

Several studies have shown positive associations between levels of docosahexaenoic acid (DHA) in blood and improvements in tests of cognitive and visual function during early life (reviewed by Ryan et al., 2010). A prospective study of 341 mother-child pairs in Massachusetts using a food frequency questionnaire to assess the mother's fish consumption during pregnancy observed that higher fish intake (>2 servings/week) compared to no fish intake was associated with higher scores on the Peabody Picture Vocabulary Test and Wide Range Assessment of Visual Motor Abilities in children at 3 years of age (Oken et al., 2008).

In another prospective cohort study of 25,446 children born to mothers in the Danish National Birth Cohort between 1997 and 2002 higher maternal fish intake during pregnancy was associated with higher developmental scores at 18 months of age. In this study mothers reported child development in a standardized interview, which was then used to generate developmental scores. (Oken et al. 2008b).

A population-based prospective birth cohort in New Bedford, Massachusetts (1993–1998) measured inattentive and impulsive/hyperactive behaviors in 8-year-old children using the Conners Rating Scale for Teachers. This study revealed an increased risk for teacher-reported inattentive/impulsive/hyperactive behaviors with increased peripartum maternal hair mercury and a reduced risk for these behaviors with consumption of >2 servings per week of fish during pregnancy. This study highlights the importance of disentangling nutritional benefits of fish consumption from the risk of low-level mercury exposure from fish (Sagiv et al., 2012).

1.3 Childhood and Adolescence

To our knowledge, few studies examining fish consumption during childhood and adolescence and neuropsychological performance have been conducted. Fish consumption during childhood and adolescence may have a different effect on brain development than prenatal exposure through maternal fish consumption. Although the majority of brain development occurs during the prenatal period, the human brain continues to develop and mature after birth well into the second decade of life. This continued growth occurs in both grey and white matter (Brain Development Cooperative Group, 2012). Thus, beneficial effects of PUFAs on cognitive function during this window as well as any adverse effect of MeHg could potentially occur. Because the existing literature focuses heavily on the impacts of fish consumption of the mother during the prenatal window the rationale for the current study was to examine the impacts of fish consumption during this later childhood and adolescent window another period of robust neurodevelopment.

While numerous intervention studies have examined PUFA supplementation during childhood and neurocognitive endpoints, the results have been inconsistent (Ryan et al., 2010; Dalton et al., 2009; McNamara and Carlson, 2006; Kennedy et al., 2008). A prospective cohort study of 3972 Swedish males reporting fish consumption levels at age 15 years found that fish consumption of more than once per week was associated with higher scores in combined intelligence, verbal performance, and visuospatial performance at age 18 years across all educational levels (Aberg et al., 2009). Notably, some studies have shown that fish oil supplementation does not confer the same benefits of fish consumption (Visioli et al., 2003; Elvevoll et al., 2006).

2. Methods

2.1 Study Population

The Cape Cod Health study is a population-based retrospective cohort study of individuals born in eight towns in the Cape Cod region of Massachusetts between 1969 and 1983. The cohort was originally designed to examine possible associations between exposure to the

solvent tetrachloroethylene (PCE) in drinking water and multiple neurological endpoints. The population was exposed to PCE when it leached from the vinyl-lining of asbestos cement drinking water pipes installed across the Northeastern United States from 1969 to 1980. Information about this exposure scenario and the associated health effects have been described in detail elsewhere (Aschengrau et al., 2008; Aschengrau et al., 2009; Aschengrau et al., 2011; Aschengrau et al., 2012; Janulewicz et al., 2008; Janulewicz et al., 2012). Study participants completed a self-administered questionnaire which included demographic information and developmental, educational, occupational, medical and residential histories (Janulewicz et al., 2012). In addition, the questionnaire gathered detailed information regarding childhood (defined as 7 – 12 years) and adolescent (defined as 13 – 18 years) fish consumption patterns including how often participants consumed fish between the years of 7 to 18 years old and their most commonly consumed varieties of fish.

2.2 Follow-up and enrollment

Follow-up and enrollment of the study participants took place between the years 2006 and 2010. Participants were traced to obtain current addresses and telephone numbers using Massachusetts residence lists; death, marriage, divorce, credit bureau and alumni records, telephone books, directory assistance, and the Internet White Pages. Recruitment letters explaining the study purpose and self-administered questionnaires were sent to all traced subjects. Comparisons of characteristics of the study participants and non-participants as well as detailed information regarding the initial exclusion criteria have been described elsewhere (Janulewicz et al., 2012). Based on the information provided in the questionnaires, 24.8% of the cohort was excluded from neuropsychological testing for one or more of the following reasons: was a twin or triplet, had a neurological condition, experienced lead or carbon monoxide poisoning, suffered a head injury with a loss of consciousness > 5 minutes, used three or more illicit drugs, or drank excessive amounts of alcoholic beverages (average daily volume > 3 drinks) (Table 1).

The study was approved by the Institutional Review Board of the Boston University Medical Center.

2.3 Data Collection

Review of birth certificates provided information on subject's date of birth, gestational duration and birth weight, and parents' ages, occupational titles and parental education. Self-administered questionnaires that were completed by the participant's mother (or father if the mother was deceased) between 2002–2003 acquired additional covariate information on subject and parents: developmental (e.g., birth defects, severe mental retardation, cerebral palsy, fetal alcohol syndrome), educational, and medical (e.g., lead poisoning) information on the subject and medical information (e.g., diabetes and pre-eclampsia, and use of legal drugs, marijuana, vitamins, and iron supplementation during pregnancy) and occupational exposures for the mother around the time of her pregnancy (Janulewicz et al., 2008).

The self-administered questionnaires that were completed by the subjects (2005–2008), included demographic information, race, marital status, occupational titles, and parental education. The questionnaire also determined the subject's own educational history, which

included the highest level of education that the participant had completed and whether or not they had experienced any learning problems. Information on smoking, alcohol consumption, and drug use was also obtained (Janulewicz et al., 2012).

The neurological tests were conducted by a qualified examiner who was masked to exposure status of the subject. Descriptions of each test are summarized in 3 (Janulewicz et al., 2012).

2.4 Assessment of fish consumption

Participant age at the time of the self-administered questionnaire ranged from 23 to 41 years of age. Participants self-reported their fish consumption patterns between the ages of 7–18 years. Fish was defined as “any kind of fish, including fish sticks and canned tuna fish,” but not including “seafood such as lobster, clams, scallops, shrimps, oysters, or any other kind of shellfish.” Frequency of fish consumption was reported by selecting a) “did not eat fish”, b) “once a month or less,” c) “a couple of times a month”, d) “about once a week”, or e) “several times a week.” These data were collapsed into three frequency categories: “ $\leq$ once per month,” “twice per month,” or “ $\geq$ once per week.” Participants also recorded the type of fish consumed most often. Additionally, they were asked “Did you eat any of the following kinds of fish?” and asked to check off fish on a list based on their popularity in the American diet (e.g. canned tuna) or known high mercury content (e.g. swordfish, tuna steak, shark). The data the participants provided in this section was used to categorize the type of fish consumption into three categories: “did not eat fish or never ate fish known to be high in MeHg,” “fish eater who occasionally consumed fish known to be high in MeHg”, and “fish eater who most frequently consumed fish known to be high in MeHg.” Fish known to be high in MeHg are reported in Supplemental Table S1. If a participant reported never eating fish or noted eating a fish not known to be high in MeHg such as “haddock” and did not check off ever consuming fish known to be high in MeHg (e.g. swordfish, tilefish, king mackerel, Supplemental Table S1), they were placed in the category “did not eat fish or never ate a fish known to be high in MeHg.” If a participant noted typically consumed “haddock” but also selected a fish known to be high in MeHg from the checklist, they were categorized as a “fish eater who occasionally consumed fish known to be high in MeHg.” If a participant wrote in “swordfish” for the fish they ate most often they were categorized as a “fish eater who most frequently consumed a fish known to high in MeHg.”

2.5 Assessment of neuropsychological performance

Of the 65 participants who underwent neuropsychological testing, two were excluded from the analysis because they failed the Test of Memory Malingering (Tombaugh, 1996) and their data were deemed unreliable (Janulewicz et al., 2012). The following measures of neuropsychological performance were assessed (Table 2): omnibus intelligence using the Wechsler Abbreviated Scales of Intelligence (WASI) (Wechsler, 1999); academic achievement using two subtests of the Wide Range Achievement Test 3 (WRAT-Reading and Arithmetic) (Wilkinson, 1993); language using the Boston Naming Test (BNT) (Kaplan et al., 1983); visuospatial skills using the Hooper Visual Organization Test (HVOT) (Hooper, 1983) and the copy condition of the Rey-Osterreith Complex Figure (ROCF) (Osterreith, 1944); learning and memory using the recall conditions of the ROCF and Wechsler Memory Scale–Visual Reproduction (Wechsler, 1945) and the California Verbal Learning Test

(CVLT) (Delis et al., 2000); attention and executive function using the Trail-making Test (TMT) (Reitan, 1992) parts A and B and, the Conners Adult ADHD Ranking Scale (Conners et al., 1999) and the continuous performance subtest of the Neurobehavioral Evaluation System-3 (NES); and motor using the finger tapping subtest of the Neurobehavioral Evaluation System-3 (NES) (Baker et al., 1985), and current mood using the Profile of Mood States (POMS) (McNair et al., 1992).

2.6 Statistical Analysis

Regression models were used to assess the relationship between frequency and type of fish consumption and test scores. We modeled “ $\leq$ once per month” as the reference group for analyses of frequency of fish consumption and “did not eat fish or never ate fish known to be high in MeHg” as the reference for analyses of type of fish consumed. Mean differences (for continuous scores) and relative risks (for dichotomized scores) were utilized to assess the strength of the association between the exposure and a particular outcome. Ninety-five percent confidence intervals were used to assess the precision of the associations. Crude analyses and adjusted analyses were conducted for each neuropsychological test result. For the adjusted analysis confounders were selected a priori based on their known associations with the outcomes. The small sample size of the study limited the number of confounders that could be included in the adjusted model. The final adjusted models for the continuous outcomes included participant’s gender, education level at time of testing, whether or not the participant was breastfed, and the mother’s education level at the time of participant’s birth. Because this cohort was originally designed to examine prenatal exposure to tetrachloroethylene (PCE), sensitivity analysis was conducted to examine possible interaction by PCE exposure status and there was determined to be no effect. Due to the small sample size dichotomous outcomes were adjusted for participant’s education at time of testing only. For some dichotomous outcomes adjusted analysis could not be performed.

3. Results

3.1 Frequency of fish consumption

For frequency of fish consumption, a total of 60 participants were included in the analysis because three of the 63 participants with reliable neuropsychological test scores had not answered the frequency of fish consumption portion of their questionnaire. 23.3% (N=14) were in the reference category “ $\leq$ once per month,” 28.3% (N=17) were in the moderate category “twice per month,” and 48.3% (N=29) were in the high category “ $>$ once per week”. Participant characteristics across the three groups were similar with the exception of whether or not they had been breastfed, which was included in the multivariate adjustment for the continuous outcomes. The subjects were an average of 29 to 30 years old at time of testing, white race, and educated beyond high school (Table 3).

3.2 Type of fish consumption

For type of fish consumption, all 63 of the participants who had reliable neuropsychological test results were included in the analysis because they all had complete information for the portion of the questionnaire asking about type of fish consumed. 36.5% (N=23) were in the reference category “did not eat fish or never ate a fish known to be high in MeHg;” 47.6%

(N=30) were in the moderate category “fish eater who occasionally consumed fish known to be high in MeHg”, 15.9% (N=10) were in the high category “fish eater who most frequently consumed a fish known to high in MeHg”. Participant characteristics across the three groups were similar with the exception of maternal education level at time of the participant’s birth, which was included in the multivariate adjustment for the continuous outcomes.

3.3 Neuropsychological test results- frequency of fish consumption

The crude and adjusted neuropsychological test results are presented in Table 4 (continuous outcomes) and Table 5 (dichotomous outcomes). There were no meaningful differences in performance in the areas of academic achievement, language, visuospatial, executive function, motor, or mood across frequency of fish consumption groups. Those who consumed fish at least twice per month had the best scores on tests assessing academic achievement, omnibus IQ, and language but the differences were quite small and not statistically significant (Tables 4 and 5). There were no consistent trends for tests across frequency of fish consumption in the domains of visuospatial ability, executive function, motor skills or mood. Consuming fish at least twice per month was associated with better performance on some tests of visual learning, memory, and attentional abilities compared to the reference group. In the visual learning and memory domain those who consumed fish twice per week performed better on the Rey-Osterreith Complex Figure test on both the Immediate Recall Condition and the Delayed Recall Condition compared to the reference group (Table 4, Rey-Osterreith Immediate Recall Raw Score Moderate Group β 5.0, 95% CI 1.1, 8.9, $p=0.01$, Delayed Recall Raw Score Moderate Group β 5.2, 95% CI 1.1, 9.3, $p=0.01$). In the attentional abilities domain, the moderate frequency fish consumers also had the best performance on Trail Making Test-Part A time to completion but this was not statistically significant. On a second test of attentional abilities, the NES III Continuous Performance Test, the moderate frequency group performed better compared to the reference group with faster reaction time to the directed stimuli (Table 4, NES III Continuous Performance test, reaction time Moderate Group β -44.9, 95% CI -70.4, -19.4, $p=0.001$). The highest frequency group, those who ate fish once or more per week also performed better than the reference group on the NES III Continuous Performance Test but did not perform as well as the moderate frequency group (Table 4, NES III Continuous Performance test, reaction time High Group β -30.7, 95% CI -55.8, -5.6, $p=0.02$). On the Conners Adult ADHD rating scale, the moderate frequency group also reported suffering fewer problems related to inattentiveness (T Score > 50 Inattention Memory Problems, Low % Yes = 35.7% (5/14), Moderate % Yes = 5.9% (1/17) and High % Yes = 31.0 (9/29) (Table 5).

3.4 Neuropsychological test results- type of fish consumed

The crude and adjusted neuropsychological test results are presented in the Supplementary Tables S1 (continuous outcomes) and S2 (dichotomous outcomes). We did not observe any consistent trends across the categories of fish consumption categorized by known methylmercury concentrations.

4. Discussion

This exploratory analysis leveraged a previously existing dataset with a robust neuropsychological battery to explore the hypothesis that childhood and adolescence may be a relevant window of exposure when assessing the effects of fish consumption on neurodevelopment. Notably, the age at time of exposure assessment may have introduced recall errors.

We performed comparisons across eight neuropsychological domains in this retrospective cohort study and it appears that moderate fish consumption may be related to enhanced performance on neuropsychological tests of visual learning, memory, and attentional abilities as measured by the Rey-Osterreith Complex Figure and the NES III Continuous Performance tests. No significant relationships were observed between type of fish consumption when fish consumption was categorized by known methylmercury levels in fish and performance in neuropsychological domains.

We did not observe a normal dose-response curve for frequency of fish consumption. We observed improvements in the moderate category of fish consumption but when fish consumption increases to once per week or greater the improvements to the visual learning, memory, and attentional domains were lost. One possible explanation for this non-monotonic dose-response is that the lowest fish consumption group may have acquired the neurodevelopmental nutritional benefit of PUFAs while the highest fish consumption group was affected by low level MeHg exposure from their high fish diet. However, this interpretation is inconsistent with the null results for type of fish consumption categorized by MeHg content. This could be explained by misclassification of the type of fish consumed most often. Another possible explanation for the lack of meaningful findings based on fish type categorized by mercury level is that associations between MeHg and neuropsychological performance may be negatively confounded by the nutritional neurodevelopmental benefit of the PUFAs in fish. We were unable to adjust for this type of confounding due to lack of data and inadequate sample size.

The existing literature focuses primarily on the prenatal period and has found evidence of deleterious neurodevelopmental effects of MeHg exposure from fish but also a significant benefit to neurodevelopment from a diet high in PUFAs. This study is one of the first to focus on exposures from fish consumption during the period from 7 to 18 years, when significant brain development is still occurring.

The interpretation of these results should reflect that this was an exploratory analysis limited by the small sample size. The neuropsychological battery in this study was designed to detect subtle changes to neuropsychological performance and is highly sensitive. However, because the effects of fish consumption are likely of small magnitude future studies of this relationship need to be adequately powered. Based on our power calculations, assuming a 2:1 unexposed to exposed ratio and a 5% risk in the unexposed you would need approximately 800 fish-consuming adolescents for 80% power to detect a relative risk of 1.5 (Rothman, 2011).

The small sample size may have limited capacity to detect statistically significant results for some tests. Because of the small numbers we were limited in how precisely we could breakdown of the exposure categories for frequency of fish consumption, which introduces some exposure misclassification. However, the final breakdown resulted in relevant comparisons in which participants who consumed fish once per month or less serve as the reference category for which we could compare people who ate fish at least twice per month or once a week or greater. We believe these groupings differentiate regular consumers of fish from those who have little to no fish in their diet. The small sample size also limited the number of covariates that could be included in multivariable models. For all continuous outcomes, we were able to adjust for participant's gender, education level at time of testing, whether or not the participant was breastfed, and the mother's education level at the time of participant's birth. Residual and unmeasured confounding likely exists because information was unavailable for some factors such as dietary habits, especially other dietary intake of PUFAs. Another key limitation is the lack of information on maternal consumption of fish during pregnancy, mother's prenatal mercury levels, or DHA levels. However, we hypothesize that the mother's fish consumption behavior is correlated with the consumption behavior of their children: mothers likely feed their children foods that they themselves eat most often. If the mother's fish consumption does align with the child's fish consumption patterns it is possible that the beneficial effects of moderate fish consumption were incurred from the mother's moderate consumption of fish not the child's. This is something we cannot disentangle given the limitations of the data but warrants further analysis in prospective birth cohorts that follow the children into the adolescent period.

Another limitation is non-differential exposure misclassification from the use of a self-administered questionnaire. Participants were between the ages of 23 to 41 years old when they were asked to recall their fish consumption behaviors when they were between 7–18 years, which likely introduced some errors in recalling information. However, there is no reason to believe the ability to recall this behavior differed across groups. Also, the Cape Cod region of Massachusetts has a rich culture and industry around fishing and seafood, which we believe would improve our participants' ability to recall the specific types of fish that they consumed and was a strength of this study. We categorized fish by mercury levels because we considered this known neurotoxicant to be most relevant to public health. However, fish can also be contaminated with other compounds, including selenium, polychlorinated biphenyls and dioxins. An analysis of the effect of fish consumption would ideally include adjustment for human biomarkers of mercury, PUFAs, and other contaminant levels in human tissues. In part due to the retrospective nature of the study, biomarkers were never collected for this study population.

It is also possible that members of the study population with lower neuropsychological performance were less likely to respond to the request to undergo neuropsychological testing. However, this source of selection bias is not likely because the exposure frequencies were similar in the participants who underwent neuropsychological testing and those who did not.

A major strength of this study is the in depth neuropsychological battery, which included testing of 9 functional domains. Another key strength is that we were able to obtain

information on a variety of fish species that the participants consumed not just the frequency of fish consumption which allowed us to assess consumption of fish known to be high in methylmercury.

The results of this study suggest that consumption of fish during childhood and adolescence is a relevant exposure period potentially impacting neuropsychological performance later in life. Future studies with larger sample size should be conducted examining this time period of exposure, gathering human biomarkers of methylmercury and DHA in addition to self-reported fish consumption.

The public health message regarding whether or not pregnant women and children should consume fish has been difficult to clearly convey and people may elect to avoid fish altogether because of concerns about MeHg. Despite the presence of MeHg at high levels in certain species that should be avoided, low mercury fish is an important part of a healthy diet. The presence of DHA confers a significant healthful benefit and fish is the primary source of exposure to this important nutrient. These preliminary findings were part of an exploratory analysis and while they suggest that moderate fish consumption during childhood and adolescence may confer a neurodevelopmental benefit, further study of this exposure window and relationship is warranted in a larger sample with an ability to disentangle prenatal and adolescent exposure effects.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- We examined childhood fish consumption and adult neuropsychological performance.
- Moderate fish consumption appears to confer benefit in some neurological domains.
- Fish consumption twice per month improved measures of visual learning, memory, and attention.
- Further studies of this relationship are warranted.

TABLE 1

Selection and enrollment of study population, by frequency of fish consumption.

	</= once per month	Twice per month	>/= once per week	Missing data on frequency of fish consumption	Total
Selected for neuropsychological testing	576	385	145	139	1245
Excluded from previous study ^a	474	323	119	110	1026
Eligible for neuropsychological testing	85	62	50	22	219
Unable to contact	59	40	15	14	128
Refused	12	5	4	5	26
Underwent testing ^b	14	17	31	3	65

^aParticipants were excluded from previous study for reasons including: living outside the geographic area, no maternal questionnaire data, only postnatal PCE exposure, multiple birth, reported used of illicit drugs, reported excessive alcohol use, history of neurological disease, possible occupational exposure to solvents, severe hearing or vision impairment, and possible environmental exposure to solvents.

^bThe total number of participants that underwent neuropsychological testing was N=65. Of these, three participants were missing data on the frequency of fish consumption (N=62) and two participants (who were in >/= once/week category) were removed from the study because their test scores were not valid based on their performance on the TOMM (N=60).

TABLE 2

Neuropsychological test description by domain

Domain	Test	Description
Omnibus Intelligence	Wechsler Abbreviated Scale of Intelligence (WASI)	Short test of omnibus intelligence with four subsets
Academic Achievement	Wide Range Achievement Test (WRAT)	Screening test of academic knowledge
Language	Boston Naming Test (BNT)	Line drawings of common objects must be named
Visuospatial	Hooper Visual Organization Test (HVOT)	Drawings of common objects presented in cut-up form. Requires identification of the object
	Rey-Osterreith Complex Figure (ROCF) –copy condition	A complex design is presented. Examinee must draw a copy of the figure.
Learning and Memory	California Verbal Learning Test II (CVLT II)	List learning task requiring examinee to learn list over 5 trials with delayed recall conditions.
	Wechsler Memory Scale (WMS) –visual reproduction	Four visual designs are presented individually. Examinee must draw each design immediately after stimulus is withdrawn and after a delay
	Rey-Osterreith Complex Figure (ROCF)	A complex design is presented. Examinee must draw immediately after stimulus is withdrawn and after a delay
Attention and executive function	Trail-Making Test- Part A and B	Circles containing numbers must be connected sequentially by a drawn line (A condition) and circles containing numbers and letters must be connected sequentially by alternating numbers and letters (B condition)
	Conners adult ADHD Rating Score	Self-report inventory of symptoms of attention deficit hyperactivity disorder
	Neurobehavioral Evaluation System III (NES III) –continuous performance test	Computer-assisted task in which animal profiles are presented. Key press required following presentation of target item.
Motor	Neurobehavioral Evaluation System III (NES III) –finger tapping test	Computer-assisted task requiring tapping of a key separately with index finger of each hand
Mood	Profile of Mood States (POMS)	60 single-item descriptors of emotional reactions in 6 dimensions are presented. Examinee indicates the intensity of response to each affective descriptor on a likert scale
Motivation	Test of Memory Malingering	Drawings of objects are presented followed by multiple choice recognition paradigm

TABLE 3

Distribution of selected characteristics by frequency of childhood and adolescent fish consumption

	Frequency of childhood and adolescent (7–18) fish consumption (servings)		
Characteristic[†]	<= once per month (N=14)	twice per month (N=17)	>= once per week (N=29)
current age (years), mean $\pm$ SD	29.6 $\pm$ 3.3	29.1 $\pm$ 3.5	30.9 $\pm$ 3.4
birthweight (grams), mean $\pm$ SD	3455 $\pm$ 501	3489 $\pm$ 417	3595 $\pm$ 443
year of birth			
1969–1974	1 (7.1)	2 (11.8)	7 (24.1)
1975–1980	7 (50.0)	9 (52.9)	18 (62.1)
1981–1983	6 (42.9)	6 (35.3)	4 (13.8)
preterm < 37 weeks gestation	0	0	1 (3.5)
male	1 (7.1)	4 (23.5)	14 (48.3)
white race	14 (100)	17 (100)	28 (100)
participant was breastfed	9 (64.3)	14 (82.4)	16 (57.1)
current level of education			
HS grad or less	1 (7.1)	2 (11.8)	3 (10.3)
Some college	2 (14.3)	4 (23.5)	2 (6.9)
4 year college grad or higher	11 (78.6)	11 (64.7)	24 (82.8)
history of mental illness	3 (21.4)	2 (11.8)	2 (6.9)
self-reported diagnosis of ADHD	0	0	1 (3.5)
self-reported learning problems	1 (7.1)	3 (18.8)	9 (31.0)
mother's age at participant's birth, mean $\pm$ SD	27.9 $\pm$ 5.2	28.2 $\pm$ 4.9	28.4 $\pm$ 4.5
father's age at participant's birth, mean $\pm$ SD	30.5 $\pm$ 5.7	30.7 $\pm$ 7.2	31.3 $\pm$ 5.5
maternal education level			
HS grad or less	1 (7.1)	3 (17.7)	5 (17.9)
Some college	5 (35.7)	4 (23.5)	8 (28.6)
4 year college grad or higher	8 (57.1)	10 (58.8)	15 (53.6)
paternal occupation			
White collar	7 (50.0)	5 (29.4)	19 (65.5)
Blue collar	5 (35.7)	9 (52.9)	5 (17.2)
Other	2 (14.3)	3 (17.7)	5 (17.2)
mother received prenatal care	13 (92.9)	15 (88.2)	26 (92.9)
maternal diabetes	1 (7.1)	0	2 (7.1)

	Frequency of childhood and adolescent (7–18) fish consumption (servings)		
Characteristic [†]	<= once per month (N=14)	twice per month (N=17)	>= once per week (N=29)
maternal prenatal vitamin use	13 (92.9)	15 (88.2)	26 (92.9)
maternal prenatal alcohol consumption			
didn't drink	6 (42.9)	6 (35.3)	9 (32.1)
1–3 drinks/month	8 (57.1)	8 (47.1)	10 (35.7)
1+ drinks/week	0	3 (17.7)	9 (32.1)
maternal prenatal smoking			
Didn't smoke	10 (71.4)	13 (76.5)	20 (71.4)
1–10 cigarettes/day	2 (14.3)	3 (17.7)	3 (10.7)
11+ cigarettes/day	2 (14.3)	1 (5.9)	5 (17.9)
maternal prenatal marijuana use	0	1 (5.9)	2 (7.1)
family history of ADHD	1 (7.1)	3 (18.8)	4 (14.3)
family history of learning disabilities	1 (7.1)	4 (25.0)	6 (20.7)
any alcohol consumption 24 hours before testing	2 (14.3)	1 (5.9)	3 (10.3)

[†] Individuals with missing data were excluded from percentages.

TABLE 4

Frequency of fish consumption age 7–18 years – neuropsychological test results – crude and adjusted continuous outcomes LOW = Fish meal $\leq$ once per month [Reference Group] MODERATE = Fish meal twice per month HIGH = Fish meal $>$ once per week

Outcome	Mean (SD)	Crude Results Beta estimate of mean difference (95% CI)	p Value	Adjusted Mean (SE)	Adjusted Results ^a Beta estimate of mean difference (95% CI)	p Value
Academic Achievement						
Wide Range Achievement Test 3						
Spelling Percentile ^b						
Low (N = 14)	58.8 (23.3)	-	-	42.4 (6.6)	-	-
Moderate (N = 17)	60.8 (23.3)	2.0 (15.0, 19.1)	0.81	46.9 (5.4)	4.5 (-10.1, 19.1)	0.54
High (N = 29)	53.6 (23.8)	-5.2 (-20.5, 10.2)	0.50	42.8 (4.8)	0.4 (-13.2, 14.0)	0.95
Reading Percentile ^b						
Low (N = 14)	58.9 (25.0)	-	-	52.0 (6.9)	-	-
Moderate (N = 17)	63.1 (19.6)	4.3 (-12.2, 20.7)	0.61	54.5 (5.7)	2.5 (-12.7, 17.8)	0.74
High (N = 29)	57.5 (23.3)	-1.4 (-16.2, 13.4)	0.85	51.4 (5.1)	-0.6 (-14.8, 13.6)	0.93
Omnibus Intelligence						
Wechsler Abbreviated Scale of Intelligence						
Verbal IQ ^b						
Low (N = 14)	105.7 (10.2)	-	-	102.1 (3.6)	-	-
Moderate (N = 17)	106.8 (10.4)	1.1 (-6.8, 8.9)	0.79	103.8 (3.0)	1.8 (-6.2, 9.7)	0.66
High (N = 29)	106.3 (11.5)	0.6 (-6.5, 7.7)	0.86	102.7 (2.6)	0.6 (-6.8, 8.0)	0.87
Performance IQ ^b						
Low (N = 14)	110.7 (8.5)	-	-	108.6 (4.02)	-	-
Moderate (N = 17)	112.5 (13.8)	1.8 (-7.4, 11.1)	0.70	111.3 (3.3)	2.7 (-6.2, 11.6)	0.54
High (N = 29)	110.7 (13.8)	-0.1 (-8.4, 8.3)	0.99	106.0 (3.0)	-2.7 (-11.0, 5.6)	0.52
Full Scale IQ ^b						
Low (N = 14)	109.2 (8.1)	-	-	105.6 (3.3)	-	-
Moderate (N = 17)	110.5 (11.4)	1.3 (-6.3, 9.0)	0.73	108.0 (2.7)	2.4 (-4.9, 9.6)	0.52
High (N = 29)	109.0 (11.1)	-0.2 (-7.1, 6.7)	0.96	104.2 (2.4)	-1.4 (-8.2, 5.3)	0.67

Outcome	Mean (SD)	Crude Results Beta estimate of mean difference (95% CI)	p Value	Adjusted Mean (SE)	Adjusted Results ^d Beta estimate of mean difference (95% CI)	p Value
Language						
<i>Boston Naming Test</i>						
Total raw score (total possible = 60) ^b						
Low (N = 14)	54.1 (3.7)	-	-	53.7 (1.1)	-	-
Moderate (N = 17)	55.7 (2.7)	1.5 (-1.0, 4.0)	0.23	55.2 (0.9)	1.5 (-1.0, 4.0)	0.24
High (N = 29)	55.4 (3.7)	1.3 (-1.0, 3.5)	0.26	54.8 (0.8)	1.2 (-1.2, 3.5)	0.33
# stimulus cues given ^c						
Low (N = 14)	6.4 (3.9)	-	-	7.0 (1.1)	-	-
Moderate (N = 17)	4.7 (2.6)	-1.7 (-4.2, 0.9)	0.20	5.2 (0.9)	-1.7 (-4.3, 0.8)	0.17
High (N = 29)	4.9 (3.8)	-1.5 (-3.8, 0.9)	0.21	5.7 (0.8)	-1.2 (-3.6, 1.1)	0.28
# phonemic cues given ^c						
Low (N = 14)	5.8 (3.7)	-	-	6.3 (1.1)	-	-
Moderate (N = 17)	4.4 (2.7)	-1.4 (-3.8, 1.1)	0.26	4.9 (0.9)	-1.4 (-3.9, 1.0)	0.25
High (N = 29)	4.6 (3.5)	-1.2 (-3.4, 1.0)	0.26	5.2 (0.8)	-1.1 (-3.4, 1.2)	0.33
Visuospatial						
<i>Rey-Osterrieth Complex Figure</i>						
Copy condition raw score (total possible = 36) ^b						
Low (N = 14)	34.6 (2.3)	-	-	34.4 (0.6)	-	-
Moderate (N = 17)	34.9 (1.7)	0.3 (-0.9, 1.6)	0.59	34.9 (0.5)	0.5 (-0.9, 1.8)	0.49
High (N = 29)	35.2 (1.4)	0.6 (-0.5, 1.8)	0.27	34.9 (0.5)	0.5 (-0.7, 1.8)	0.40
Learning and Memory						
<i>Wechsler Memory Scale</i>						
Immediate recall raw score (total possible = 14) ^b						
Low (N = 14)	8.6 (2.4)	-	-	7.4 (0.8)	-	-
Moderate (N = 17)	8.9 (2.1)	0.3 (-1.5, 2.2)	0.74	8.0 (0.6)	0.7 (-1.1, 2.4)	0.45
High (N = 29)	8.2 (2.8)	-0.4 (-2.0, 1.3)	0.66	6.8 (0.6)	-0.6 (-2.2, 1.0)	0.44
Delayed recall raw score (total possible = 14) ^b						
Low (N = 14)	6.9 (2.0)	-	-	6.1 (1.0)	-	-

Outcome	Mean (SD)	Crude Results Beta estimate of mean difference (95% CI)	p Value	Adjusted Mean (SE)	Adjusted Results ^d Beta estimate of mean difference (95% CI)	p Value
Moderate (N = 17)	7.8 (3.2)	0.8 (-1.2, 2.9)	0.42	7.4 (0.8)	1.2 (-0.9, 3.4)	0.25
High (N = 29)	6.7 (3.0)	-0.2 (-2.1, 1.6)	0.80	5.8 (0.7)	-0.4 (-2.4, 1.6)	0.71
California Verbal Learning Test						
Trials 1–5 free recall t-score ^b						
Low (N = 14)	59.8 (10.1)	-	-	57.2 (3.1)	-	-
Moderate (N = 17)	58.1 (9.8)	-1.7 (-8.4, 5.1)	0.62	56.3 (2.6)	-0.9 (-7.8, 5.6)	0.80
High (N = 29)	58.6 (8.8)	-1.2 (-7.3, 4.9)	0.69	56.5 (2.3)	-0.7 (-7.1, 5.7)	0.83
Short delay free recall raw score (total possible = 16) ^b						
Low (N = 14)	12.8 (2.8)	-	-	12.1 (0.9)	-	-
Moderate (N = 17)	13.4 (2.1)	0.60 (-1.4, 2.6)	0.55	13.0 (0.8)	0.9 (-1.1, 3.0)	0.36
High (N = 29)	12.9 (2.6)	0.11 (-1.7, 1.9)	0.90	12.7 (0.7)	0.6 (-1.4, 2.6)	0.53
Long delay free recall raw score (total possible = 16) ^b						
Low (N = 14)	13.0 (3.3)	-	-	11.8 (1.0)	-	-
Moderate (N = 17)	13.2 (2.8)	0.60 (-1.4, 2.6)	0.83	12.6 (0.8)	0.8 (-1.3, 3.0)	0.44
High (N = 29)	12.5 (2.9)	0.11 (-1.7, 1.9)	0.57	11.8 (0.7)	-0.1 (-2.1, 1.9)	0.95
Long delay recognition –false positive raw score ^c						
Low (N = 14)	1.2 (2.2)	-	-	2.3 (0.8)	-	-
Moderate (N = 17)	1.8 (3.8)	0.6 (-1.2, 2.4)	0.50	2.3 (0.7)	0.0 (-1.8, 1.9)	0.97
High (N = 29)	1.2 (1.6)	0.0 (-1.7, 1.6)	0.96	2.0 (0.6)	-0.3 (-2.1, 1.4)	0.70
Total number of intrusions raw score ^c						
Low (N = 14)	1.9 (3.1)	-	-	3.0 (0.9)	-	-
Moderate (N = 17)	1.1 (1.2)	-0.7 (-2.8, 1.3)	0.47	1.8 (0.8)	-1.3 (-3.3, 0.8)	0.23
High (N = 29)	2.7 (3.3)	0.9 (-1.0, 2.7)	0.35	3.6 (0.7)	0.6 (-1.3, 2.5)	0.54
Total number of repetitions raw score ^c						
Low (N = 14)	3.8 (4.0)	-	-	4.7 (1.5)	-	-
Moderate (N = 17)	4.9 (4.2)	1.2 (-1.8, 4.2)	0.44	5.4 (1.2)	0.6 (-2.6, 3.8)	0.70
High (N = 29)	5.6 (4.2)	1.8 (-0.9, 4.5)	0.19	5.9 (1.1)	1.2 (-1.8, 4.2)	0.44
Rey-Osterrieth Complex Figure						

Outcome	Mean (SD)	Crude Results Beta estimate of mean difference (95% CI)	p Value	Adjusted Mean (SE)	Adjusted Results ^d Beta estimate of mean difference (95% CI)	p Value
Immediate recall raw score (total possible = 36) ^b						
Low (N = 14)	21.2 (5.3)	-	-	20.1 (1.8)	-	-
Moderate (N = 17)	25.7 (3.9)	4.6 (0.9, 8.2)	0.02	25.1 (1.4)	5.0 (1.1, 8.9)	0.01
High (N = 29)	22.6 (5.6)	1.4 (-1.9, 4.7)	0.40	21.4 (1.3)	1.3 (-2.3, 4.9)	0.47
Delayed recall raw score (total possible = 36) ^b						
Low (N = 14)	20.6 (5.2)	-	-	19.1 (1.9)	-	-
Moderate (N = 17)	25.2 (4.8)	4.6 (0.7, 8.5)	0.02	24.3 (1.5)	5.2 (1.1, 9.3)	0.01
High (N = 29)	21.9 (5.8)	1.3 (-2.2, 4.9)	0.45	20.4 (1.4)	1.4 (-2.5, 5.2)	0.48
Attention and executive function						
Trail Making Test						
Part A – time to completion (s) ^c						
Low (N = 14)	22.8 (8.2)	-	-	25.5 (2.0)	-	-
Moderate (N = 17)	19.3 (5.0)	-3.5 (-7.9, 0.9)	0.12	21.1 (1.7)	-4.3 (-8.8, 0.2)	0.06
High (N = 29)	20.5 (5.6)	-2.3 (-6.3, 1.7)	0.25	21.8 (1.5)	-3.7 (-7.8, 0.5)	0.08
Part A – percentile ^b						
Low (N = 14)	55.0 (29.2)	-	-	44.7 (8.1)	-	-
Moderate (N = 17)	67.1 (21.5)	12.1 (-5.6, 29.7)	0.18	60.4 (6.7)	15.7 (-2.2, 33.7)	0.08
High (N = 29)	63.6 (23.5)	8.6 (-7.3, 24.5)	0.28	57.8 (6.0)	13.1 (-3.6, 29.9)	0.12
Part B – time to completion (s) ^c						
Low (N = 14)	51.1 (9.6)	-	-	66.7 (5.1)	-	-
Moderate (N = 17)	49.4 (15.9)	-1.7 (-14.6, 11.2)	0.79	59.4 (4.2)	-7.4 (-18.6, 3.8)	0.19
High (N = 29)	59.2 (21.5)	8.1 (-3.5, 19.7)	0.17	66.6 (3.7)	-0.2 (-10.6, 10.2)	0.98
Part B – percentile ^b						
Low (N = 14)	52.1 (23.8)	-	-	23.8 (8.9)	-	-
Moderate (N = 17)	55.3 (31.7)	3.2 (-19.4, 25.7)	0.78	37.7 (7.3)	13.9 (-5.7, 33.6)	0.16
High (N = 29)	42.6 (33.8)	-9.6 (-29.9, 10.8)	0.35	26.5 (6.5)	2.7 (-15.6, 21.0)	0.77
Neurobehavioral Evaluation System III						
Continuous performance test reaction time (ms) ^c						

Outcome	Mean (SD)	Crude Results Beta estimate of mean difference (95% CI)	p Value	Adjusted Mean (SE)	Adjusted Results ^a Beta estimate of mean difference (95% CI)	p Value
Low (N = 11)	488.5 (32.2)	-	-	495.7 (12.0)	-	-
Moderate (N = 16)	445.4 (31.2)	-43.1 (-67.8, -18.3)	0.001	450.8 (9.3)	-44.9 (-70.4, -19.4)	0.001
High (N = 26)	456.7 (31.3)	-31.8 (-54.5, -9.1)	0.007	465.0 (8.8)	-30.7 (-55.8, -5.6)	0.02
Motor						
Neurobehavioral Evaluation System III						
Finger tapping						
Mean # taps dominant hand ^b						
Low (N = 11)	50.9 (7.9)	-	-	49.3 (2.5)	-	-
Moderate (N = 16)	51.9 (7.0)	0.99 (-4.2, 6.2)	0.70	50.4 (1.9)	1.2 (-4.2, 6.5)	0.66
High (N = 26)	55.9 (5.6)	4.9 (0.2, 9.7)	0.04	53.0 (1.8)	3.8 (-1.5, 9.0)	0.16
Mean # taps non dominant hand ^b						
Low (N = 11)	47.5 (9.5)	-	-	48.3 (2.6)	-	-
Moderate (N = 16)	47.4 (5.0)	-0.1 (-5.5, 5.2)	0.96	47.3 (2.0)	-0.9 (-6.5, 4.7)	0.74
High (N = 26)	51.6 (6.5)	4.1 (-0.9, 9.0)	0.10	50.3 (1.9)	2.0 (-3.5, 7.5)	0.47

^a Adjusted for gender, education at time of testing, mother's education at time of birth, and whether or not participant was breastfed.

^b Higher score = better performance.

^c Lower score = better performance.

Frequency of Fish Consumption Age 7–18 years – Neuropsychological Test Results – crude and adjusted dichotomous outcomes LOW = Fish meal </= once per month [Reference Group] MODERATE = Fish meal twice per month HIGH = Fish meal >/= once per week

TABLE 5

Outcome	% Yes (n/N)	Crude relative risk (95% CI)	p Value	Adjusted relative risk (95% CI) ^a	p Value
Visuospatial					
Hooper Visual Organization Test					
Total score = < 24 ^{b,d}					
Low (N = 14)	7.1 (1/14)	-	-	-	-
Moderate (N = 17)	5.9 (1/17)	0.8 (0.1, 12.0)	0.88	0.9 (0.1, 12.6)	0.92
High (N = 29)	17.2 (5/29)	2.4 (0.3, 18.8)	0.40	2.4 (0.3, 18.5)	0.40
Attention and Executive Function					
Trail Making Test					
Part A Errors > 0 ^c					
Low (N = 14)	28.6 (4/14)	-	-	-	-
Moderate (N = 17)	5.9 (1/17)	0.2 (0.02, 1.6)	0.13	0.2 (0.03, 1.9)	0.18
High (N = 29)	20.7 (6/29)	0.7 (0.2, 2.6)	0.56	0.7 (0.3, 2.2)	0.59
Part B Errors > 0 ^c					
Low (N = 14)	28.6 (4/14)	-	-	-	-
Moderate (N = 17)	17.6 (3/17)	0.6 (0.2, 2.3)	0.47	0.5 (0.1, 2.0)	0.34
High (N = 29)	31.0 (9/29)	1.1 (0.4, 2.9)	0.87	0.9 (0.3, 2.4)	0.78
Conners Adult ADHD Rating Scale^e					
Inattention Memory Problems (T score > 50) ^c					
Low (N = 14)	35.7 (5/14)	-	-	-	-
Moderate (N = 17)	5.9 (1/17)	0.2 (0.02, 1.3)	0.08	0.1 (0.02, 0.9)	0.05
High (N = 29)	31.0 (9/29)	0.9 (0.4, 2.1)	0.76	0.8 (0.3, 1.8)	0.53
Hyperactivity/Restlessness (T score > 50) ^c					
Low (N = 14)	35.7 (5/14)	-	-	-	-
Moderate (N = 17)	11.8 (2/17)	0.3 (0.08, 1.4)	0.14	0.3 (0.1, 1.4)	0.12
High (N = 29)	37.9 (11/29)	1.1 (0.5, 2.5)	0.89	1.0 (0.5, 2.4)	0.92

Outcome	% Yes (n/N)	Crude relative risk (95% CI)	p Value	Adjusted relative risk (95% CI) ^a	p Value
Impulsivity/emotional lability (T score > 50) ^c					
Low (N = 14)	35.7 (5/14)	-	-		-
Moderate (N = 17)	5.9 (1/17)	0.2 (0.02, 1.3)	0.08		0.06
High (N = 29)	20.7 (6/29)	0.6 (0.2, 1.6)	0.29		0.21
Problems with self-concept (T score > 50) ^c					
Low (N = 14)	28.6 (4/14)	-	-	---f	---f
Moderate (N = 17)	11.8 (2/17)	0.4 (0.1, 1.9)	0.26	-	-
High (N = 29)	27.6 (8/29)	1.0 (0.3, 2.7)	0.95		-
DSM-IV inattentive symptoms (T score > 50) ^c					
Low (N = 14)	28.6 (4/14)	-	-	---f	---f
Moderate (N = 17)	11.8 (2/17)	0.4 (0.1, 1.9)	0.26	-	-
High (N = 29)	34.5 (10/29)	1.2 (0.5, 3.2)	0.70		-
DSM-IV hyperactive-impulsive symptoms (T score > 50) ^c					
Low (N = 14)	21.4 (3/14)	-	-	0.8 (0.2, 3.4)	-
Moderate (N = 17)	17.7 (3/17)	0.8 (0.2, 3.5)	0.79	1.4 (0.4, 4.3)	0.77
High (N = 29)	27.6 (8/29)	1.3 (0.4, 4.1)	0.67		0.61
DSM-IV ADHD symptoms total (T score > 50) ^c					
Low (N = 14)	28.6 (4/14)	-	-	0.6 (0.2, 2.1)	-
Moderate (N = 17)	17.7 (3/17)	0.6 (0.2, 2.3)	0.47	1.6 (0.6, 4.4)	0.42
High (N = 29)	34.5 (10/29)	1.2 (0.5, 3.2)	0.70		0.36
ADHD index (T score > 50) ^c					
Low (N = 14)	28.6 (4/14)	-	-	---f	---f
Moderate (N = 17)	0.0 (0/17)	0.0	0.99	-	-
High (N = 29)	20.7 (6/29)	0.7 (0.2, 2.2)	0.56	-	-
Mood					
Profile of Mood States^e					
Tension (T score > 50) ^c		-	-	-	-
Low (N = 14)	35.7 (5/14)				

Outcome	% Yes (n/N)	Crude relative risk (95% CI)	p Value	Adjusted relative risk (95% CI) ^a	p Value
Moderate (N = 17)	47.1 (8/17)	1.3 (0.6, 3.1)	0.53	1.3 (0.6, 3.2)	0.51
High (N = 29)	58.6 (17/29)	1.6 (0.8, 3.5)	0.21	1.6 (0.8, 3.5)	0.20
Depression (T score > 50) ^c					
Low (N = 14)	21.4 (3/14)	-	-	-	-
Moderate (N = 17)	23.5 (4/17)	1.1 (0.3, 4.1)	0.89	1.2 (0.3, 4.5)	0.81
High (N = 29)	17.2 (5/29)	0.8 (0.2, 2.9)	0.74	0.8 (0.2, 3.0)	0.77
Anger (T score > 50) ^c					
Low (N = 14)	21.4 (3/14)	-	-	-	-
Moderate (N = 17)	29.4 (5/17)	1.4 (0.4, 4.8)	0.62	1.4 (0.4, 5.1)	0.57
High (N = 29)	34.5 (10/29)	1.6 (0.5, 4.9)	0.41	1.6 (0.5, 5.0)	0.40
Fatigue (T score > 50) ^c					
Low (N = 14)	35.7 (5/14)	-	-	-	-
Moderate (N = 17)	35.3 (6/17)	1.0 (0.4, 2.6)	0.98	1.0 (0.4, 2.6)	0.97
High (N = 29)	48.3 (14/29)	1.4 (0.6, 3.0)	0.46	1.4 (0.6, 3.0)	0.43
Confusion (T score > 50) ^c					
Low (N = 14)	28.6 (4/14)	-	-	-	-
Moderate (N = 17)	41.2 (7/17)	1.4 (0.5, 3.9)	0.48	1.4 (0.5, 3.9)	0.48
High (N = 29)	37.9 (11/29)	1.3 (0.5, 3.4)	0.56	1.3 (0.5, 3.4)	0.56
Vigor (T score ≤/ < 50) ^b					
Low (N = 14)	57.1 (8/14)	-	-	-	-
Moderate (N = 17)	76.5 (13/17)	1.3 (0.8, 2.3)	0.28	1.4 (0.8, 2.4)	0.25
High (N = 29)	69.0 (20/29)	1.2 (0.7, 2.0)	0.47	1.2 (0.7, 2.1)	0.45
Total mood disturbance (T score > 50) ^c					
Low (N = 14)	35.7 (5/14)	-	-	-	-
Moderate (N = 17)	47.1 (8/17)	1.3 (0.6, 3.1)	0.53	1.3 (0.6, 3.2)	0.51
High (N = 29)	41.4 (12/29)	1.2 (0.5, 2.6)	0.73	1.2 (0.5, 2.7)	0.70

^a Adjusted for education.^b Higher score = better performance.^c Lower score = better performance.

f Adjusted analyses were not performed

e Clinical cut off score = 50.

d Clinical cut off score = 24.

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